THE TRIMETHYLSILYL GROUP IN ORGANIC SYNTHESIS

by

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

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September 1983.

ABSTRACT

A general method for the formation of acetals using chlorotrimethylsilane has been developed. Dioxolanes are formed from most carbonyl groups whereas methyl acetals are only formed from electron-poor carbonyl groups. The intermediacy of a silicon-bound carbonyl species is discussed.

The method has been extended to the formation of esters. In a solution of the alcohol to be esterified, methyl, ethyl, benzyl and 2-trimethylsilylethyl esters are readily formed in the presence of chlorotrimethylsilane. Using ^{29}Si-N.M.R., a trimethylsilyl ester has been shown to be an intermediate in the reaction.

The Lewis acid catalyzed condensation of 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene with a variety of dielectrophiles, in a 1,2 relationship, has been investigated. The relative order of electrophilic reactivity towards this compound has been found to be;

$$RR'C(Cl)SC_6H_5 > ArCOCHO > ArCOCHO > RC(OCH_3)_2, RC(OCH_3)SC_6H_5 > RCHCl_2$$

The dialkylation of 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene has been shown to lead to hydroxycyclopentenones with the same substitution pattern as the prostaglandins skeleton. Using ^{29}Si-N.M.R., the mechanism of this reaction has been shown to proceed in two sequential steps; reaction at the γ-position takes place first to give a titanium-bound intermediate, the thus formed intermediate then undergoes α-alkylation to give the cyclopentenone compound.

RESUME

Une méthode générale pour la formation d'acétals employant le chlorotriméthylsilane a été developpée. Les dioxolanes sont formés à partir de la plupart des groupements carbonyles alors que les acetals méthyliques sont seulement formés à partir de groupements carbonyles pauvres en électrons. La présence intermédiare d'une espèce carbonyle liée au siliciume est discutée.

La méthode a été étendue à la formation d'esters. Dans une solution de l'alcool devant être estérifié, les esters méthylique, éthylique, benzylique et triméthylsilyl-2 éthylique sont facilement formés en presence de chlorotriméthylsilane. Une triméthylsilyl ester a été identifié comme intermédiare de réaction par l'emploi de R.M.N. ^{29}Si.

La condensation catalysée par un acide de Lewis du *bis*-triméthylsiloxy-1,3 méthoxy-1 butadiène-1,3 avec divers diélectrophiles dans un rapport 1,2 a été etudiée. L'ordre relatif suivant de réactivité électrophile envers ce composé a été établi;

$$RC(Cl)SC_6H_5 > ArCOCHO > ArCOCHO > RC(OCH_3)_2, RC(OCH_3)SC_6H_5 > RCHCl_2$$

Il a été demontré que la dialkylation du *bis*-triméthylsiloxy-1,3 méthoxy-1 butadiène-1,3 mène à des hydroxycyclopentenones ayant le même patron de substitution que le squelette des prostaglandins. Par R.M.N. ^{29}Si, il fut établi que le méchanisme de cette réaction procède en deux étapes séquentielles; la réaction en position-γ se produit d'abord donnant un intermédiaire lié au titanim, l'intermédiaire ainsi formé subit alors une α-alkylation menant au composé cyclopenténone.

ACKNOWLEDGEMENTS

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

I would also like to thank my many colleagues, particularly Dr. Pierre Potvin, Dr. Daniel Payette, Mr. John Honek, Mr. Richard Camicioli, and M. Pierre Bedard for many helpful and interesting discussions. I would like to express my thanks to Dr. Francoise Sauriol and Dr. John Finkenbine for performing N.M.R. and mass spectral analyses on my behalf. I wish to express my appreciation to Mrs. Christina Brook for a great deal of editorial assistance and to Mlle. Suzanne Boisvert for the translation of the abstract. Finally, I would like to thank the Natural Sciences and Engineering Research Council of Canada for financial support during my time at McGill Univeristy.

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List of Abbreviations

Bu	butyl
Cp	cyclopentadienyl
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
Et	ethyl
G.L.C.	Gas Liquid Chromatography
H.P.L.C.	High Pressure Liquid Chromatography
INEPT	Insensitive Nuclei Enhanced By Polarization Transfer
Me	methyl
N.M.R.	Nuclear Magnetic Resonance
PG	prostaglandins
Ph	phenyl
Pr	propyl
RNA	ribonucleic acid
Tf	trifluoromethanesulfonate
T.L.C.	Thin Layer Chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMSBr	bromotrimethylsilane
TMSCl	chlorotrimethylsilane
TMSI	iodotrimethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate

With my Love

To My Parents

Mig and Granther

Ma and Pa van't Hof

and Adriana, who makes it interesting,

and to **Tina,**

who makes it all worthwhile.

1. INTRODUCTION

With the clarity of vision which hindsight has given us, it is possible to observe milestones along the path of scientific history. These are always associated with men of astonishing vision; Pythagorus, da Vinci, Lavoisier, Mendeleev, Einstein and many, many more. In the context of this thesis, it is also appropriate to remember the contributions of contemporary chemists who have shaped the way in which one thinks about organic chemistry; such as, van't Hoff, Barton, Stork, Robinson, and Woodward. Within the field of organic chemistry a fundamental change has been slowly taking place over the past two decades which reflects the influence of these and other chemists. The precise classical barriers between the many fields of chemistry, erected in the early part of this century, are losing definition. Technologies unimagined even forty years ago are now linking many areas of chemistry. One example is nuclear magnetic resonance. This technique was developed by physical chemists, subsequently used by organic chemists for the identification of organic moieties, based on proton resonance, and finally, was used by inorganic chemists in the analysis of most of the elements in the periodic table.

For the organic chemist, this change in the perspective of chemistry is reflected in the "total organic synthesis". Presently, extensive use is made of main group inorganic and organometallic moieties. The design of such inorganic and organometallic reagents for use in organic synthesis has become an established field in organic chemistry, a situation which would not have been acceptable even twenty years ago when the barriers between chemical fields were quite rigid. Of all the "heteroelements" being broadly exploited in the field of organic synthesis, silicon is

becoming more often the element of choice. Even though the presence c silicon in the final molecule has been of little utility up to the presen time, the unusual properties of this element make it ideal for th protection of organic functionalities and in mediating a variety o reactions.

The work upon which this thesis is based pursues the study of silico in organic synthetic reactions. A brief history of silicon and organo-silicon chemistry will be outlined to clarify those properties of silico which can be exploited in organic synthesis*.

1.1 The Development of Organosilicon Chemistry

Silicon has been used by human civilization since remote antiquity in the form of sand, gravel, or clay, and later, in the making of pottery, vitreous enamel, glass and cement[4]. All of these advancements preceded the conception of chemistry as a science. These developments in the usage of silicon surely arose from its ready availability**.

In one of the earliest chemical citations of a silicon species, water glass (sodium silicate in aqueous solution) was described by Glauber in

* Much of following introduction is based on references 1, 2, and 3, and further specific references to these works will not be made.

** Silicon is the second most abundant element in the earth's crust although it is rarely found in pure form. Assuming a crust of 10 mile depth (16 km), the elemental composition was estimated to be 46.5% oxygen and 27.6% silicon[5].

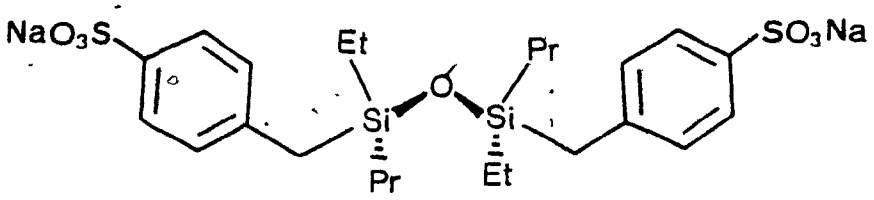
1648[6]. At that time, silica was considered to be an element because of its great stability. Lavoisier (1743-1794), however, doubted this and considered silica to be molecular rather than elemental in nature. It was not until 1807 when HF became available that the decomposition of silica was first recorded, proving Lavoisier correct. Upon exposure to HF, silica was converted to H_2SiF_6 and volatile SiF_4. The former compound was isolated as its potassium salt (K_2SiF_6). Later, Berzelius made the first pure silicon by the action of potassium metal on K_2SiF_6. He further converted the silicon into silicon tetrachloride by igniting it in a stream of chlorine. These two materials, silicon and silicon tetrachloride, are still most often used as starting materials for the synthesis of organosilicon compounds. In 1863, Wöhler made silane and trichlorosilane[6] and further proposed that the chemistry of silicon might mimic that of carbon. Friedel and Crafts were also working in this area and synthesized the first known truly organosilicon moiety, tetraethylsilane, from silicon tetrachloride and diethylzinc[7]. Thus, by 1872, many tetravalent silicon compounds had been prepared. The extent to which the chemistry of carbon paralleled the chemistry of silicon, however, especially with respect to its tetrahedral nature, remained to be established.

The modern father of silicon chemistry is F.S. Kipping. Kipping began his research in the hope of isolating an optically active silicon species. He was able to show that Grignard reagents were very useful for the synthesis of organosilanes (Scheme 1.1)[8].

$$SiCl_4 \xrightarrow{RMgBr} RSiCl_3 \xrightarrow{R'MgBr} RR'SiCl_2$$

Scheme 1.1

Kipping also helped elucidate the relationship between the chemistries of carbon and silicon. During an attempted distillation of Ph_3SiOH to increase its purity, Kipping was only able to isolate a "sticky mass", a situation with which the present author has great sympathy, that "melts, not sharply, at about 109° and would seem to be diphenylsilicone"[9]. In his view, this was the parallel silicon compound to diphenylketone. Although this misnomer has stayed with silicon chemistry, he had in fact, isolated a diphenylsilicone oligomer. He eventually realized his error and stated "So far, no silicon analogue of a ketone has been obtained"[10]. Subsequently, he was able to isolate the optically active silane 1 which showed that the arrangement about a tetravalent silicon species was tetrahedral[11].



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In light of all of his experimental work, Kipping's thoughts with respect to the overall relationship of the chemistries of silicon and carbon were:

> "Even after a very short experience, it was evident that corresponding derivatives of the two elements in question showed very considerable diffefences in their chemical properties; it may now be said that the principal if not the only case in which they exhibit a really close resemblance is that of the paraffins and those particular silicohydrocarbons, containing a silicon

atom directly united to four alkyl radicals.

> But of far greater importance in any general comparison of carbon compounds with the organic derivatives of silicon is the fact that many, if not most, of the more important types of the former are not represented among the latter. Apparently this is not merely a consequence of the insufficient experimental investigation of silicon derivatives but is due to the fundamental differences in the properties of the atoms of silicon and carbon;....."[10]

Kipping's polymeric nuisances (oils, jellies, glues, "sticky masses") are the bread and butter of the silicone industry. These compounds are presently available as fluids, resins, rubbers, greases and so on[12,13]. They have the unique properties of low toxicity, stability over a large range of temperatures and stability to a wide variety of chemicals[1]. Literally thousands of these compounds exist and their unusual properties make them ubiquitous in modern society.

The silicone industry is the leading producer and consumer of organosilicon products. As of 1978, more than 40,000 silicon containing compounds, the majority of them polymeric in nature (silicones), had been described in the literature[14]. The most important silicones, from an industrial point of view, are the dimethylsilicones[15] which may be obtained directly from the hydrolysis of dihalodimethylsilanes[16]. These latter compounds can be obtained by the Grignard route of Kipping from silicon tetrachloride but are more often prepared by the "Direct Process"[17]. This procedure, discovered by Rochow in 1940 and subsequently

by Müller a year later, involves heating Cu-Si in the presence of CH_3Cl to generate predominantly $(CH_3)_2SiCl_2$, still the most important precursor in the silicone field.

The interest in silicon in an organic context rather than an inorganic or polymeric context, started somewhat later. The basic organic chemistry of silicon developed over a period of about twenty-five years following Rochow's discovery of the Direct Process. During this time, pioneering research into organosilicon derivatives was pursued for their own intrinsic interest. The availability of simple organohalosilanes, because of their industrial importance, helped to stimulate the study of organosilicon chemistry.

It is beyond the scope of this text to discuss the basic organic chemistry of silicon, however, Eaborn has described this area in detail[18]. Furthermore, Sommer has clearly elucidated the mechanisms of many simple silicon reactions using chiral silicon moieties[19].

1.2 Contemporary Organosilicon Chemistry

The year 1968 was a watershed in the development of organosilicon chemistry. The true potential of these compounds was finally discovered by organic chemists, although their value had been apparent to silicon chemists for some time. It was the year when the silicon chemists Eaborn and Bott shared their insight on the silicon-carbon bond[20]. Their conclusions were as follows: (i) a silyl group is often more easily displaced from a given carbon atom than a proton from the corresponding carbon atom, (this has been subsequently shown to be true only if the nucleophile is oxygen-based or a halogen and steric restraints are not

present), (ii) a silicon–carbon bond stabilizes a β-carbonium ion more than a hydrogen-carbon or carbon-carbon bond, and (iii) whereas silyl groups have high reactivity when adjacent to a suitable functionality, when more remote from that functionality they are usually able to survive most reaction conditions used in organic synthesis.

The work published in and around 1968 also delineated some of the major areas of organosilicon chemistry still under investigation at the present time. For example, Pierce showed the facility with which alcohols could be silylated and desilylated (Scheme 1.2a)[21]. However, trimethylsilyl ethers proved too acid and base sensitive to be of general utility. It was Corey who later popularized the use of silicon protecting groups[22]. He developed the reagent *t*-butyldimethylsilyl chloride and methods for its introduction to and removal from alcohols (Scheme 1.2b).

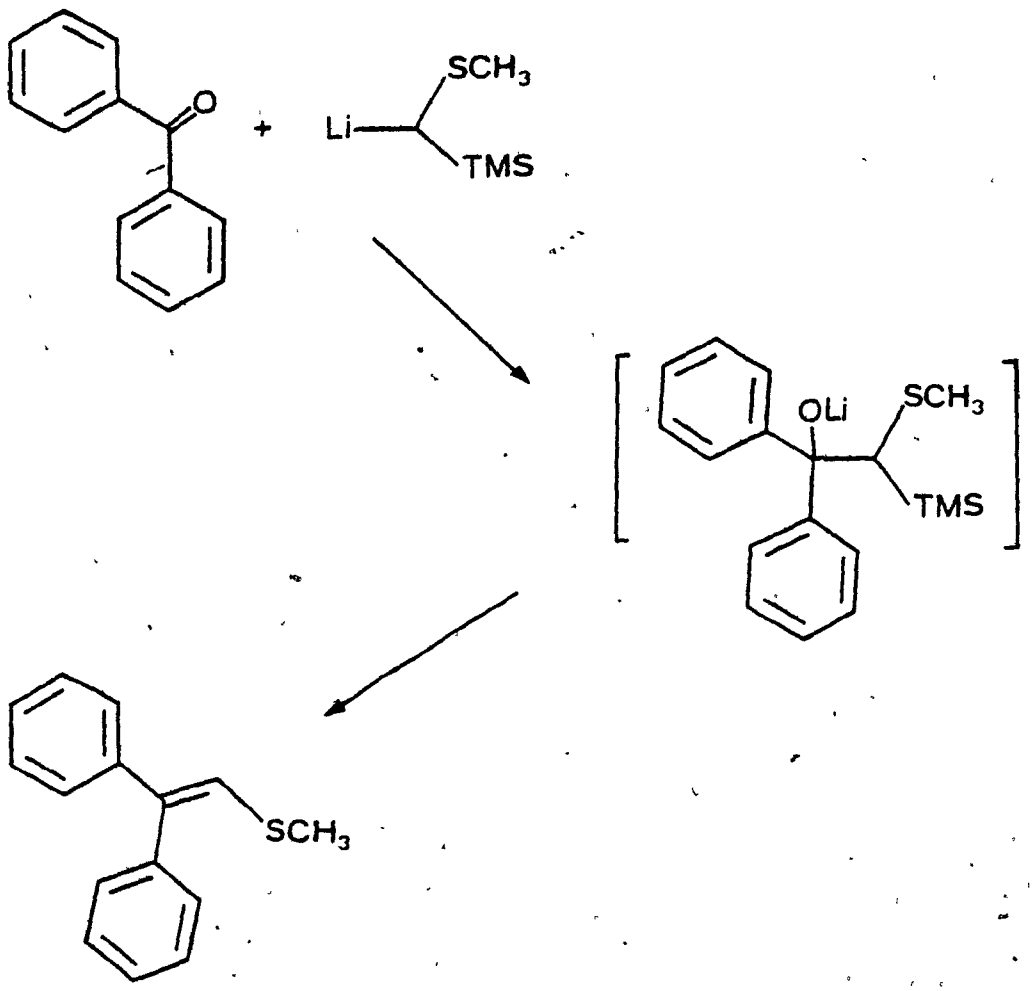
$$ROH \underset{ii}{\overset{i}{\rightleftharpoons}} ROSi(CH_3)_2R'$$

a) i = $(CH_3)_3SiCl$, $((CH_3)_3Si)_2NH$, ii = CH_3OH, $R' = CH_3$

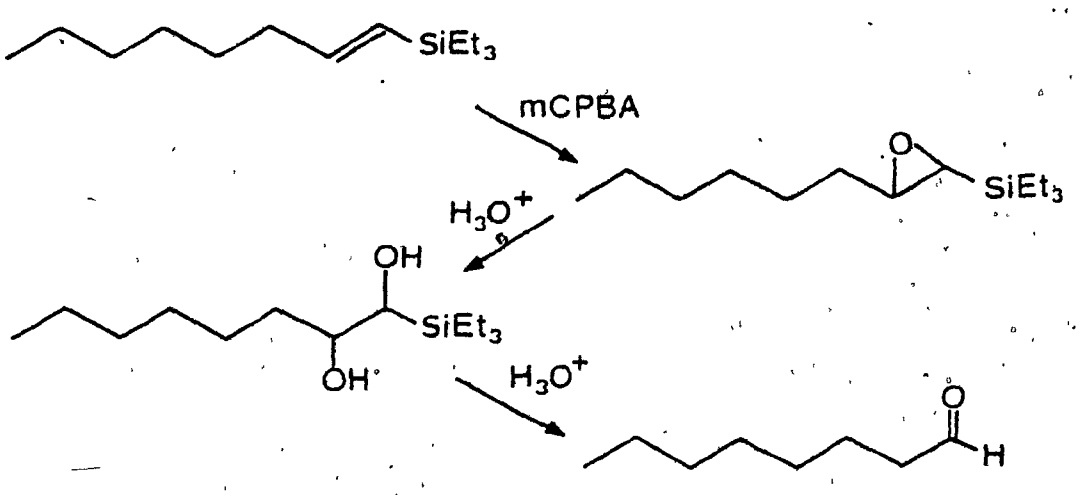
b) i = $^tBu(CH_3)_2SiCl$, DMF, imidazole, ii = $^nBu_4NF$, $R' = {}^tBu$

Scheme 1.2

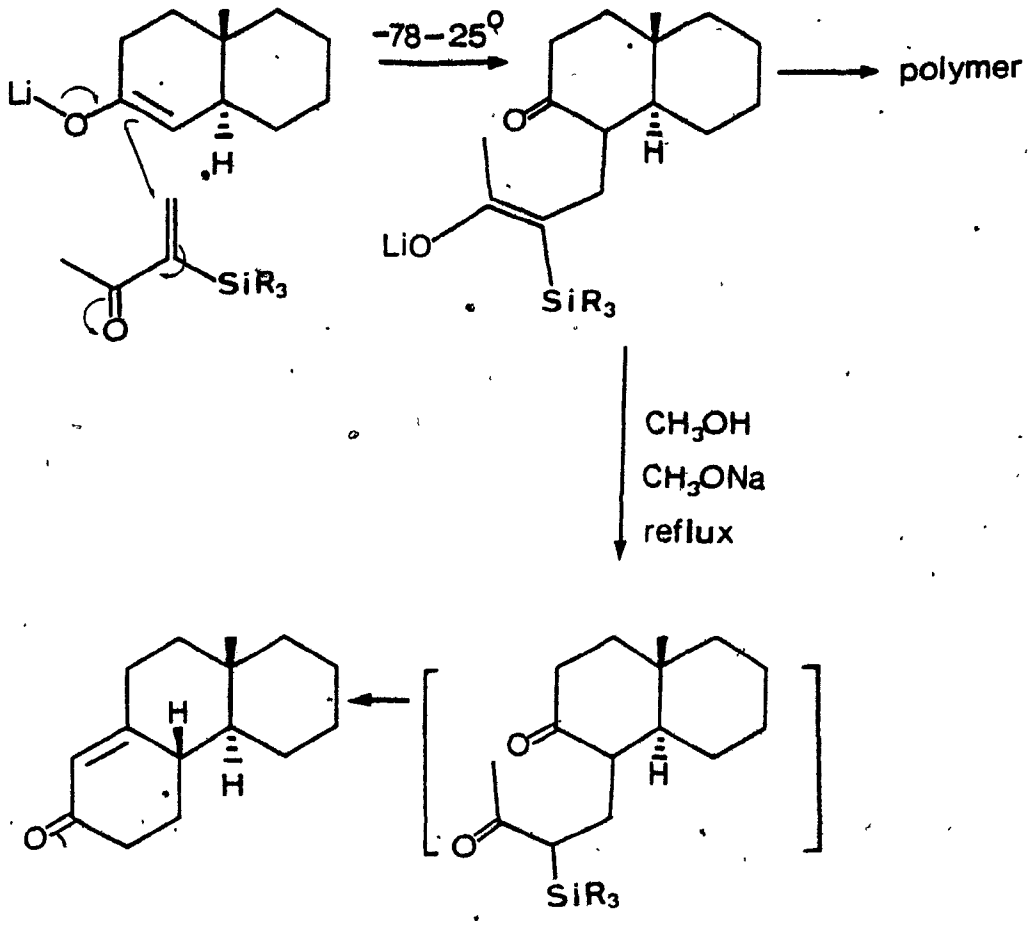
Peterson described the silyl version of the Wittig reaction (Scheme 1.3)[23]. Carbon-bound silicon chemistry was explored by Stork a few years later (Scheme 1.4 and 1.5)[24,25,26].



Scheme 1.3

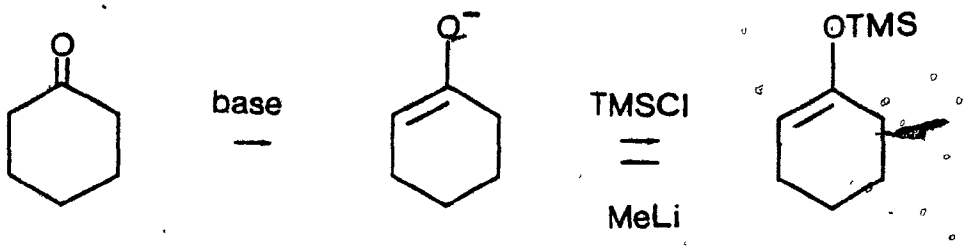


Scheme 1.4

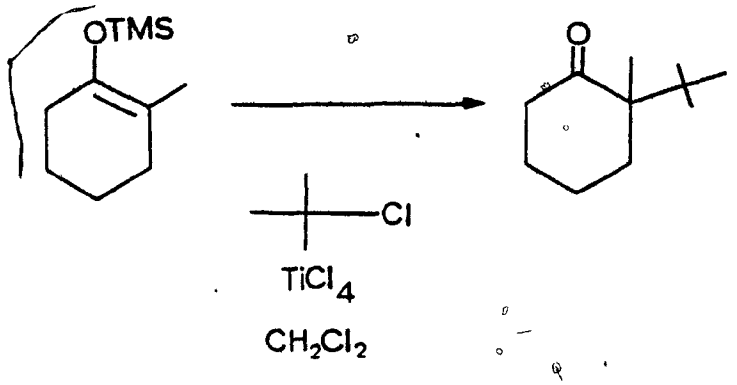


Scheme 1.5

As well, Stork and Hudrlik described the trapping of enolates with silyl groups and showed that lithium enolates could be regenerated regiospecifically (Scheme 1.6)[27,28,29]. Later, the use of enol silyl ethers for aldol reactions was developed by Mukaiyama[30,31]. The utility of the method was subsequently expanded by Chan (Scheme 1.7)[32], among others, to include α-alkylation of the parent carbonyl compound.

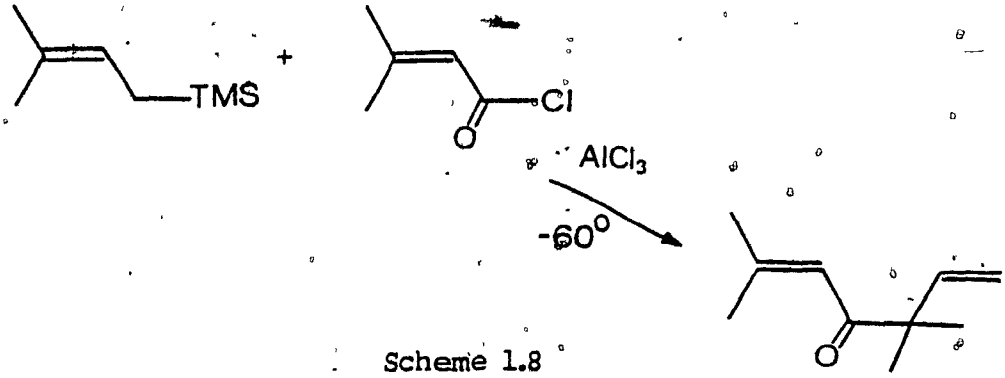


Scheme 1.6



Scheme 1.7

Another major area of active research today is the use of allylsilanes in carbon-carbon bond forming reactions (Scheme 1.8)[33,34]. This work, however, was initiated by Sommer at a much earlier time than the work mentioned above[35].



Scheme 1.8

1.3 The Properties of Organosilicon Compounds

The reactions just described occur because of the unusual properties of silicon, but what properties does silicon possess which allows these reactions to take place, and what advantages does the use of silicon provide? Table 1.1 gives a representative sampling of approximate bond dissociation energies of a series of silicon and carbon-bound species[36].

Table 1.1: Approximate Bond Dissociation Energies (D) for Si-X and C-X

Bond	Compound	D (kJ/mol)	Bond	D (kJ/mol)
Si-C	Me_4Si	318	C-C	334
Si-H	Me_3SiH	339	C-H	420
	Cl_3SiH	378		
Si-O	Me_3SiOMe	531	C-O	340
	$(Me_3Si)_2O$	812		
Si-F	Me_3SiF	807	C-F	452
Si-Cl	Me_3SiCl	471	C-Cl	335
Si-Br	Me_3SiBr	403	C-Br	268

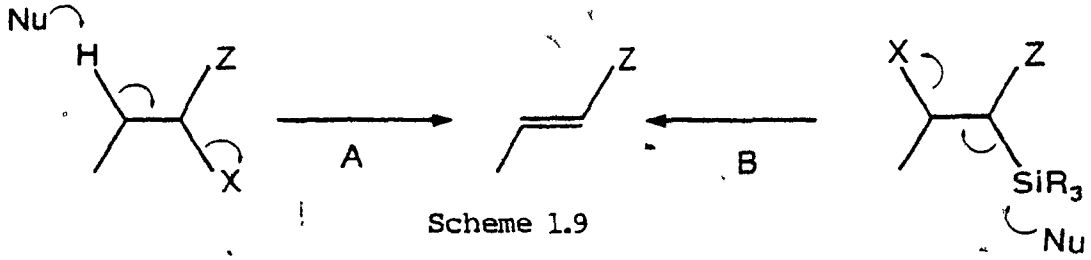
It can be readily seen that whereas silicon-carbon and silicon-hydrogen bonds are weaker than the corresponding carbon bonds, the silicon-oxygen and silicon-halogen bonds, particularly fluorine, are markedly stronger. Another fundamental property to consider is electronegativity. The relative electronegativities of some selected elements are shown in Table 1.2[37].

Table 1.2:Relative Electronegativity

H	B	C	N	O	F
2.79	1.84	2.35	3.16	3.52	4.0
	Al	Si	P	S	Cl
	1.40	1.64	2.11	2.52	2.84
		Ge	As	Se	Br
		1.69	1.99	2.4	2.52

Although many different electronegativity scales exist, silicon is always significantly more electropositive than carbon. This might be one reason why heterolysis of the carbon-silicon bond readily occurs under ionic conditions, either nucleophilic at silicon or electrophilic at carbon. If the carbon-containing moiety is a good leaving group and the attacking nucleophile is oxygen-based or a halogen, then silicon-carbon bond cleavage is particularly facile. Homolytic cleavage, however, is not generally observed.

Carbon-hydrogen bonds C^{-}-H^{+} are polarized in the same way as carbon-silicon bonds C^{-}-Si^{+}. As a result, the reactivity of the former serves as a good indicator of the relative reactivity of the latter in terms of the direction, although not necessarily the rate of reaction. For example, just as Ar-H bonds are broken by treatment with electrophiles, such as bromine, so are Ar-Si bonds. In the same manner, although β -elimination reactions generally occur more readily in systems of type B than type A, both occur in the same direction (Scheme 1.9)[38].



Scheme 1.9

A difference in the reactivity of these two bonds, however, exists towards nucleophilic attack. The C-H bond tends to be more reactive to nucleophiles/bases of nitrogen and carbon, whereas the C-Si bond favours those of oxygen and the halogens. Reactions of this type are driven or assisted, to a certain extent, by the formation of very strong silicon-oxygen or silicon-halogen bonds. It should also be noted that the silicon-carbon bond polarization is rather weak in comparison to other organometallic reagents, and hence, silicon compounds can usually be handled in much less stringent conditions (exclusion of air and/or moisture) than other organometallic compounds.

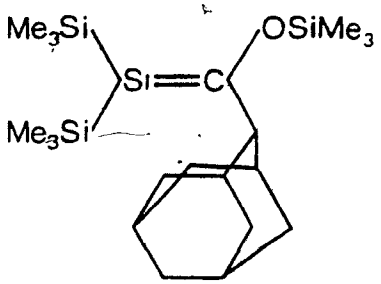
When one considers $Si^{+}-H^{-}$ versus $C^{-}-H^{+}$ bonds, the relative polarities are different. As a result, a quite different course of events is followed upon reaction with a carbon base (Scheme 1.10)[39].

$$(C_6H_5)_3SiH + MeLi \longrightarrow (C_6H_5)_3SiMe + LiH$$

$$(C_6H_5)_3CH + MeLi \longrightarrow (C_6H_5)_3CLi + MeH$$

Scheme 1.10

Multiple bonding has only recently been observed by spectroscopy with the silicon species 1,1-dimethylsilylethylene and trimethylsilyldiazomethane[40,41,42]. Brook[43] synthesized the first stable silylethylene 2 at room temperature and pressure in crystalline form and West[44] isolated a stable disilene 3.



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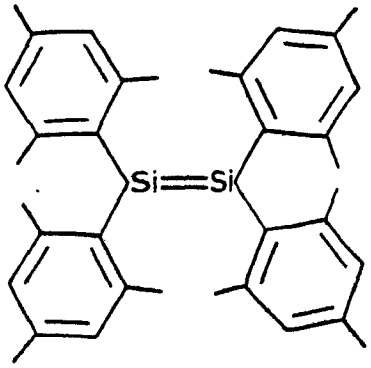

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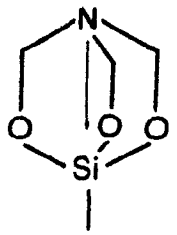
The strength of the silicon-carbon multiple bond is such that one would expect to observe them frequently. For example, the dissociation energy of the Si-C π-bond in 1,1-dimethylsilylethylene was found to be 34 kcal/mol (142 kJ/mol)[40]. Multiple bonding, however, is still a very rare phenomenon in silicon chemistry, contrary to the case with carbon. The reasons for this are probably twofold. First, the bond is extremely reactive due to its strong polarization, and second, the reactivity is further increased due to the presence of a relatively low lying π^*-antibonding orbital[39].

Silicon is usually tetrahedral and quadrivalent, although it does possess low-lying d-orbitals which could participate in bonding. One example in which d-orbitals do participate is the anion SiF_6^{2-}. It has an octahedral structure which implies sp^3d^2 hybridization. There is also a wealth of information which indicates that valence expansion in silicon takes place between nitrogen and silicon in compounds such as the silatranes 4[45,46,47,48], again suggesting d-orbital participation.



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d-Orbitals likely play a role in the reactions of silicon. Corriu, for example, has shown that hypervalent intermediates are present in many reactions of silicon catalyzed by nucleophiles, especially fluoride[49]. As well, S_N2 reactions are extremely facile at silicon and often proceed with retention of stereochemistry[19]. As a result of these observations, it was proposed that d-orbitals interact to lower the transition state energies involved in frontal attack (resulting in retention), although this would also act to lower those involved in backside attack (resulting in inversion)[50]. This proposal, although inconclusive, is at least consistent with the proposal of d-orbital participation in transition state development.

Many of the important properties of silicon have been outlined in the previous paragraphs. A list of the more pertinent ones which could be of use to the organic synthetic chemist would include: (i) strong bonding to oxygen and the halogens, (ii) electropositive characteristics; when bonded to carbon the polarization is intermediate to a C-H and a C-metal bond, and (iii) only a small propensity for multiple bonding. Two other important properties of silicon which should also be mentioned are; the ability to stabilize a carbonium ion in the β-position, the so-called β-effect, and to stabilize a carbanion in the α-position[51].

1.4 The Utility of Silicon Reagents in Organic Chemistry

Regardless of the limited understanding of the mode of reactivity of silicon, it has been utilized by organic chemists in four different ways: (i) silicon compounds are used to promote specific reactions, (ii) silicon is employed as a "ferryman", Colvin's[52] term, whereby it participates in a reaction sequence as follows; silicon is introduced into the compound, remains dormant until required, allows a specific reaction to occur, and then is removed, thus carrying with it, to the molecule, a specific reactivity; (iii) silicon is used to protect functionalities from reacting, in particular hydroxyl groups, and (iv) silicon is introduced into a compound for its own intrinsic value. While the latter is an almost neglected field, organosilicon compounds are beginning to be used in the pharmaceutical industry. At least two drugs are presently in clinical testing and show superior activity to the the corresponding carbon analogues[46,53]. The experimental work upon which this thesis is based focuses upon two of these approaches. In the first chapter, the use of trimethylchlorosilane as an agent to promote acetalization and esterification is evaluated (type (i)). In the latter part of the thesis, the exploitation of silylated enolates in a ring forming reaction leading to cyclopentenones is described (type (ii)).

2. ACETALIZATION AND ESTERIFICATION PROMOTED BY CHLOROTRIMETHYLSILANE

In a synthetic organic scheme, selectivity is of primary importance. Reasonable yields cannot be obtained if reactions are taking place at more than one site in the molecule. Therefore, the protection of all but one reactive site is an acknowledged necessity at most stages in a total organic synthesis. The ideal protecting group is one which: (i) can be formed selectively to give a projected substrate that is stable to the projected reaction, (ii) can be removed selectively in good yield by readily available, preferably non-toxic reagents that do not attack the regenerated functional group, (iii) forms a crystalline derivative (without the formation of new chiral centres) that can be easily separated from side products associated with its formation or cleavage, and (iv) should have a minimum of additional functionality to avoid further sites of reaction[54].

Two groups which must very often be protected are the carbonyl and carboxyl groups. The protecting groups most frequently used for the protection of these functionalities, which fulfil quite well the requirements listed above, are acetals and esters, respectively. There is a need, therefore, to devise methods for the formation of these protected substrates. Such a method will be the focus of the following chapter.

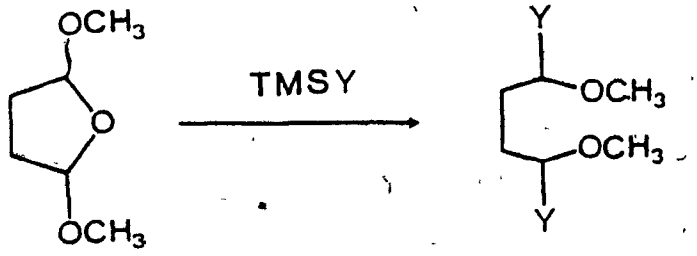
2.1 TRIMETHYLSILYL-BASED REAGENTS

Silicon reagents have been used to promote a variety of different

transformations under very mild conditions. To delineate their reactive properties, a description of some of the more useful reactions promoted by trimethylsilyl moieties, which do not involve the isolation of a silylated product (with the exception of trimethylsilyl ethers), will be given.

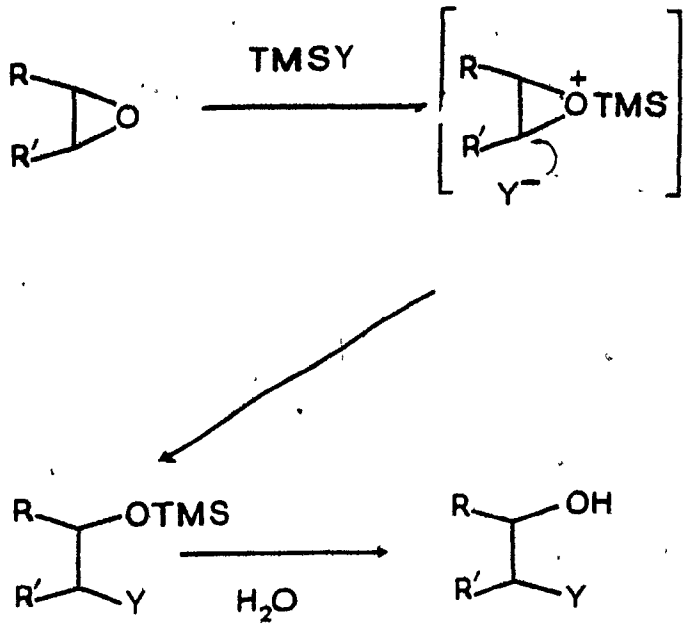
2.1.1 Ether and Ester Cleavage

The formal replacement of the proton of a range of inorganic acids by the trimethylsilyl moiety gives a group of reagents which can behave as hard acids, particularly in reactions where silicon-oxygen bond formation takes place[55]. Perhaps the most widely used reagents of this type are the iodo-, bromo-, and trifluoromethylsulfonyl- (triflate) trimethylsilanes. All three can be readily synthesized and their only disadvantageous property is an extreme sensitivity to moisture. Because the anion of the parent acid is a soft base/good nucleophile, it can attack, for example, an ether molecule at the carbon atom carrying the now complexed oxygen. This leads to dealkylation or deoxygenation depending on the fragment being followed (Schemes 2.1 and 2.2)[56].



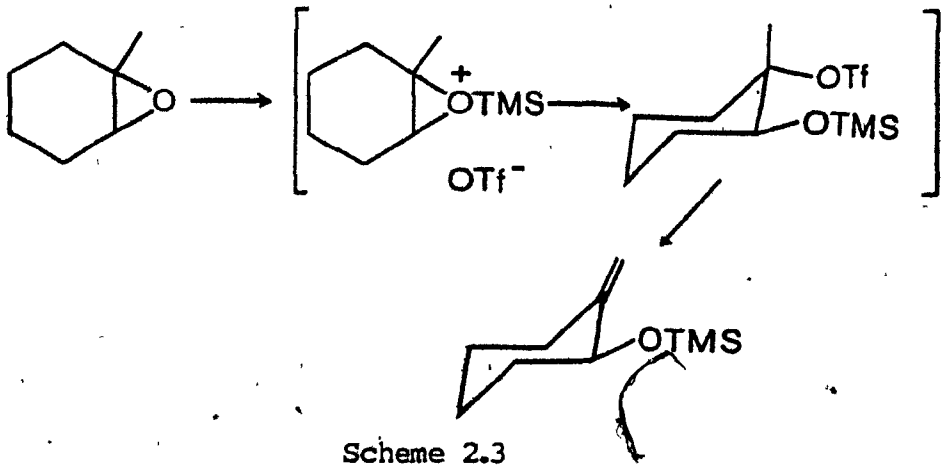
Y=Cl, Br, I

Scheme 2.1



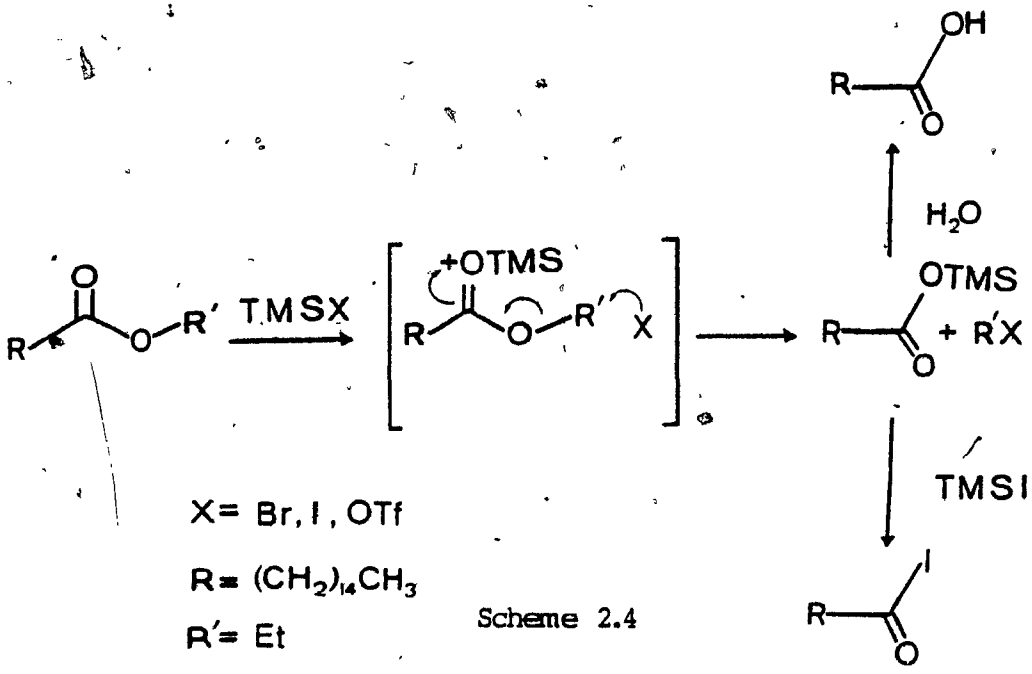
Scheme 2.2

In the presence of a base, these vicinal trimethylsilylhalohydrins (or pseudohalohydrins) can further react to give the allylic alcohols (Scheme 2.3)[57].



Scheme 2.3

Related processes can take place with carboxylic esters as well (Scheme 2.4)[58,59].

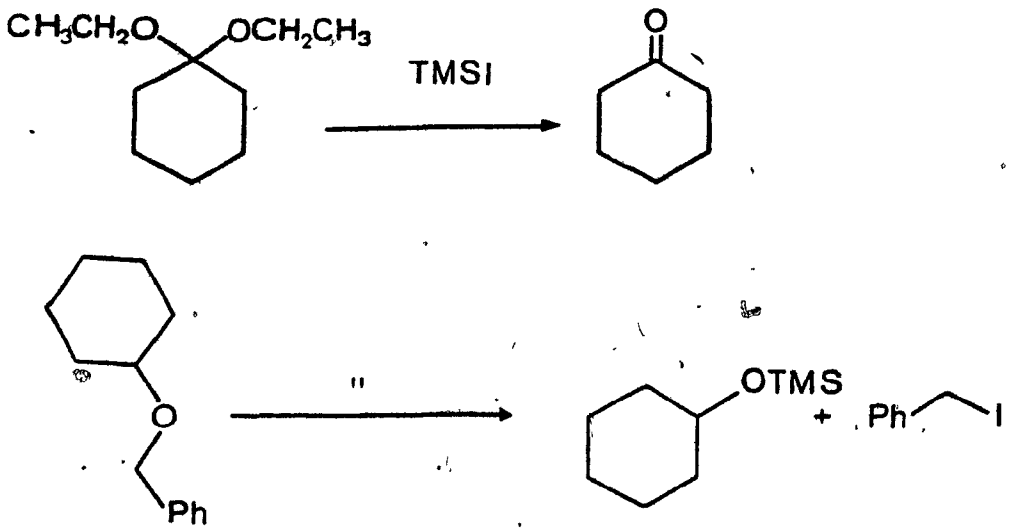


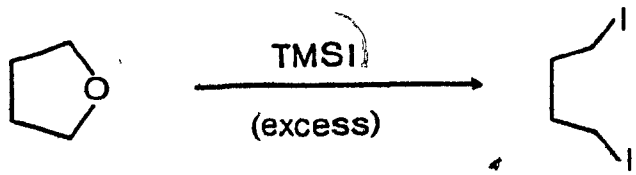
X= Br, I, OTf

R= $(CH_2)_{14}CH_3$

R'= Et

Scheme 2.4





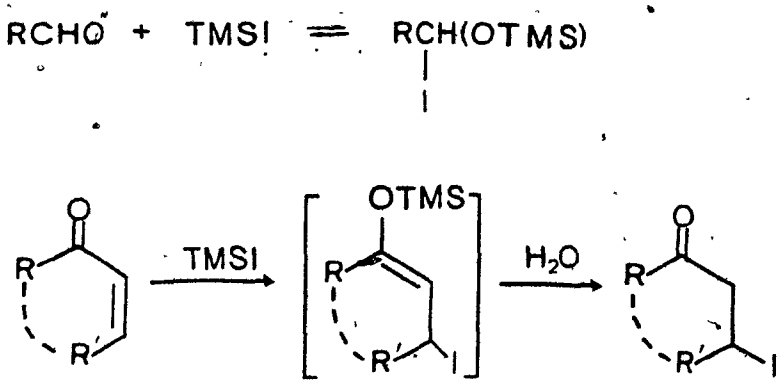
Scheme 2.5

For many reactions with ether-based oxygen systems such as ethers[60]

and acetals[61], trimethylsilyl iodide is the reagent of choice because of its high reactivity. In general, iodides or α-iodotrimethylsiloxides are formed which in themselves are good synthons for further modification (Scheme 2.5). These reactions generally proceed in good yield under relatively mild conditions; they are performed in aprotic media which are neutral or mildly acidic.

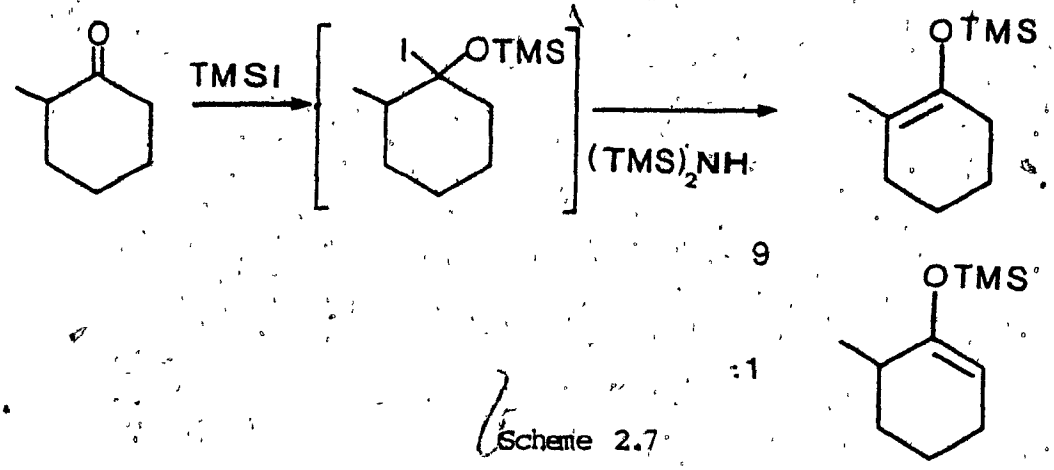
2.1.2 Carbonyl Addition Compounds

Trimethylsilyl compounds can also react with carbonyl compounds in a 1,2-sense,[62] or with α,β-unsaturated carbonyl compounds in a 1,4-sense (Scheme 2.6)[63].



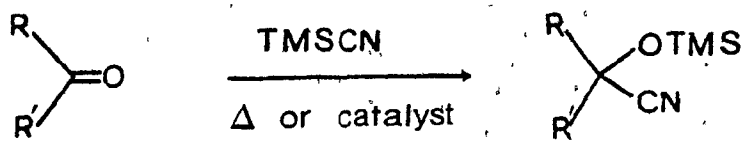
Scheme 2.6

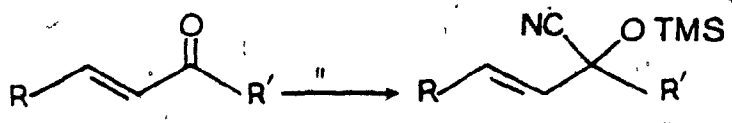
From silylated iodohydrins, enol silyl ethers can be formed in the presence of a base under mild conditions; remarkably, enol ether formation takes place over ester cleavage in bifunctional substrates (Scheme 2.7)[64].



Scheme 2.7

Although iodotrimethylsilane undergoes carbonyl addition reactions with facility, the reaction with cyanotrimethylsilane is far more useful synthetically (Scheme 2.8)[65]. Either thermal[66] or catalyzed[67] conditions lead to the silyl ethers of the cyanohydrins.

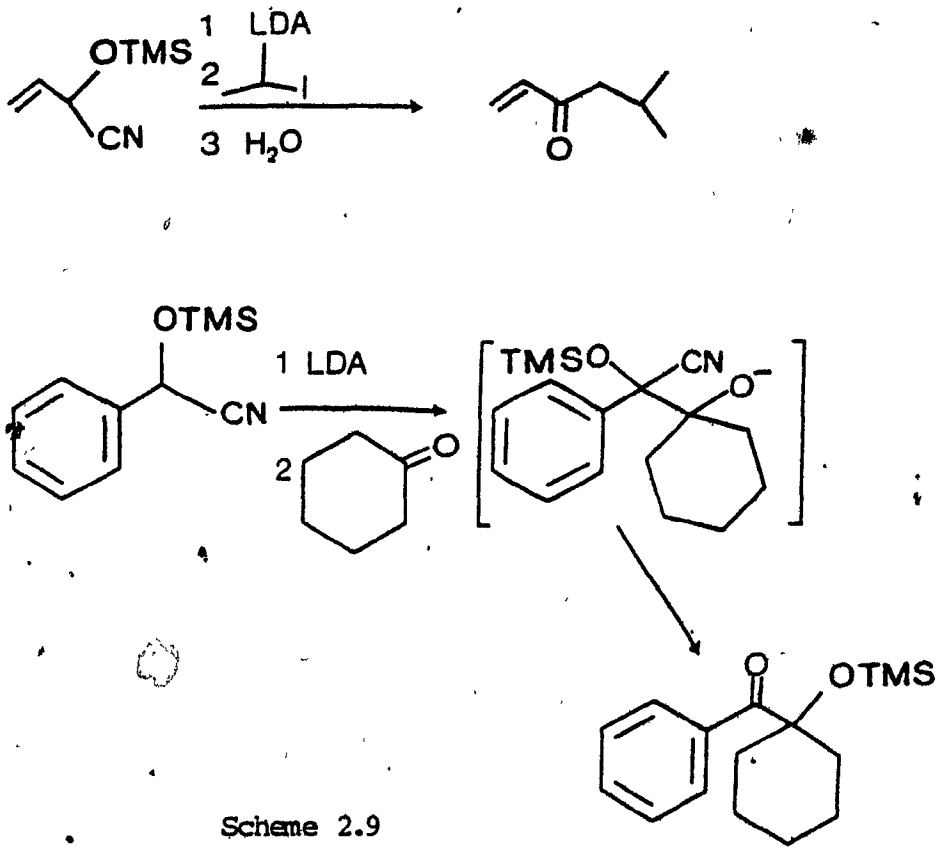




Scheme 2.8

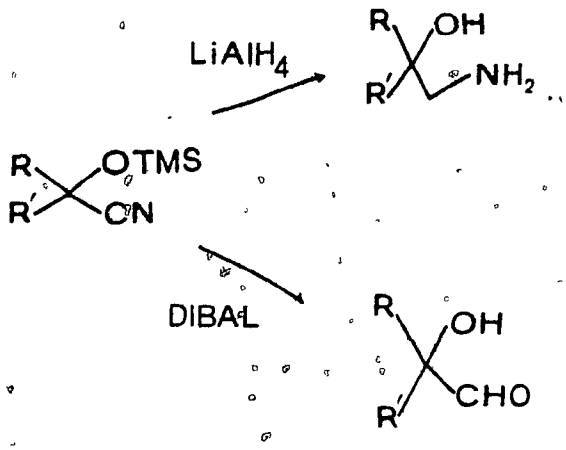
The synthetic utility of these compounds arises from the ease of formation

of stabilized anions from them. The silylated cyanohydrins can be used in three distinct ways; nucleophilic alkylation and acylation, carbonyl protection and chain homologation (Scheme 2.9).



Scheme 2.9

They may also be reduced with lithium aluminum hydride to the β-amino alcohols, without the problems which arise upon the reduction of the cyanohydrin acetates[68,69], or with DIBAL to α-trimethylsiloxy aldehydes (Scheme 2.10)[70].



Scheme 2.10

2.1.3 Ether and Ester Formation

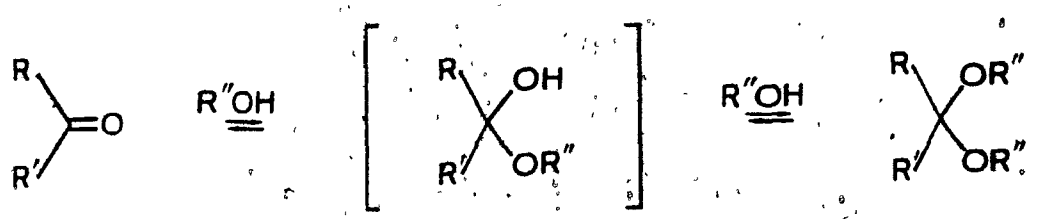
Although many other examples of reactions promoted by trimethylsilyl reagents exist, the preceeding two groups of reactions are illustrative of the reactivity of the trimethylsilyl group. In ether and ester cleavage, dealkylation-deoxygenation takes place because of the stability of the siloxane bond formed during the reaction. All of the carbonyl addition reactions occur because of the strong attraction of the silicon for the carbonyl oxygen. It is ironic, therefore, that the oxophilicity of silicon, the preference of silicon for the carbonyl oxygen, and the facility for the formation of siloxane bonds, can lead to carbon-oxygen bond formation rather than the carbon-oxygen bond cleavage described above. Whereas trimethylsilyl bromide and iodide can readily cleave alkyl carbon-oxygen bonds in esters and ethers, chlorotrimethylsilane* can be

* Although I.U.P.A.C. nomenclature has adopted chlorotrimethylsilane as the correct name[119], trimethylchlorosilane and trimethylsilyl chloride will also be used interchangeably throughout this thesis.

used to promote acetal (ether) and ester formation.

2.2 THE SYNTHESIS OF ACETALS AND KETALS USING CHLOROTRIMETHYLSILANE

α-Keto-acetals can be used as electrophiles in condensation reactions with enol silyl ethers. In these condensations, acetals are employed to replace unprotected carbonyl groups. They are usually reactive enough to undergo aldol type reactions but are less reactive than unprotected carbonyl groups. This allows some product control in the reaction (see Chapter 3.4 and 3.6-3.8). The traditional methods of acetal synthesis usually involve the reaction of a carbonyl compound with an alcohol, under acidic conditions, utilizing either physical or chemical dehydration (Scheme 2.12)[71].



Scheme 2.12

During an attempt to synthesize the dimethyl acetal* of phenylglyoxal 6, Trost's acetalization procedure was employed. It entailed the use of

* As a result of I.U.P.A.C. rule C-331.1, the word ketal has been removed from the chemical vocabulary[71]. An acetal may now describe the *gem*-dialkoxide formed from either an aldehyde or a ketone. For the purpose of this thesis, however, the traditional nomenclature will be used. That is, an acetal is the *gem*-dialkoxide formed from an aldehyde, and a ketal is that formed from a ketone.

ammonium chloride as the acidic catalyst and trimethyl orthoformate as the dehydrating agent[72]. The work-up was performed in a mildly basic aqueous solution (Scheme 2.14a). It became apparent, however, that the method of Trost was inadequate for our purposes. A yield of only 48% was realized, as compared with Trost's of 90%, due most likely to the problems associated with product isolation from an aqueous solution. It was obvious that a more efficient reaction was required.

As acetalization is an equilibrium process, the simplest way to expedite the reaction is to force the equilibrium to the right by the removal of water. It seemed probable that a silicon reagent might effectively mediate this relatively simple reaction. It is well known that a silicon species with a relatively labile bond will rapidly form a silicon-oxygen bond on exposure to water[18]. This is a consequence of the strong silicon-oxygen bond (112-117 kcal/mol, 469-490 kJ/mol)[73]. For example, the organosilicon halides, with the exception of the fluorides for which the equilibrium lies far to the left (Scheme 2.12)[74], are rapidly hydrolysed to form silanols[75]. For the less substituted silanols, condensation is spontaneous; silanol itself has never been isolated[76]. Under acidic or basic conditions other silanols condense to form disilyl ethers (disiloxanes) in the case of monohalo-organosilanes, and silicone oligomers and polymers from more highly halogenated species[77].

$$R_3SiX + H_2O \rightleftharpoons R_3SiOH + HX \rightleftharpoons R_3SiOSiR_3 + H_2O$$

Scheme 2.12

It was anticipated that trimethylchlorosilane would be an effective

dehydrating agent, as it is known to form, essentially irreversibly, hexamethyldisiloxane upon hydrolysis. There are other predictable advantages in the use of this reagent. First, hydrolysis of the silyl-chloride would generate hydrogen chloride (Scheme 2.13), *in situ*, which is expected to catalyse the reaction. Second, the disiloxane, which would be subsequently formed, is volatile enough to be removed under a mild vacuum.

$$(CH_3)_3SiCl + H_2O \rightleftharpoons (CH_3)_3SiOH + HCl$$

$$\Big| \quad TMSCl$$

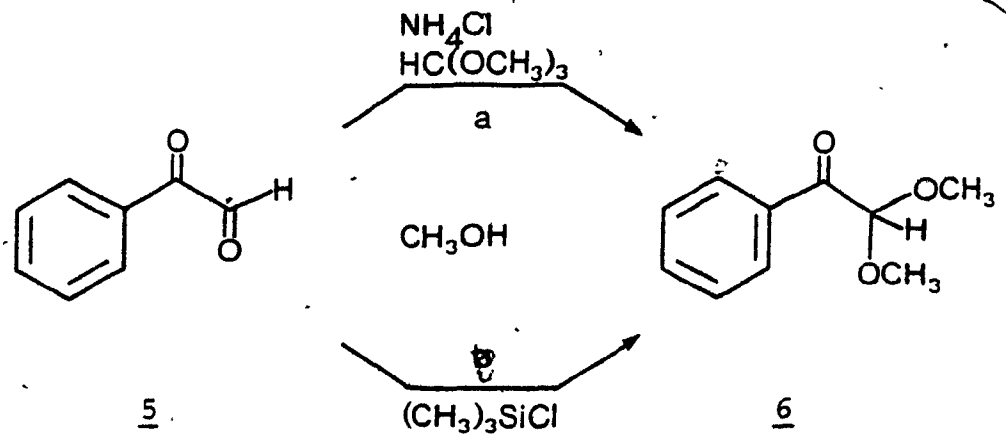
$$(CH_3)_3SiOSi(CH_3)_3 + H_2O$$

Scheme 2.13

2.2.1 Acetals From Activated Carbonyl Compounds

By simply stirring freshly distilled phenylglyoxal 5 in a solution of methanol and 2.2 equivalents of trimethylsilyl chloride (Method A), at room temperature, α,α-dimethoxyacetophenone 6 is obtained in 83% yield after distillation (Scheme 2.14b). It is clear that sufficient activation occurs when ketones, esters or dichloroalkyl groups are located adjacent to the carbonyl group, with the exception of aromatic ketones which will be discussed later. Activation is provided by the presence of an electron withdrawing group in the α-position to the carbonyl group to be acetalized. This methodology, the use of trimethylchlorosilane as a dehydrating agent and a means of generating an acidic catalyst, with methanol as the solvent, appears to be a general route for the preparation of dimethylketals or acetals from activated carbonyl compounds. Table 2.1

shows examples of activated carbonyl compounds acetalized in this way.

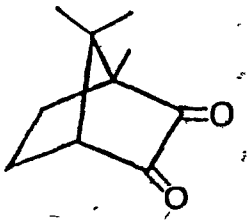
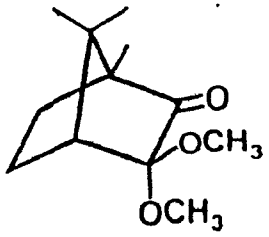


5 6

Scheme 2.14

At the completion of the reaction, as judged by T.L.C. or G.L.C., it is quenched with base. Essentially two methods are used to work-up the reaction. In the first method, the reaction mixture is brought to approximately pH 6 (moist alk-acid paper) with a 5% solution of sodium methoxide in methanol[78]. Most of the solvents are removed under reduced pressure and the residue is dissolved in ether, filtered through Celite or silica gel and the solvents are removed *in vacuo*. The crude residue is then purified using flash[79] or mesh[80] chromatography, fractional distillation, or Kugelrohr distillation. This method proves especially advantageous for water soluble molecules, such as 1,1-dichloro-2,2-dimethoxypropane 13, with which aqueous work-up results in much lower isolated yields. In the second method, the reaction is quenched with a 5% aqueous solution of sodium bicarbonate. The solution is extracted with ether, washed with water and brine, and the ether extracts are dried over either anhydrous magnesium or sodium sulfate. After filtration and removal of the solvents under reduced pressure, the crude residues are purified as described above.

Table 2.1:Examples of Acetals Prepared from the Precursor Activated Carbonyl Compounds.

Entry	Starting Material	Product	(Compound Number)	Yield	Method	Equiv. TMSCl.	b.p./torr (m.p.)°C. Found	Literature	Ref.
1	$PhCOCHO$	$PhCOCH(OCH_3)_2$	6	83	A	2.2	89/.62	101/4.5	147
2	$p\text{-}CH_3PhCOCHO$	$p\text{-}CH_3PhCOCH(OCH_3)_2$	8	98	A a	2.2		108-113/1	148
3	$PhCOCOOCH_3$	$PhC(OCH_3)_2COOCH_3$	10	55	A abc	2.2			
4	$CH_3COCOOCH_3$	$CH_3C(OCH_3)_2COOCH_3$	11	92	A a	2.2		62-63/12	78
5	$CH_3COCHCl_2$	$CH_3C(OCH_3)_2CHCl_2$	13	71	A ad	2.2			149
6	$CH_3COCOCH_3$	$CH_3C(OCH_3)_2COCH_3$	14	91	A	2.2	58/28	145-6	150
7	$CH_3COCOCH_3$	$CH_3C(OCH_2CH_3)_2COCH_3$	15	60	A	2.2	70/23.5	163-5	151,331
8	$CH_3(CH_2)_6COCHO$	$CH_3(CH_2)_6COCH(OCH_3)_2$	17	76	A	2.6	96-106		152
9			19	84	A e	2.5			153

a. Purified using flash chromatography (16g 40-63mm. silica, E. Merck, ethyl acetate-hexanes mixtures used as the eluent).

b. Yield after correction for recovered starting material was 74%.

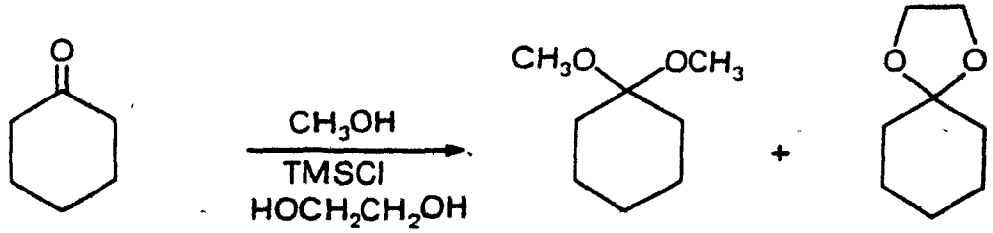
c. All new compounds were characterised by proper spectroscopic analysis, and purity ascertained by GC/MS. See experimental section for analytical details.

d. G.C. Yield. The isolated yield was 42%, due in part to the high volatility of the product.

e. The ratio of the 3:2 methyl acetal was 83:17.

2.2.2 Acetals From Unactivated Carbonyl Compounds

Unactivated ketones and aldehydes prove to be completely resistant to methyl acetal formation in the presence of chlorotrimethylsilane and methanol. It is possible, however, to form 1,3-dioxolanes in the presence of ethylene glycol under otherwise identical conditions (Method B). Surprisingly, in methanolic solution with cyclohexanone as the carbonyl compound, for example, formation of the ethylene ketal 26 is observed, without concomitant formation of the dimethyl acetal (Scheme 2.15). This characteristic of the reaction would allow one to selectively form a methyl acetal from an activated carbonyl group in a molecule also containing unactivated carbonyl groups.

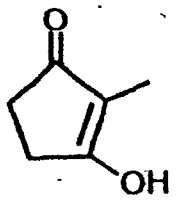
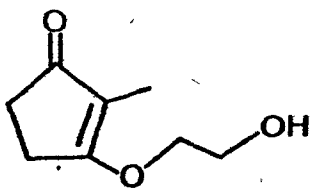


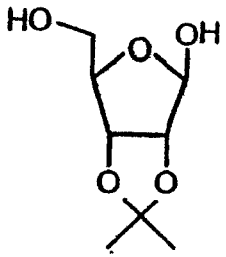
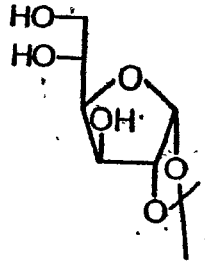
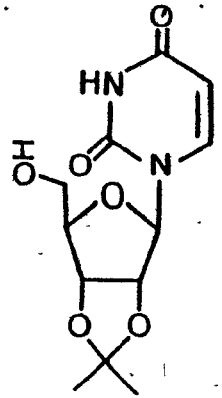
Scheme 2.15 26

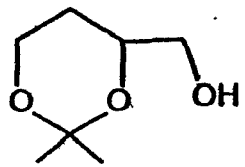
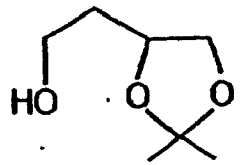
Many 1,3-dioxolanes are isolated in higher yields when the reaction is carried out in refluxing methylene chloride (Method C). The work-up and purification procedures are very similar to those described above for the activated carbonyls (Table 2.2).

Aromatic carbonyl compounds, with or without activating groups present, prove to form dioxolanes extremely slowly with trimethylsilyl chloride. For example, benzaldehyde the most reactive of the aromatic compounds tested, requires a much longer reaction time to form the corresponding dioxolane 20, than do the aliphatic compounds mentioned

Table 2.2:Examples of Ethylene Acetals Prepared from Precursor Carbonyl Compounds.

Entry	Starting Material	Product	(Compound Number)	Yield	Method	Equiv. TMSCl.	b.p./torr Found	(m.p.)°C. Literature	Ref.
1	PhCHO	$PhCH(OCH_2CH_2O)$	20	64	B a	2.2		107-8/13	154,155
2				77	D a	2.2			
3	$PhCOCH_3$	$PhC(OCH_2CH_2O)CH_3$	21	78	D b	6.6	(61)	(61)	156
4	$PhCOCH_2Cl$	$PhC(OCH_2CH_2O)CH_2Cl$	23	99	D b	4.4	(90)		157
5	$PhCOCHCl_2$	$PhC(OCH_2CH_2O)CHCl_2$	25	78	D b	2.2	(58.5-59)	(59-61)	158
6			26	83	B a	2.2		174-80	159,160
7				95	D a	2.2			
8	$C_8H_{17}CHO$	$C_8H_{17}CH(OCH_2CH_2O)$	27	64	B a	2.2		141-2/40	161
9				98	C c	2.2	117-35/14		
10	$CHCOCOCH_3$	$[CH_3C(OCH_2CH_2O)]_2$	28	95	C d	2.2	(90)	(90)	162
11			30				(80-2)		83

12	ribose		32	72	E ae	4.4	—	—	163,350
13	glucose		33	86	E ae	5.1	(159–60)	(160–1)	137
14	uridine		34	88	E ae	2.2	(161–2)	(159–60)	138

15		(+ 17% 36)	35	91	F afg	3.7	145
16		(+ 10% 35)	36	57	F afh	2.9	145

a. Purified using flash chromatography (16g 40-63mm. silica, E. Merck, ethyl acetate-hexanes mixtures used as the eluant).

b. Recrystallized from methanol.

c. Purified using Kugelrohr distillation.

d. Recrystallized from hexanes.

e. The solvent system was 3:1 acetone-methanol, v/v (method E).

f. The solvent system was acetone (Method F).

g. Reaction temperature was -90°C.

h. Reaction temperature was ambient.

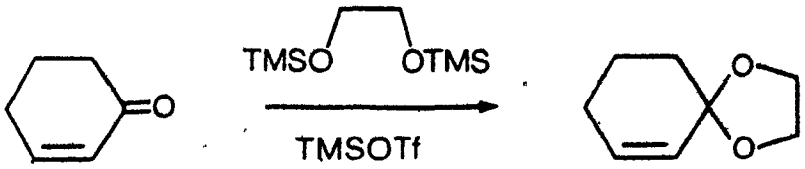
above. The isolated yields for both the aromatic and aliphatic series of compounds, however, are similar. Even though forcing the equilibrium to the right by the use of a greater excess of chlorotrimethylsilane results in shorter reaction times, no difference in the isolated yield of the final product can be detected.

The activating effect by electron withdrawal from the carbonyl centre could also be noted for the formation of acetals from aromatic carbonyl compounds. Table 2.2 lists experimental results which indicate that the amount of chlorotrimethylsilane required to effect the transformation decreases with the increasing activation provided by the electronegative chlorine atoms within the series of acetophenone 21, α-chloroacetophenone 23 and α,α-dichloroacetophenone 25. These reactions are done in ethylene glycol since the reaction proceeds more slowly in other solvents (Method D).

2.2.3 The Attempted Acetalization of α,β-Unsaturated Carbonyl Compounds

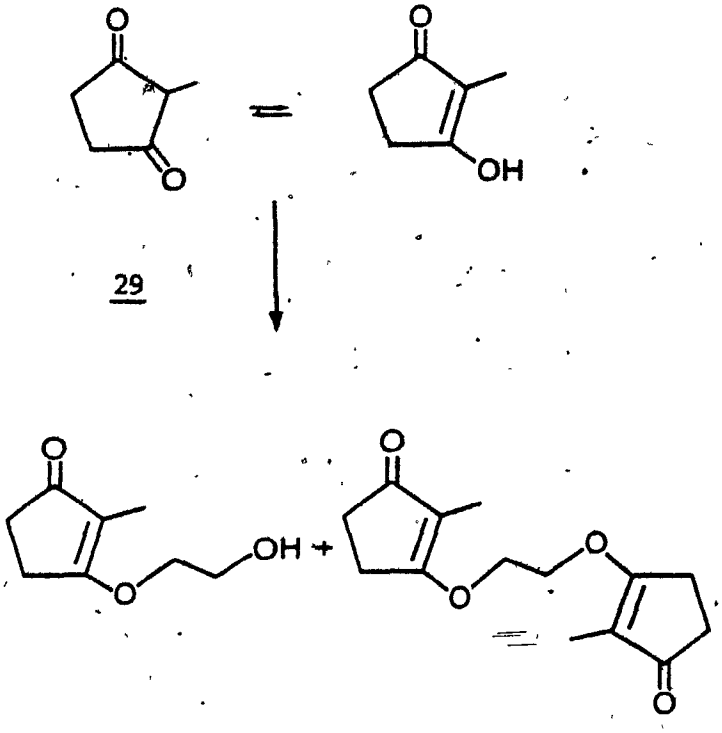
With many methods of acetalization, the conversion of cyclohex-2-enone to its acetal, for example, is accompanied by an undesirable shift in the position of the double bond[81]. Thus, this conversion is one way of evaluating a new acetalization procedure. A report in the literature describes the use of pre-silylated alcohols (Scheme 2.16) for the formation of the ethylene acetal of cyclohex-2-enone[82]. Since the experimental conditions are reasonably similar to those of acetalization with trimethylchlorosilane, it was anticipated that the latter reaction would proceed smoothly. However, the reaction of cyclohex-2-enone with ethylene glycol, utilizing chlorotrimethylsilane under a variety of

conditions, fails to give the desired dioxolane. Similar attempts to synthesize the dimethyl acetal using methanol also failed; although there is the possibility that 1,1,3-trimethoxycyclohexane is formed (see experimental section).



Scheme 2.16

A pseudo α,β-unsaturated compound is 2-methyl-1,3-cyclopentanedione 29, which exists predominantly in the enol form (83% as determined by ^{1}H-N.M.R.). The acetalization of this compound, with catalysis by *p*-toluenesulfonic acid in the presence of ethylene glycol, is reported to give a mixture of α,β-unsaturated products (Scheme 2.17)[83].



29

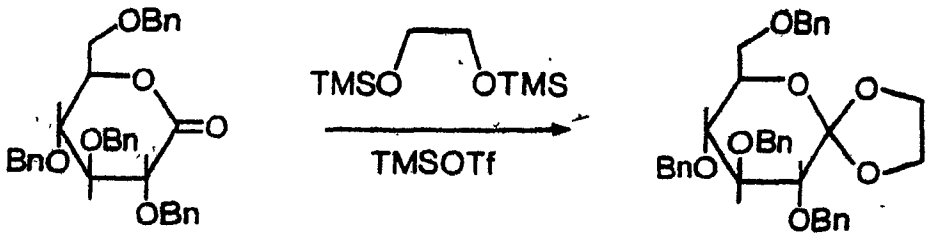
30 Scheme 2.17 31

When this reaction is promoted with chlorotrimethylsilane, the monomeric product 30 can be isolated. This suggests that the reaction is catalyzed by the hydrogen chloride formed *in situ* from trimethylchlorosilane, or that the mechanism in the presence of the trimethylsilyl group mimics acidic catalysis. The dimeric product 31 could not be isolated, although this undoubtedly arises from the experimental conditions used (10 fold excess of ethylene glycol).

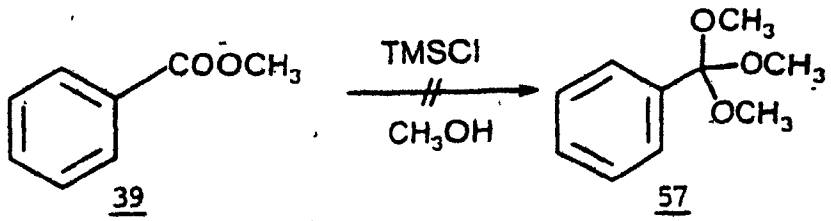
2.2.4 The Formation of Ortho Esters

A special case of acetalization is the conversion of an ester to an ortho ester, a reaction not known to occur in an alcoholic solution under acidic conditions[84]. However, work with silylated ethylene glycol has been shown to result in formation of spiro-ortho lactones (Scheme 2.18)[85] and it had been hoped that this type of reaction would also take place in the presence of chlorotrimethylsilane. Unfortunately, chlorotrimethylsilane fails to induce the transformation of methyl benzoate 39 to trimethylorthobenzoate 57 either in the pure alcohol or in a solution of the alcohol in dry tetrahydrofuran (Scheme 2.19). As dioxolanes are formed more readily than methyl acetals and aromatic carbonyl groups acetalize more sluggishly than aliphatic compounds, the corresponding conversion of an aliphatic ester to an aliphatic spiro-ortho ester would appear to be more promising. However, the attempt to form 2-benzyl-2-methoxy-1,3-dioxolane 58 from methyl phenylacetate 46 was unsuccessful (Scheme 2.19). Since trimethylsilyl chloride and other acids fail to catalyse the reaction, it is concluded that the difference in the relative stabilities of the products and reactants is such that a shift in

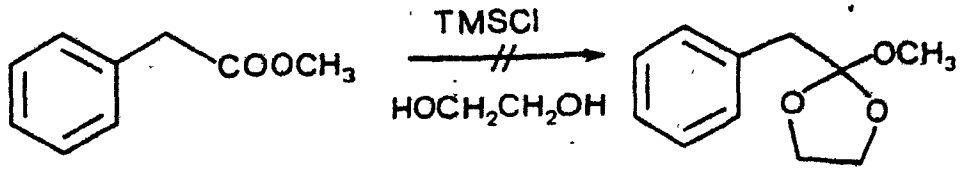
the equilibrium to the right cannot take place.



Scheme 2.18



39 57

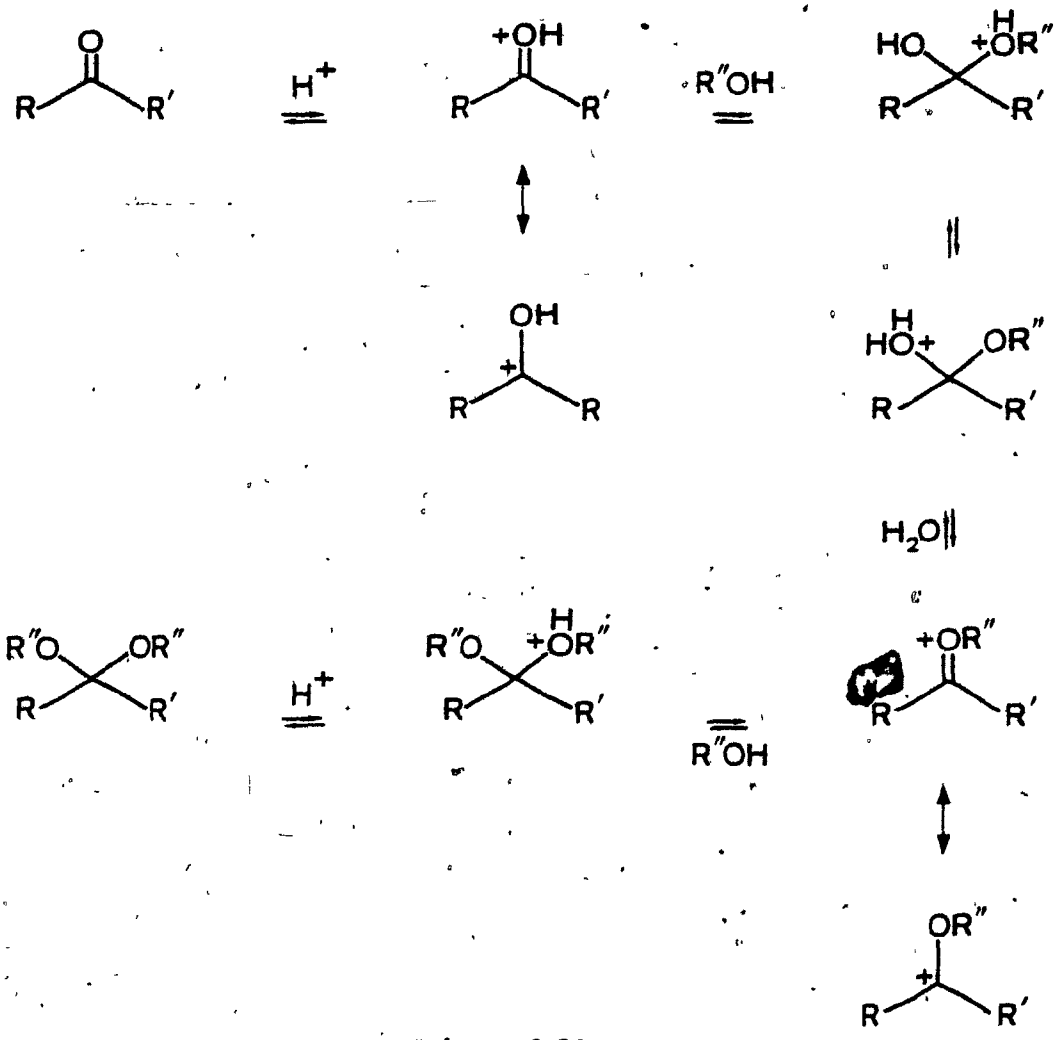


38 Scheme 2.19 58

2.3 THE MECHANISM OF ACETALIZATION

The mechanism of acetal hydrolysis has been far more thoroughly investigated that that of acetal formation. As a result, the following discussion will draw inferences from the mechanism of the hydrolysis reaction and attempt to apply them to the case of acetal formation. The mechanism of the hydrolysis of acetals (A1) has been well studied and follows the scheme shown below (Scheme 2.19)[86,87]. Of particular importance are the relative magnitudes of the equilibrium constants between the intermediates and as well, the determination of the rate determining step. The latter has been the focus of some controversy. Some of the problems which exist in the determination of the relative

rates of reaction and equilibrium constants, especially in the study acetal formation, arise as a result of the properties of the intermediat and the acetals themselves.



Scheme 2.20

2.3.1 Hemiacetals as Intermediates in Acetalization

That hemiacetals are intermediates in acetal formation is well documented, although the extent to which hemiacetal formation occurs for some carbonyl compounds remains contentious. Studies which have been undertaken have utilized the measurements of the heat of reaction[88],

deviations from additivity of the refractive index[89,90,91], ^{1}H-N.M.R.[92,93], and the extensive measurement of U.V. absorbances[94]. The extent of hemiacetal formation in a variety of neutral alcohols is documented in Table 2.3.

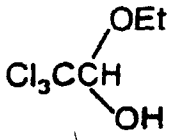
Table 2.3:The Extent of Hemiacetal Formation in Neutral Alcoholic Solution (given as a percentage)

Carbonyl Compound	MeOH[93]	EtOH[95]	*i*-PrOH[95]	*t*-BuOH[95]	$PhCH_2OH$[93]
CH_3CHO	78/97*	91	71	12	59
CH_3CH_2CHO	95*	87	58	—	—
$(CH_3)_2CHCHO$	68/90*	81	42	—	31
$(CH_3)_3CCHO$	66	—	—	—	21
$CH_3COCOCH_3$	34	—	—	—	9
$ClCH_2COCH_3$	17	—	—	—	0
$BrCH_2COCH_3$	47[95]	22	16	—	—
CH_3COCH_3	0.3[96]	—	—	—	—
p-ClC_6H_4CHO	0[96]	—	—	—	—
$-(CH_2)_5CO-$	10[96]	—	—	—	—

* From Ref. 95.

It is evident from the data in Table 2.3 that steric effects are quite important. An increase in the steric bulk at either the aldehyde or the alcohol decreases the amount of hemiacetal formation.

Electronic effects are even more significant. Hemiacetals have been isolated in only a few cases, such as chloral[97] 59, cyclopropenone[98] 60 and ethyl glyoxylate[99] 61;



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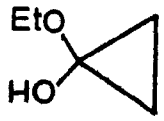

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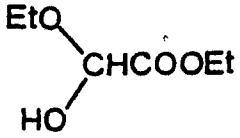
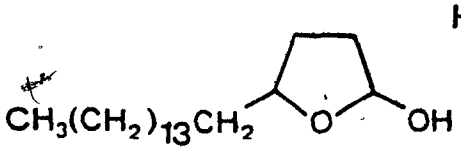


61

for which the stabilization is attributed to an electron deficient parent carbonyl compound. This relationship has been further explored by a quantitative study of the promotion of hemiacetal formation by halogen substitution[100]. Hemiacetal formation in ethanol, observed using U.V. spectroscopy, strongly increases with successive chlorine substitution in the following series of compounds; acetaldehyde, monochloro-, dichloro- and trichloroacetaldehyde.

Hemiacetals have also been isolated whose stability is due to their cyclical structure (62, 32 and 63)[101,102]. The well known variety of stable cyclic sugars fall into this category.



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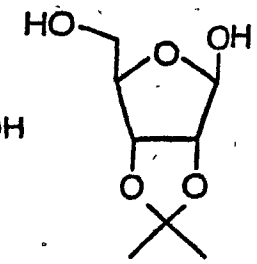

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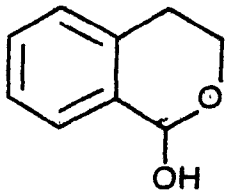

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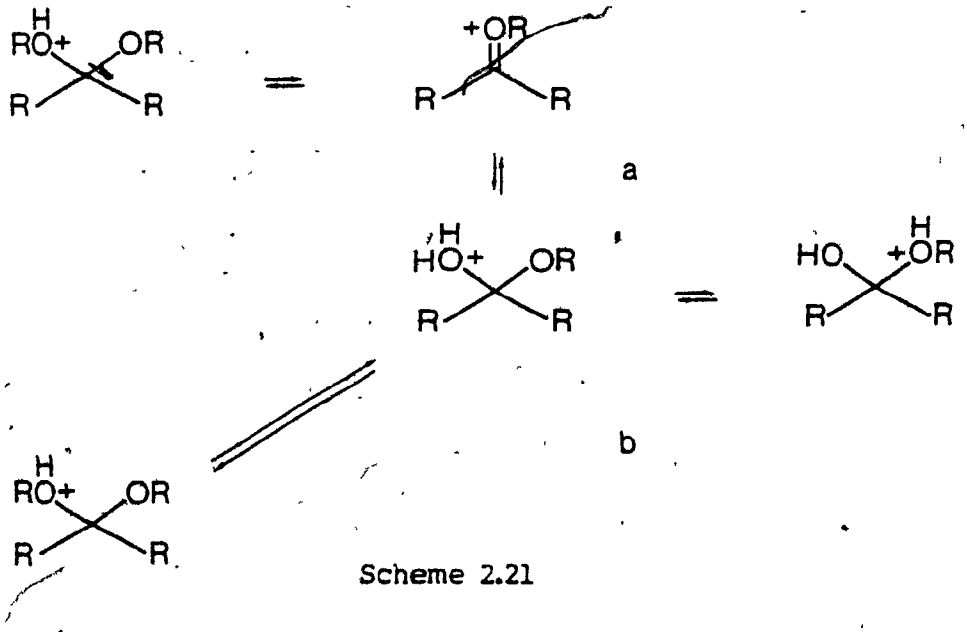
2.3.2 Oxocarbonium Ions as Intermediates in Acetalization

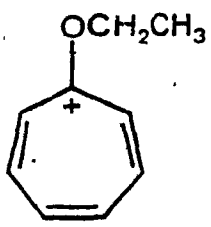
Another intermediate which proves elusive to detection is the oxocarbonium ion. The postulation that the reaction goes via this intermediate (Scheme 2.21a) rather than the nucleophilic pathway (Scheme 2.21b) is supported by the following observations[103,104]: (i) acetals are extremely resistant to nucleophilic attack by hydroxide or other

nucleophiles, (ii) the volumes of activation for the acid catalyzed hydrolyses of dimethoxymethane, dimethoxy and diethoxyethane are close to zero or slightly positive[86,105], (iii) the entropies of activation for the hydrolysis of many acetals and ketals are near zero or slightly positive[106], (iv) steric effects are of secondary importance in acetal hydrolysis[107], making unlikely the participation of a nucleophilic reagent, and (v) the observed ρ^* for the hydrolysis of aliphatic ketals and acetals is -3.60.



Scheme 2.21

McClelland and Ahmad were able to isolate several oxocarbonium ions, for example 64 and 65, which are stabilized for a variety of reasons[108,109]. The study of the hydrolyses of these oxocarbonium ions shows that the same mechanistic pathway, as that for a normal acid-catalyzed acetal hydrolysis, is followed. This strongly suggests that oxocarbonium ions intermediates in the acid-catalyzed hydrolyses of acetals and ketals.



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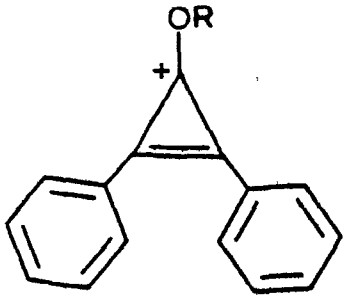


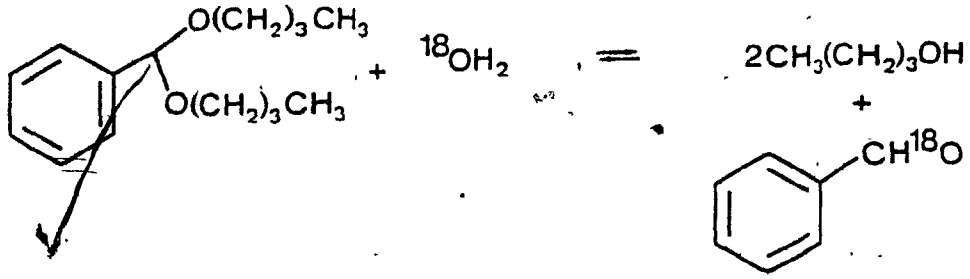
65

During an acetalization process, these intermediates can also be trapped[110] or observed indirectly using ^{1}H-N.M.R.[103] and U.V. spectroscopy[111,112].

2.3.3 Acetals and Properties Affecting Their Formation

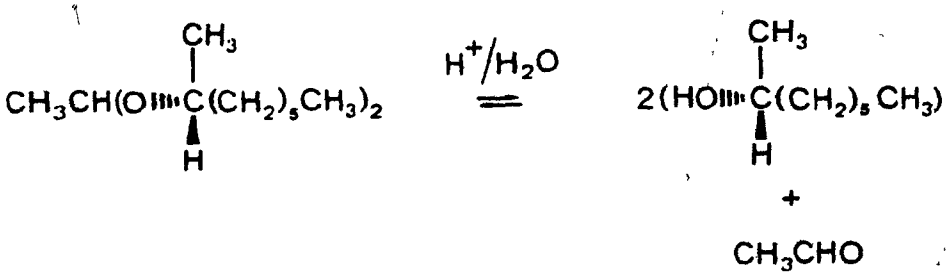
Under neutral conditions, acetal formation is not generally observed for the mixture of an aldehyde or ketone with an alcohol[113,114]. In the presence of an acid catalyst, however, acetals are readily formed, although in general the reaction does not usually go to completion[115].

In acetal formation or hydrolysis, bond cleavage takes place between the alcohol oxygen and the aldehyde carbon. This can be seen with ^{18}O labeling experiments in the formation of n-butyl benzal 66 (Scheme 2.22)[116].



66 Scheme 2.22

In agreement with these findings, the product of hydrolysis of D-2-octylacetal 67 is D-2-octanol, with an unchanged optical configuration (Scheme 2.23)[117].



67 Scheme 2.23

Table 2.4 lists the percent of acetal formation in acidic alcohol solutions. A comparison of Table 2.4 with Table 2.3 indicates that, as is the case with hemiacetal formation, increasing substitution decreases the extent of acetal formation. Moreover, electron withdrawing groups similarly favour acetal formation. For example, the equilibrium constant for acetalization with ethanol is 0.074 for acetaldehyde and 0.112 for bromoacetaldehyde[118].

Table 2.4:Percent of Acetal Formation in Acidic Alcohol Solution[115]

(A mixture of RCHO:R'OH, 1:5)

Aldehyde	EtOH	*i*-PrOH	*t*-BuOH
CH_3CHO	78	43	23
$(CH_3)_2CHCH_2CHO$	71	23	—
$(CH_3)_3CCHO$	56	11	—
C_6H_5CHO	39	13	—

In an attempt to quantify these structure-activity relationships, Kreevoy and Taft[107] studied the hydrolyses of twenty-one ethyl acetals and ketals at 24°C in 50% dioxane-water. They were able to develop an equation which correlated the observed rates of hydrolysis:

$$\log(k/k_o) = (\Sigma\sigma^*)\rho^*$$

$\Sigma\sigma^*$ is the sum of the Taft σ^* values[119] of R_1 and R_2 in $R_1R_2C(OCH_2CH_3)_2$ and the standard reaction (rate coefficient k_o) is the acid catalyzed hydrolysis of 2,2-diethoxypropane ($(CH_3)_2C(OCH_2CH_3)_2$). They observed three straight lines in a plot of $\log(k/k_o)$ *versus* σ^*, representing a series of acetals, ketals and α,β-unsaturated acetals, respectively. All three lines have essentially the same slope, $\rho^* = -3.60$. This high negative value for ρ^* indicates that the hydrolysis is accelerated by groups with electron-releasing inductive effects (negative σ^*). An example of this effect is shown in the dramatic increase in the rate coefficient, approximately $10^{3.5}$, for each substitution of H by CH_3 in the α-position of diethylformal.

$$H_2C(OCH_2CH_3)_2 < H_3CCH(OCH_2CH_3)_2 < (CH_3)_2C(OCH_2CH_3)_2$$

$$k = 4.13\times10^{-5} \qquad k = 0.245 \qquad k = 7.52\times10^{2}$$

They attempted to modify the equation to account for the difference between acetals and ketals. The modified equation includes a term which relates the effect of hyperconjugative protons α- to the central carbon:

$$\log(k/k_o) = (\Sigma\sigma^*)\rho^* + (\Delta n)h$$

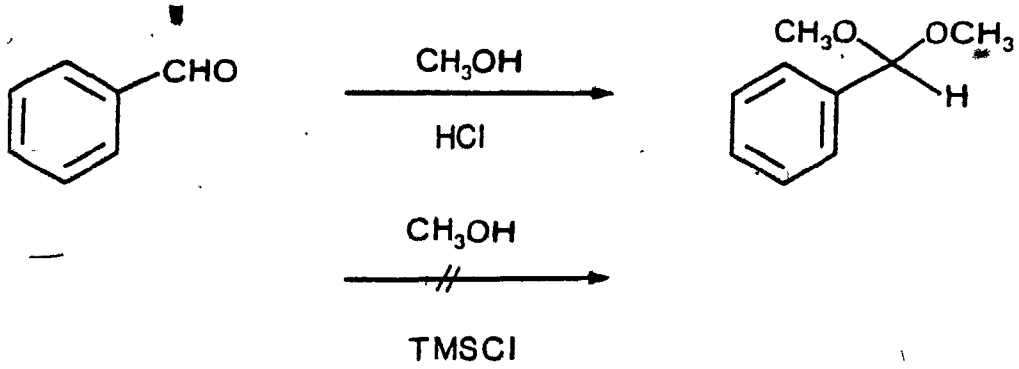
The constant h, represents the stabilization of the reaction transition state by a single α-hydrogen atom ($h=0.54\pm.006$). Δn represents the total number of α-hydrogen atoms (6-n). While this correction allows the correlation of the acetals of aliphatic aldehydes and ketones, it does not allow the correlation of the series of α,β-unsaturated aldehydes. From their studies they were able to conclude that; polar effects are proportional to the substituent constants σ^* and are additive, polar and C-H resonance effects are separate and independent, hyperconjugative effects are directly proportional to the number of α-hydrogen atoms, and steric effects are second order in comparison to polar and resonance effects.

Studies on the formation rather than the hydrolysis of acetals and ketals confirm the dependence of the rate on electronic effects. Bell *et al* found the slope of a log K/K_o *versus* σ^* plot to be $\rho^*=+3.05$ for the formation of a variety of methyl acetals[96]. That is, acetal formation is facilitated by electron withdrawing groups. To this extent, they are in agreement with Kreevoy and Taft.

From the preceeding arguments it can be concluded that the gross features of the mechanism of acetalization are: (i) hemiacetal formation, (ii) oxocarbonium ion formation, (iii) acetal formation under acidic catalysis, and (iv) elimination of the carbonyl oxygen in the reaction as water.

2.3.4 The Mechanism of Acetalization Promoted by Chlorotrimethylsilane

The classical conditions for acetalization involve the use of a strong acid in alcoholic solution. For example, benzaldehyde is converted to the dimethyl acetal in methanol with catalysis by hydrogen chloride (Scheme 2.24)[120].



Scheme 2.24

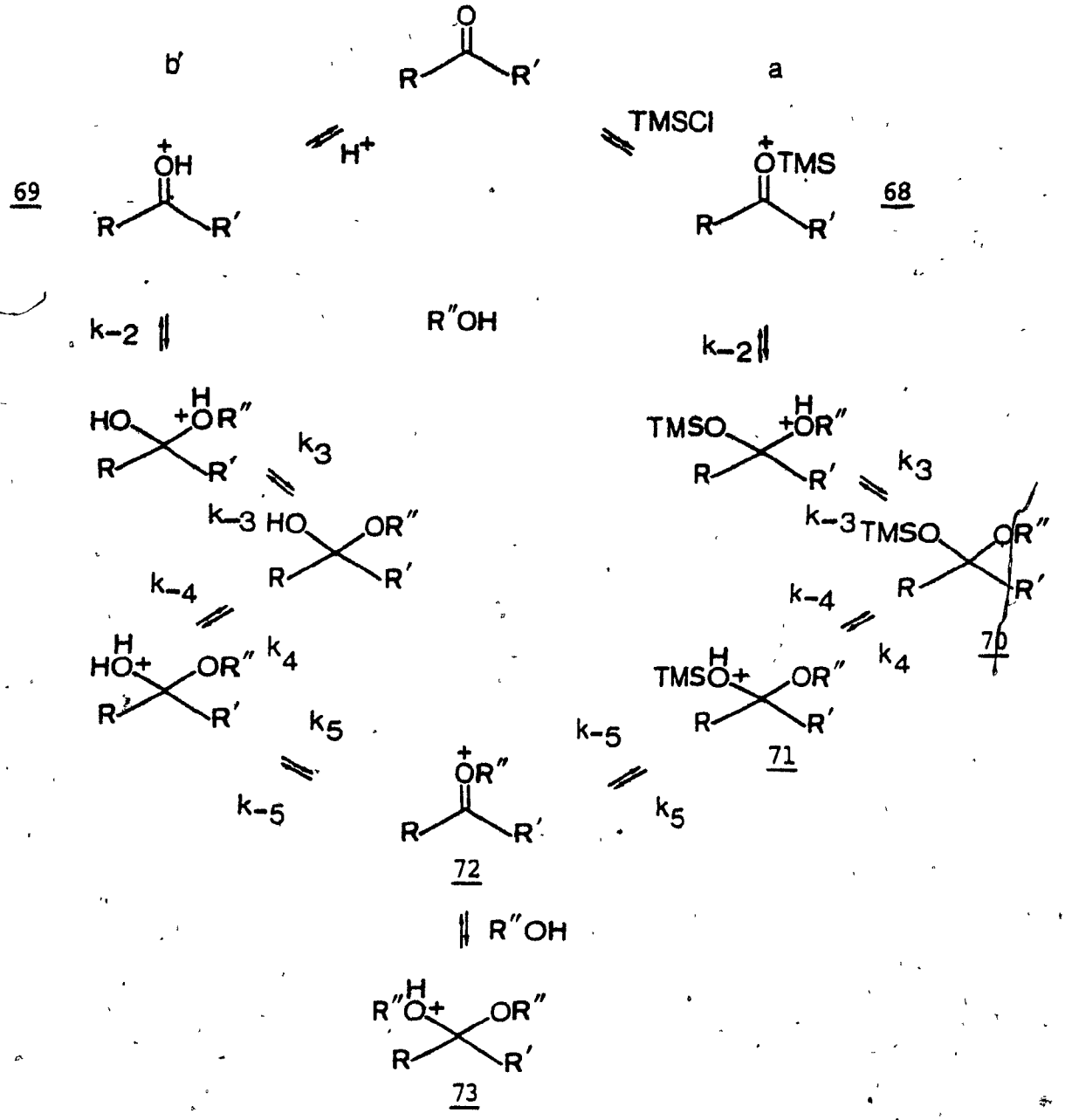
Chlorotrimethylsilane in methanolic solution exists in equilibrium with trimethylsilylmethoxide and hydrogen chloride (Scheme 2.25)[121,122].

$$2\ (CH_3)_3SiCl + H_2O \rightleftharpoons (CH_3)_3SiOSi(CH_3)_3 + 2\ HCl$$

Scheme 2.25

It could be anticipated, therefore, that the hydrogen chloride generated from chlorotrimethylsilane and methanol will catalyze the same acetal formation from benzaldehyde. However, under the conditions used (Method A), no detectable amount of α,α-dimethoxytoluene is formed, and therefore, the reaction cannot be proceeding by protonic catalysis. The proposed mechanism must account for the failure of benzaldehyde to form a methyl acetal in the presence of the hydrogen chloride generated from chlorotrimethylsilane. It must also account for the vast difference

between the overall equilibrium constants, in the presence of trimethylchlorosilane, of the formation of other unactivated acetals and activated acetals (Scheme 2.26).



Scheme 2.26

In the proposed acetalization mechanism the trimethylsilyl group forms a complex of the type 68, based on the known oxophilicity of

silicon. The differences between the intermediates 68 and 69 will affect the overall equilibria of the two reactions. In addition, the other silylated intermediates subsequently formed will affect the equilibrium of the silicon promoted mechanism itself. The first factor to affect the equilibrium involves the properties of the trimethylsilanol and water formed during the reactions. The relative basicities of trimethylsilanol and water are such that the ease of elimination should be similar for both. However, the large size of the trimethylsilanol will render it much less mobile in solution. Its poor mobility is exacerbated by its hydrophobicity which is starkly different to that of water. Both of these factors lead to the possibility of a rapid elimination-recombination sequence in the silicon-based acetalization mechanism (71-->72-->71). That is, the likelihood of methanol trapping the oxocarbonium ion 72 derived from the intermediate 71 before recombination with the silanol can take place, is reduced. This effect would act to push the equilibrium to the left, making this reaction step less favourable than the corresponding one in the proton catalyzed reaction ($K_5(H_2O) > K_5(Me_3SiOH)$).

A second factor to affect the equilibrium is the stability of the silicon intermediate 68. It should be much greater than the corresponding protonic intermediate 69, since silicon is known to effectively stabilize a carbonium ion in the β-position, the so-called β-effect. Upon formation of the siloxycarbonium ion the positive charge can delocalize, essentially spreading over three atoms. This delocalization is not possible in the case of the intermediate 69 where the positive charge is spread over only two atoms. This stabilization will act to push the silyl equilibrium to the left when compared to the proton catalyzed equilibrium ($k_{-2}(Me_3SiOH) > k_{-2}(H_2O)$).

This latter effect will also alter the position of the equilibrium of the chlorotrimethylsilane promoted mechanism itself; the alkyl carboxonium ion will be less stable than the silyl-carbonium ion, pushing the equilibrium to the left ($k_{-2} > k_5$). Another factor which could affect the silicon promoted reaction equilibrium is the protonation of the intermediate 70. The protonation of the siloxy group is less favoured than that of the alkoxy group because of the relative basicity of the two oxygen atoms. Although electronegativity calculations would predict the opposite, electron donation from the oxygen back to the silicon reduces the electron density on oxygen, increasing the overall acidity of the silicon-bound oxygen species[123]. The acidity of silanols, for example, is known to be much higher than the corresponding carbinols. Thus, the preferred protonation of alkoxy groups should result in a greater facility for the elimination of the alcohol, which in turn should push the equilibrium to the left ($k_{-3} > k_4$). However, in light of the rapid rate of proton transfer[124], and especially in consideration of the proximity of the two oxygen atoms, the probability that this is a significant effect is extremely low.

All of the effects described above show that the equilibrium of the silicon promoted reaction has a much lower value than that for the corresponding proton catalyzed reaction. Indeed, with unactivated carbonyl groups, methyl acetal formation is not observed. Why is it then, that methyl acetal formation can occur with activated carbonyl groups? The rate determining step in the proton catalyzed acetalization may be the addition of the alcohol to the carbonium ion (72-->73). This postulation results from the value of the Taft parameter ρ^* for the formation of methyl acetals in acidic methanol[96]. The value of ρ^* is 3.05, indicating

that the development of a positive charge at the reaction centre will increase the rate of reaction. As hemiacetal formation occurs readily, this is the only step in the reaction sequence in which the rate of reaction will be dramatically enhanced by the development of a positive charge*. If this is true for the reaction promoted by trimethylchlorosilane, then it should be possible to observe a relationship between the rate of formation of acetals and the electron density of the carbonyl group being acetalized. Such a relationship exists; activated carbonyls readily form methyl acetals. Activation is provided by the presence of strongly electron withdrawing groups. This activation can be interpreted as an increase in the electrophilicity of the oxocarbonium ion which increases the rate of methanol attack over the re-addition of trimethylsilanol. No reaction is observed with unactivated carbonyls.

The role of the trimethylsilyl chloride in the acetalization reaction then, is twofold. First, the silicon must preferentially bind to the carbonyl group. With preferential silicon binding, the protonic catalysis route is effectively eliminated. Second, the trimethylsilanol must have a lower mobility in solution than water. This lower mobility allows for recombination of the carbonium ion with the silanol before methanol can nucleophilically attack ($k_{-5}(Me_3SiOH) > k_{-5}(H_2O)$), lowering the overall equilibrium constant. The result is that methyl acetal formation under these conditions can only take place with very electrophilic carboxonium

* It should be noted that the elimination of trimethylsilanol to form the oxocarbonium ion should have a negative ρ^* since a positive charge is developing in the transition state, and therefore, seems an unlikely candidate for the rate determining step.

ions. That is, when sufficient electron withdrawal exists to activate the oxocarbonium ion to nucleophilic attack by methanol. Therefore, the reaction mechanism appears to be in agreement with a modified A1 mechanism in which activation by a proton is substituted with activation by a trimethylsilyl group.

2.4 CYCLIC KETALS AND ACETALS

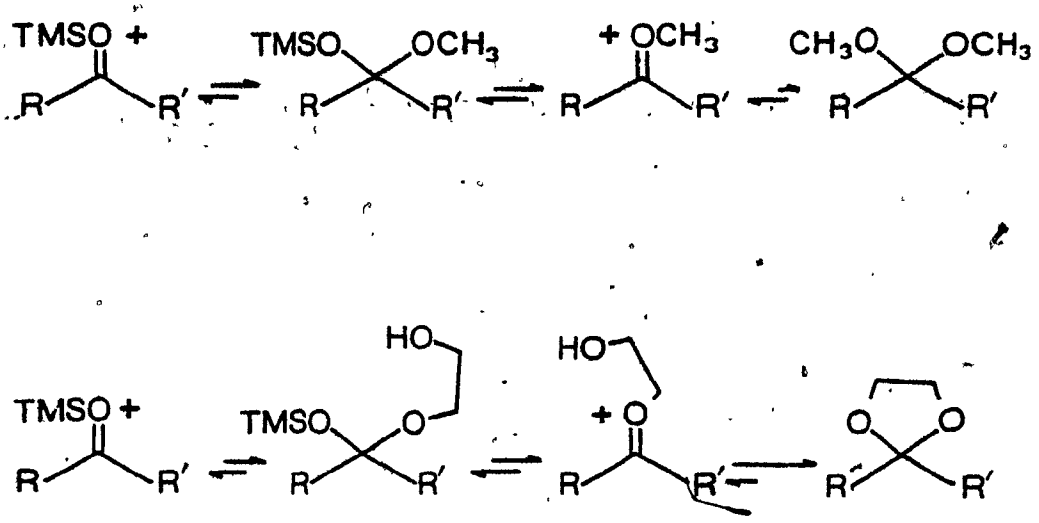
An abundance of data suggest that cyclic ketals and acetals react quite differently from the acyclic compounds described above. For instance, all known examples of cyclic ketal and acetal hydrolysis have entropies of activation ($\Delta S^{\ddagger}$) less than zero and are generally lower by ~10 e.u. than the corresponding diethyl ketals or acetals[125]. The only exceptions to this are the hydrolyses of 1,3-dioxolane, 2-methyl-1,3-dioxolane and 2,2-dimethyl-1,3-dioxolane, all of which have $\Delta S^{\ddagger}$'s equal to or greater than zero, as do the dialkyl ketals and acetals. The rate data is also indicative of a difference between these two classes of compounds. For example, the rates of hydrolysis (*vide supra*) of the diethyl ketals of formal, methyl formal and dimethyl formal increase $\sim 10^{3.5}$ for each substitution of an α-hydrogen with an α-methyl group[96], an electronic effect. Although the rate of hydrolysis of the corresponding 1,3-dioxolane is increased by a factor of $\sim 10^{3.5}$ on the substitution of a 2-hydrogen with a 2-methyl group, an increase of only $\sim 10^{1}$ is observed with the substitution of a second methyl-group[125]. In general, the rate coefficients of hydrolysis of the 1,3-dioxolanes are $\sim 10^{1.5}$ lower than those for the corresponding diethyl acetals and $\sim 10^{4.4}$ lower than those for the diethyl ketals[126]. This demonstrates the great

dependence of the reaction rate, for the hydrolyses of a series of 1,3-dioxolanes, on the steric bulk of the groups surrounding the central carbon. Another striking example of this can be seen in the vast difference in the rates of the hydrolyses of 2-phenyl-1,3-dioxolane and 2-methyl-2-phenyl-1,3-dioxolane[127]. The rate of the latter is only one-fifth that of the former even though electronically the substitution with a methyl group is expected to accelerate the reaction.

It is clear that steric and electronic factors affect the cyclic and acyclic acetals differently under hydrolytic conditions. Any differences in the ease of formation of these two types of acetals should also be attributable to those factors which affect the rates of hydrolysis. In the case of dioxolane formation promoted by chlorotrimethylsilane, both steric and electronic factors affect the amount of observed acetal formation. For example, a comparison of the formation of the dioxolanes formed from benzaldehyde 20 and acetophenone 21, shows that the less sterically bulky carbonyl group, benzaldehyde, requires far less stringent conditions for good yields of the dioxolane to be isolated. In consideration of electronic factors, the electron withdrawing effect of the α-chlorine atoms decrease the severity of conditions required to effect dioxolane formation from α,α-dichloroacetophenone 25, in comparison with acetophenone 21 (Table 2.2).

It has been postulated that the rate determining step in acetal formation is the addition of the alcohol to the oxycarbonium ion. If the mechanism for cyclic acetal formation parallels that of acyclic acetal formation, a fundamental difference exists in the transformation which occurs in the rate determining step. Whereas the acyclic system must undergo an intermolecular attack of an alcohol on the oxycarbonium ion,

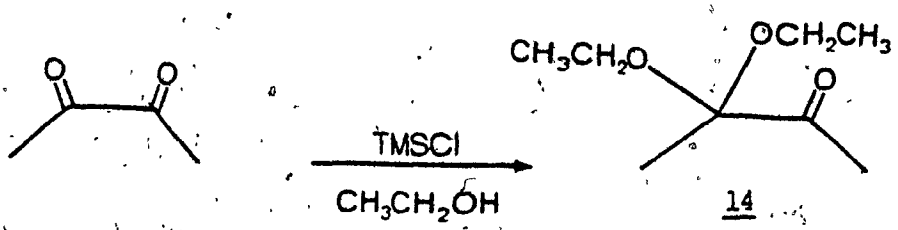
the cyclic system can react in an intramolecular fashion; the second alcohol is already appropriately placed upon the formation of the carboxonium ion. Intramolecular ring closure is a more facile step than intermolecular attack. When dioxolane formation is promoted by chlorotrimethylsilane, this difference between intra- and intermolecular attack is readily observed. All of the aldehydes and ketones tested form dioxolanes readily. On the other hand, only those carbonyls with substantial electron withdrawal from the carbonyl centre, "activated carbonyls", undergo methyl acetal formation. This is easily understood in terms of the difference in the type of transformation occurring in the rate determining step (Scheme 2.27).



Scheme 2.27

2.4.1 The Stability of 2,3-Butanedione Cyclic Acetals

It has been shown that cyclic acetals are more readily synthesized than acyclic acetals. This difference in the stability and the ease of formation of cyclic and acyclic acetals is particularly well illustrated in the case of 2,3-butanedione. The acetalization of 2,3-butanedione, an activated carbonyl compound by the definition given above, can be expected to form both methyl acetals and dioxolanes readily, although the latter reaction should occur with greater facility. Whereas the monomethyl (14) and monoethyl (15) acetals are easily made using chlorotrimethylsilane in the appropriate alcohol as solvent (Scheme 2.28) it is impossible to isolate the corresponding monodioxolane 74 from ethylene glycol under otherwise identical conditions. Neither can this compound be isolated under classical conditions with catalysis by *p*-toluenesulfonic acid[128]. Instead the very stable *bis*-dioxolane 28 is isolated in both cases (Scheme 2.29).



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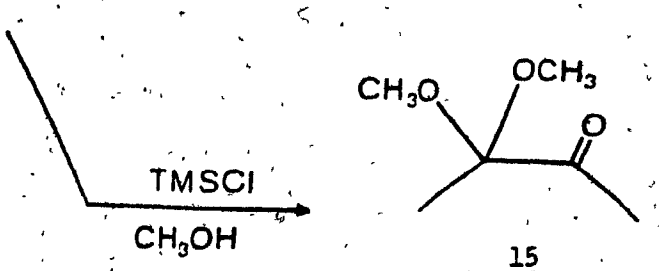

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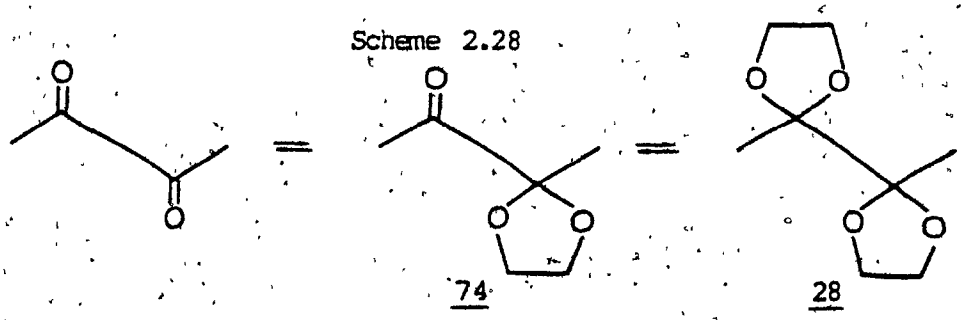
Scheme 2.28



74 28

Scheme 2.29

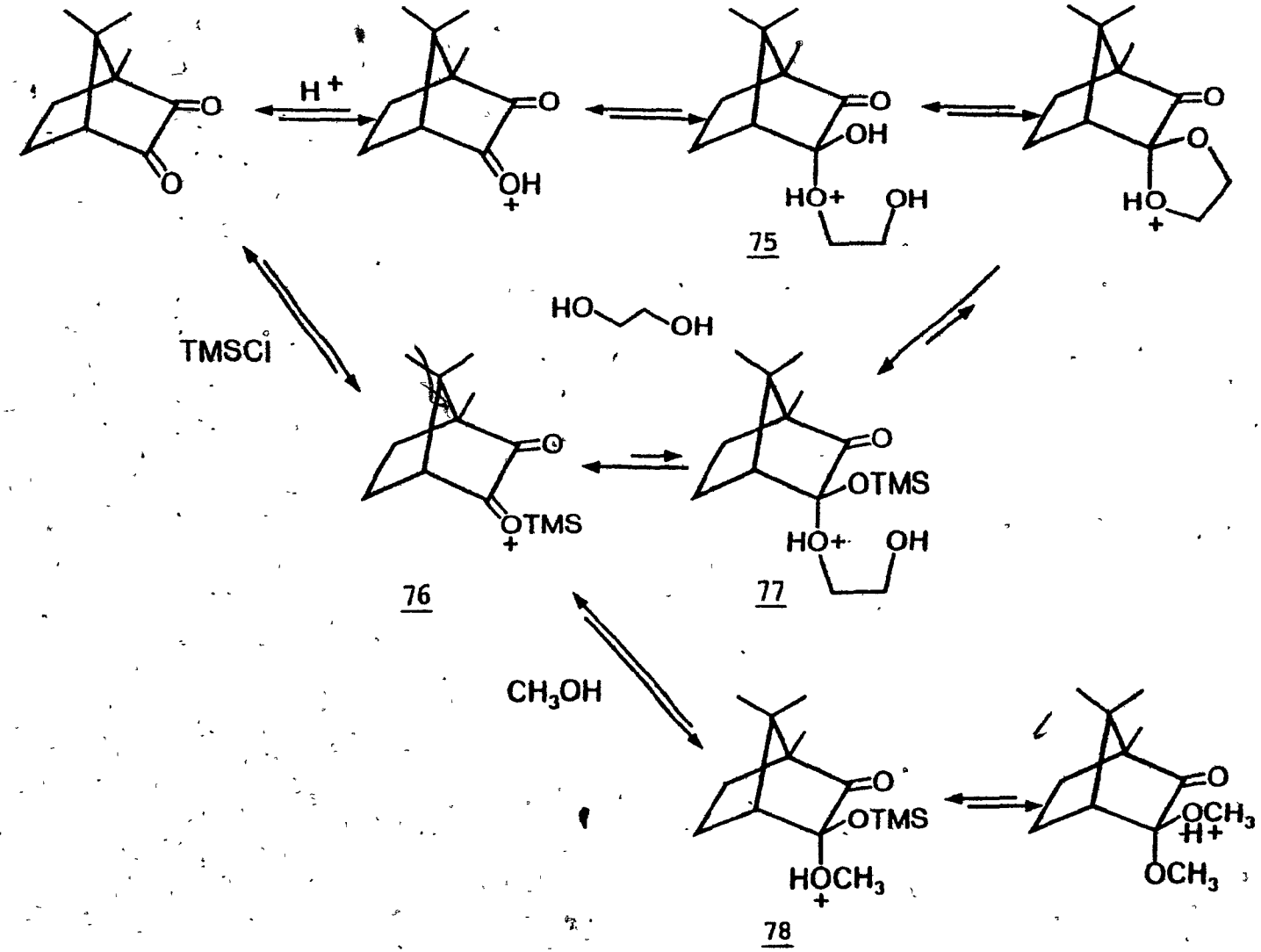
A variety of reaction conditions were examined in an attempt to isolate the monodioxolane. Restricting the equivalents of the dione, trimethylchlorosilane or the alcohol, at room temperature, led to mixtures of only the starting material and the *bis*-dioxolane. Therefore, a temperature profile of the reaction was undertaken using G.L.C. analysis. At -78°C, no reaction products were observed; starting materials only were detected. At -25°C, a mixture of the *bis*-dioxolane and starting materials was detected. However, in the range of temperatures between -60 to -40°C, peaks were detected which corresponded to the starting dione, the *bis*-dioxolane, and a peak of intermediate retention time which was tentatively assigned to 2-methyl-2-acetyl-1,3-dioxolane. Unfortunately, all attempts to isolate this product were unsuccessful (see the experimental section).

Thus, the acetalization of 2,3-butanedione, which leads exclusively to *bis*-dioxolane from ethylene glycol, is illustrative of the greater stability of the cyclic system and their correspondingly greater ease of formation.

2.5 CONFIRMATION OF THE MECHANISM?

An interesting experimental result which seems to confirm the participation of the trimethylsilyl group in the acetalization mechanism is the reaction of camphorquinone 18. Using traditional methods, this compound is not known to form acetals easily[129] and only after recycling the unreacted recovered starting material several times, is it possible to synthesize the ethylene glycol acetal in reasonable yields[130]. Because this molecule is of the activated type, it is expected to form both the ethylene glycol and dimethyl acetals with chlorotrimethylsilane. Surprisingly, in the presence of chlorotrimethylsilane, it is not possible to synthesize the ethylene glycol acetal at either the 2- or the 3-position. However, it is a simple procedure to make the dimethyl acetal at predominantly the 3-position (structural assignments were made based on reported ^{1}H-N.M.R. data[131]). The inability of camphorquinone to form dioxolanes, an acetal which is usually easier to synthesize than methyl acetals, (*vide supra*), appears to confirm the presence of a carbonyl-trimethylsilyl complex (Scheme 2.30, following page).

Whereas the classical protonic catalysis generates an intermediate which has very small steric requirements 75, reactions promoted by chlorotrimethylsilane are postulated to proceed with the formation of a carbonyl-trimethylsilyl complex 76 as an intermediate. Upon formation of


H+
OH
HO+
OH
75
TMSCl
HO
OH
OTMS
OTMS
HO+
OH
76
77
CH3OH
OTMS
HOCH3
OCH3
H+
OCH3
78

the siloxy-ethylene glycol acetal 77, the rather bulky ethylene glycol group forces the sterically demanding trimethylsiloxy group into the radii of the C7-*gem*-dimethyl group. This intermediate should not be very stable on the basis of these steric considerations. It may never form, but if formed, should rapidly revert to 76. The smaller methoxyl group will affect, to a much lesser extent, the position of the trimethylsiloxy group in 78 and the formation of the dimethyl acetal is, therefore, favourable enough to be observed.

The experimental results are most easily explained in terms of steric bulk in the transition state which is a result of the presence of the trimethylsilyl group. Although direct evidence for silicon containing intermediates has not been observed in silicon promoted acetalizations, intermediates of this type have been postulated in other similar reactions[132,133]. A mechanism of this type, therefore, seems to be the most reasonable of those which can be postulated.

2.6 REGIOSELECTIVITY USING CHLOROTRIMETHYLSILANE FOR THE PROTECTION OF POLYOLS AS ACETONIDES

Much of the previous discussion has been devoted to the protection of interesting carbonyl groups as acetals with simple alcohols. In an analogous sense, however, one could consider the use of the chlorotrimethylsilane procedure as a way to protect an interesting polyol with a simple ketone such as acetone. For example, the use of trimethylchlorosilane would seem to be ideally suited for the protection of sugar derivatives. Compounds of this type usually have more than one pair of hydroxyl groups which could be protected and it is important to be able to

synthesize only the desired regioisomer. The use of chlorotrimethylsilane has been shown to be accompanied by some chemoselectivity; methyl acetals are only formed from activated carbonyl groups, and with the sterically demanding camphorquinone molecule the formation of methyl acetals is preferred at the C3-position. It is of interest, therefore, to see if the use of trimethylchlorosilane can offer any advantages in terms of regioselectivity in the case of cyclic acetals formed from polyhydroxylated compounds.

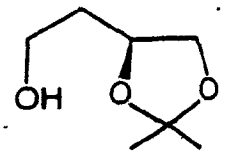
Since it is now established that unactivated carbonyl groups are unaffected in methanolic-chlorotrimethylsilane solutions, a 1:3 mixture of methanol (to increase the solubility of the polar sugars) and acetone (for ketalization) can be used as the solvent system. Under these conditions, ribose is can be converted to 2,3-ribofuranose acetonide 32. This product is the same as that which one would obtain when using strong acids such as sulfuric acid in acetone[134]. However, the work-up in the case of the chlorotrimethylsilane procedure is somewhat less complicated.

The situation is quite different with the acetalization of glucose. It is surprising to discover that glucose reacts to form the 1,2-glucofuranose acetonide 33. Literature procedures indicate that this is not the compound normally formed from glucose under acetalization conditions. Instead, under kinetic conditions utilizing alkyl *iso*-propenyl ethers, for example, the 4,6-glucopyranose acetonide is selectively formed[135]. Using the more classical conditions of strong acids in acetone, 1,2,5,6-glucofuranose diacetonide is the main product to be isolated[136]. The 1,2-glucofuranose acetonide is usually obtained by partial hydrolysis of the 1,2,5,6-diacetonide, for example, in sulfuric acid[137]. Methodologies have also been reported for the direct isolation of the 1,2-acetonide from

glucose, but these make use of several steps, albeit in a "one-pot" reaction sequence. Whether the 1,2,5,6-diacetonide is the penultimate product in the acetalization using chlorotrimethylsilane has not been established. However, it is interesting that this simple procedure gives directly the thermodynamic monoacetal.

Nucleosides can also be successfully protected by using chlorotrimethylsilane; for example, uridine is converted to the 2',3'-*iso*propylidine derivative 34 (Table 2.2). This product is the same as that which one would obtain using classical procedures[138].

A simple compound which has been the focus of some interest is the dioxolane 79[139,140,141,142,143,144]. 1,2,4-Butanetriol, the starting material used for the formation of the dioxolane, can be obtained as either the R- or S-enantiomer. As a result, the dioxolane provides a way to introduce a chiral fragment of known stereochemistry directly into a molecule. Corey, among others, has used the compound to good advantage. He was able to synthesize both 12-HETE ((S)-12-hydroxy-5,8,14-*cis*-10-*trans*-eicosatetraenoic acid)[140] and prostaglandins E_3 and $F_{3\alpha}$[139].



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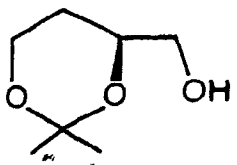

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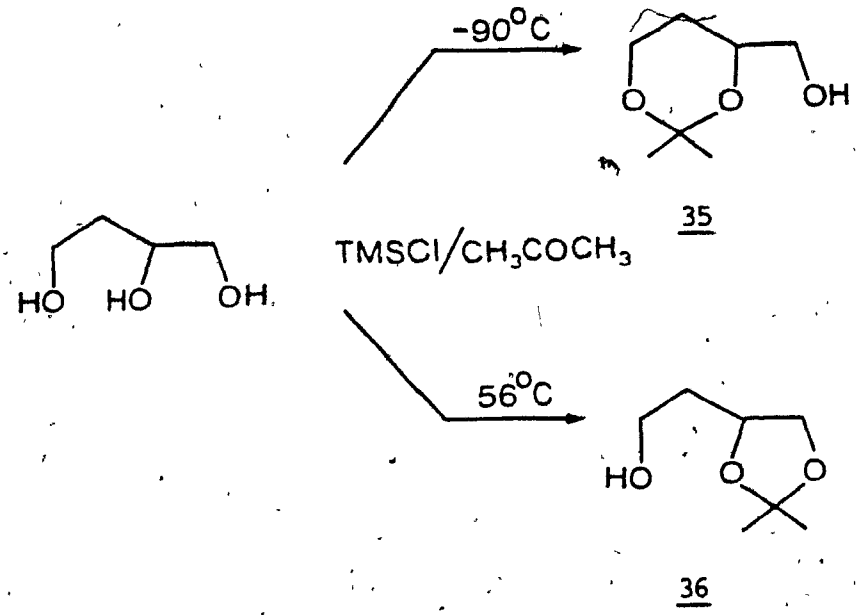
Although attempts to synthesize 36 from 1,2,4-butanetriol have been reported to give the desired thermodynamic product, the dioxolane, exclusively, its formation is usually accompanied by contamination with the dioxane 35 (for example, catalysis with *p*-toluenesulfonic acid in acetone at room temperature yields a mixture of 9:1 dioxolane:dioxane[141]).

Meyers and Lawson proved the presence of both isomers by isolating the dioxane and the dioxolane as their 3,5-dinitrobenzoate esters[145]. They conclude that most of the literature preparations of the dioxolane, which had been reported as regiospecific, in fact contain up to 10% of the undesired dioxane.

As chlorotrimethylsilane has been shown to promote dioxolane formation with sugar derivatives, it was hoped that the formation of the acetonide from 1,2,4-butanetriol would proceed, and take place with a greater degree of regioselectivity than occurs under classical conditions. The reaction of trimethylchlorosilane with 1,2,4-butanetriol in acetone, at room temperature or reflux, leads to an isolated dioxolane:dioxane ratio of 9:1, similar to that found by Meyers, in 57% overall yield. However, the interesting feature of the reaction is observed at -90°C. The selectivity of the reaction is completely inverted. That is, the dioxolane:dioxane ratio is 2:11, isolated in a total yield of 91%. The structural assignments were confirmed by comparing the ^{1}H-N.M.R. spectra of the 3,5-dinitrobenzoate esters made from the chlorotrimethylsilane procedure at both temperatures, with a sample prepared by the method of Hayashi[141].

The advantage of the use of chlorotrimethylsilane, therefore, is the obtention of both acetals, the dioxolane 36 and the dioxane 35 (Scheme 2.31). The regioselectivity of the reaction when promoted by chlorotrimethylsilane at elevated temperatures is about the same as that for classical conditions; the dioxolane 36 is favoured. However, unlike the classical conditions, this reagent is reactive enough to be utilized at reduced temperatures and these milder conditions allow the trapping of kinetic product, the dioxane 35. Thus, the use of trimethylchlorosilane

allows the isolation of either of the desired acetonides. When a single enantiomer of 1,2,4-butanetriol is used as the starting material, it should be possible to use the same starting chiral fragment to introduce a chiral centre to a molecule in two different ways; from the 1-hydroxyl group of the dioxane or from the 4-hydroxyl group of the dioxolane. Thus the use of this reagent allows some control of the regioselectivity of the acetalization reaction of polyhydroxylated compounds over that of traditional methods and increases the potential utility of simple molecules, such as 1,2,4-butanetriol, in the total synthesis of chiral moieties.



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Scheme 2.31

2.7 ESTERS OF CARBOXYLIC ACIDS

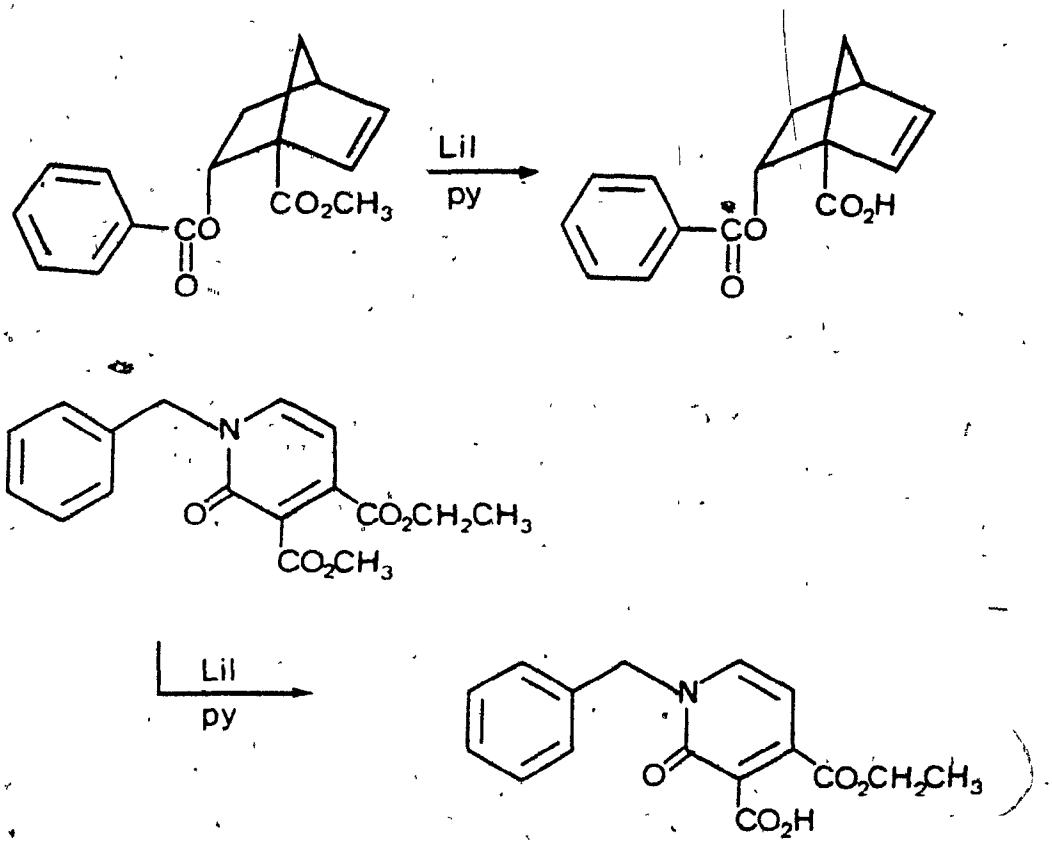
The carboxyl group is a classical example of a functional group which

requires protection in a synthetic organic scheme. There are generally two approaches to the use of esters as a protecting group for this functionality. First, readily prepared esters can be used or synthesized, such as methyl and ethyl esters. Then mild, selective, and if possible, non-hydrolytic conditions can be devised for their cleavage in an attempt to prevent the decomposition of acid or base sensitive groups in the rest of the molecule. Second, novel types of esters can be devised which are cleaved under non-hydrolytic conditions. Esters of this second group can be removed by making use of the chemical principles of oxidation, reduction, hydrogenolysis, and so on. The limitation of this technique, quite often, is in the difficulty of preparing the ester. Paralleling this work in carboxyl group protection is the search for different means to activate the carboxyl group to esterification, to lactonization, or to the formation of amide bonds. Thus, when choosing esters for the protection of carboxylic acids, one must consider not only the ease and conditions of formation, but also the mode of activation of the carboxyl group to nucleophilic attack and, equally importantly, the ease and conditions of deblocking the carboxyl group.

2.7.1 Deprotection of Esters

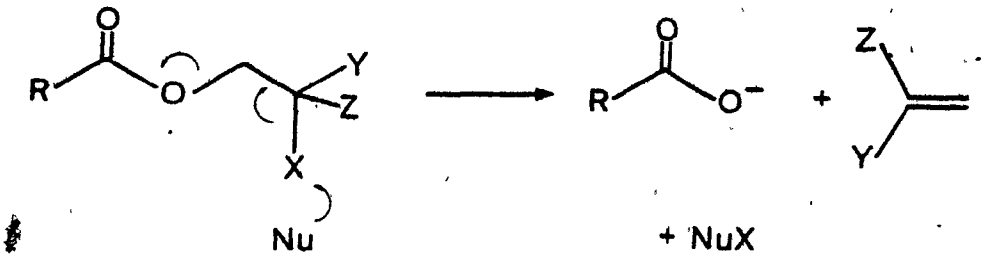
Methyl and ethyl esters can be selectively removed under mild conditions. These esters are particularly simple to remove by anions (iodide[164], chloride[165] and thiolate[166]) or neutral molecules (thiols[167], DBN[168] or DBU[169]) in dipolar aprotic media. The small steric hindrance of these alkyl esters at the reaction site does not prohibit their S_N2 displacement under the conditions employed. The synthetic utility of this

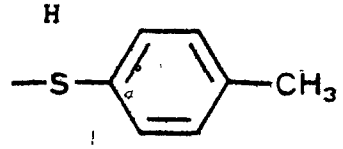
S_N2 reaction for the deprotecting of esters became popular on the advent of its use by Eschenmoser[170]. Two examples of this type of selective de-esterification are shown below (Scheme 2.32)[171].



Scheme 2.32

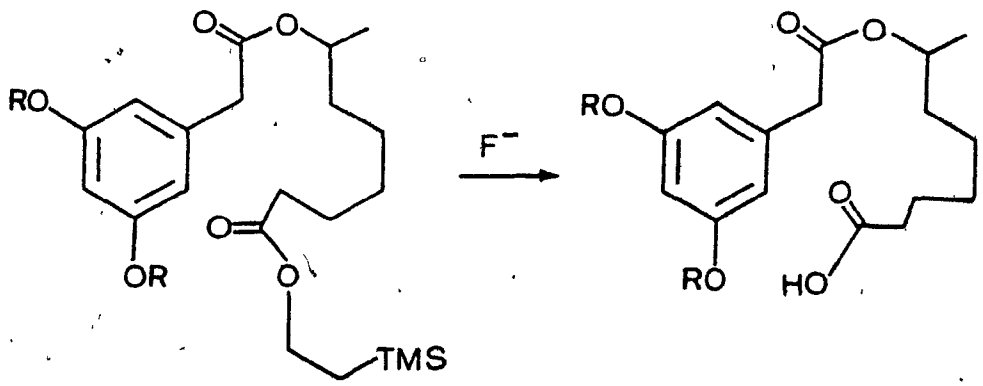
A second class of esters of interest is composed of those which have a greater steric bulk than methyl or ethyl esters but can still be deblocked under mild, aprotic conditions. The particular esters in question are the 2,2,2-trichloroethyl, 2-trimethylsilylethyl and other β-substituted ethyl ester derivatives. The ease of their de-esterification is a result of the facility for the elimination of ethenic components (Scheme 2.33).



Nu	X	Y	Z
Zn	Cl	Cl	Cl
F^-	$SiMe_3$	H	H
OH^-	H	H	

Scheme 3.33.

As with so many concepts in modern synthetic organic chemistry, the perception that this transformation would occur readily originated with R.B. Woodward. He was able to use the 2,2,2-trichloroethyl ester, which was subsequently cleaved using zinc-acetic acid, in the synthesis of cephalosporin[239]. An analogous transformation is the β-elimination of 2-trimethylsilylethyl esters, which can be easily removed in the presence of fluoride ions in anhydrous media[172,173]. This reaction is usually chemoselective for the silyl ester group (Scheme 2.34).



Scheme 2.34

On occasion, the conditions required for cleavage of β-substituted esters cause the decomposition of other functionalities in the molecule. In those cases, the mild conditions for cleavage of benzyl esters make them the protecting group of choice. Benzyl esters are easily cleaved by hydrogenolysis[174,175], or if properly substituted, in mildly acidic solution[176,177]. The former process can be carried out catalytically on a column of palladium on charcoal at room temperature[178].

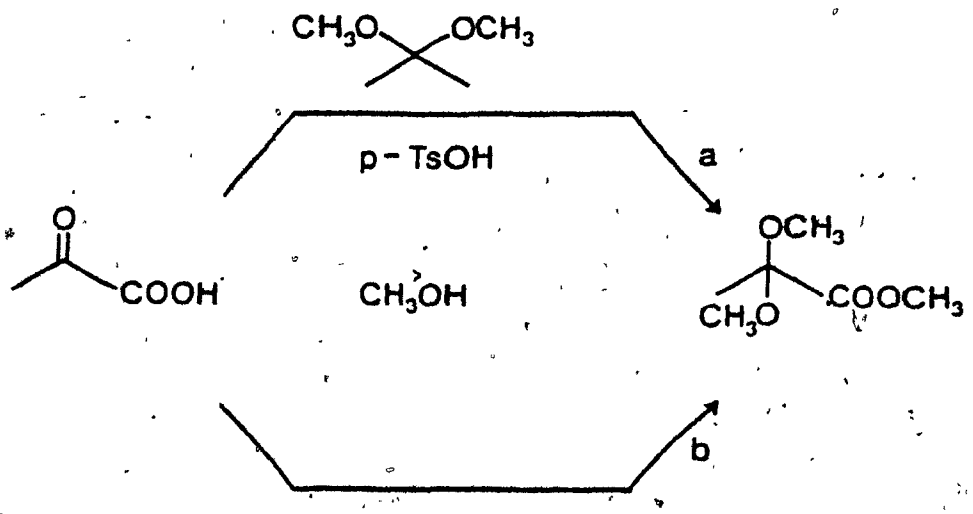
For situations in which the alkaline saponification of esters is not possible[179], the properties of *t*-butyl esters make them especially attractive as protecting groups. They are resistant to hydrogenolysis, and under normal conditions, ammonolysis and base catalysed hydrolysis. They can, however, be cleaved in acidic conditions. The fission of the alkyl-oxygen bond leads to the splitting off of the *t*-butyl group as *iso*-butylene. The acidic conditions required are usually mild; for example, trifluoroacetic acid at room temperature[180] or *p*-toluenesulfonic acid in refluxing benzene[181].

In light of these well known techniques for deblocking carboxylic esters, there is an interest in methods which promote the formation of such esters under mild conditions.

2.8 ESTER FORMATION PROMOTED BY CHLOROTRIMETHYLSILANE

Hoffman and Kandathil[78] have described the conversion of pyruvic acid to methyl 2,2-dimethoxypropionate (37) (Scheme 2.35a). Both esterification and acetalization are achieved in a single step. In view of the successful use of chlorotrimethylsilane in the promotion of acetalization, it was important to discover if chlorotrimethylsilane would promote both

the expected acetalization of this activated carbonyl group and the esterification of the carboxylic acid. Using methanol as the solvent, pyruvic acid is indeed converted to the acetal-ester (37) (Scheme 2.35b).



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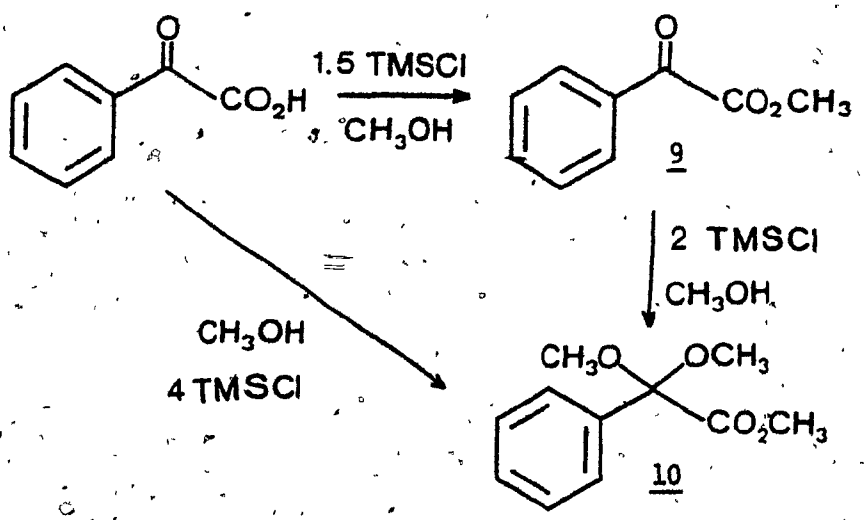
Scheme 2.35

However, it remained to be determined which transformation was occurring first; if indeed the relative rates of the two reactions are significantly different. To this end, the reaction of benzoylformic acid (phenylglyoxylic acid), an easier compound to handle, was studied. It is observed that esterification is the first reaction to take place and that the reaction sequence can be stopped at either the ester (9) or the acetal-ester stage (10) (Scheme 2.36).



Scheme 2.36

The scope of the esterification procedure was further investigated using a diverse selection of both alcohols and carboxylic acids.

2.8.1 The Preparation of Synthetically Useful Carboxylic Esters

A variety of carboxylic acids are converted to their methyl or ethyl esters simply by stirring the acid in the appropriate alcohol with 2.2 equivalents of chlorotrimethylsilane[182]. The reactions are performed at room temperature under an inert atmosphere (Method A). In most cases, the work-up simply involves removal of the solvents under reduced pressure followed by purification of the crude residues by chromatography or distillation.

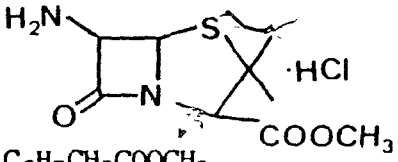
It is surprising to discover the extremely large range of carboxylic acids which are readily converted to esters. A selection of aromatic and simple aliphatic acids, such as benzoic, *p*-nitrobenzoic, phenylacetic and 12-hydroxydodecanoic acids, can be isolated as their methyl and ethyl esters (Table 2.5). Amino acids are particularly suitable molecules to

esterify; methyl leucinate, methyl and ethyl hippurate and methyl 6-amino-penicillanoate, are all isolated as their hydrochloride salts. An example of the mildness of the reaction can be seen with the latter compound. The methyl ester is isolated in 84% yield after a 5 minute reaction at room temperature, without scission of the labile β-lactam bond. One particularly interesting example shows the selectivity of this esterification method for certain carboxyl groups. While 1,12-dodecanedioic acid is readily protected as the dimethyl ester, the method displays a selectivity for the 5-carboxyl group of glutamic acid. In either methanol of ethanol, the corresponding 5-alkyl ester is isolated after reaction times of just 6-30 minutes, respectively. In either case, only small amounts of the dialkyl ester can be observed, even when the conditions are more forcing, for example, with excess chloro-trimethylsilane.

In addition to methyl and ethyl esters, several other esters are often required in organic synthesis viz. the 2-trimethylsilylethyl, *t*-butyl, trichloroethyl and benzyl esters. Usually, the cost of the precursor alcohols precludes their use as a solvent. To take account of this fact, dry tetrahydrofuran and an excess of the alcohol are used as the solvent system. In this solvent system, the carboxylic acid to be esterified is refluxed for 1.5-2.5 days (Method B, Table 2.6) in the presence of an excess of chlorotrimethylsilane.

Excellent results are obtained with this method in the synthesis of both benzyl and β-trimethylsilylethyl esters, although the results with benzyl alcohol are uncharacteristic of the esterification reactions with other alcohols (*vide infra*). Allyl and crotyl esters can also be formed using this technique. In the esterification of N-carbobenzoxyglycine with

Table 2.5:Examples of Esters Prepared from the Precursor Carboxylic Acids

Entry	Product	(Compound Number)	Method	Reaction Time(h)	Equiv. TMSCl	Equiv. R'OH	Reaction Temp.(°C)	Yield(%)[a]	b.p./torr Found	(m.p.) Literature	Ref.
1	$CH_3C(OCH_3)_2COOMe$	37	A bc	ON d	2.2	125	22	92		62-63/12	78
2	PhCOCOOMe	9	A be	72	2.2	17	22	89 e		246-248	222,223
3	PhCOOMe	39	A b	ON	2.2	125	22	98		198-200	222,224
4	$MeOOC(CH_2)_{10}COOMe$	40	A bf	ON	4.4	125	22	85	(30.5-31)	(31)	222,225,226
5	$HO(CH_2)_{11}COOMe$	41	A bf	ON	2.2	125	22	96	(31-2)	(33-34)	222,227
6	$PhCONHCH_2COOMe$	43	A b	ON	2.3	490	22	85	(80.5-81)	(85)	222,230,231
7	$(CH_3)_2CHCH_2CH(NH_3Cl)COOMe$	44	A gh	66	4.4	125	22	97	(145-6)	(146)	222,232
8	$HOOCCH(NH_3Cl)CH_2CH_2COOMe$	42	A gh	0.1	2.2	82	22	85	(157-8)	(160-1)	228,229
9		45	A gh	0.1	2.4	750	22	84	(136-40)		233
10	$C_6H_5CH_2COOCH_3$	46	A b	ON	2.2	50	22	84		215	222
11	$p\text{-}CH_3PhCOOEt$	47	A b	18	2.2	85	78	96		228	222,234
11	$p\text{-}NO_2PhCOOEt$	48	A b	48	2.3	89	78	81	(55.5-57)	(56)	222,235
12	$PhCONHCH_2COOEt$	49	A i	40	2.2	190	22	97	(61.5)	(67.5)	222,236
13	$HOOCCH(NH_3Cl)CH_2CH_2COOEt$	50	A gh	40	2.2	85	22	67 j	(166.5-7.5)	(170-0.5)	222,237

a. Isolated, after purification. The purity of the final product was confirmed by NMR, and by GC (5% OV 101 on Chromosorb W) or TLC (Aluminum backed silica gel 60 plates, 0.2mm using as eluant 1:1:1:1 acetic acid:water:n-butanol:ethyl acetate for the amino acids and ethyl acetate-hexane mixtures for the rest). The purity of the crude residues (liquids), before purification, ranged from 74-100%.

b. Purified by flash chromatography (16g 40-63mm silica, E. Merck, hexanes-ethyl acetate mixtures used as eluant).

c. The starting material was pyruvic acid. Under these conditions, the reaction could not be stopped at the ester, but formed the acetal ester.

d. Overnight. No attempt was made to minimize the reaction time.

e. If Method A was used, only the acetal ester was isolated (55%). GC yield, the remaining 11% was the acetal ester (Isolated yield 83%).

f. The solvent system was 25 mL methanol, 10 mL hexane, and 15 mL ether. The solution was neutralized to pH6 with a 5% solution of sodium methoxide in methanol; evaporated and purified by flash chromatography.

g. The starting material was the free amino acid, not the hydrochloride salt.

h. Recrystallized from methanol-ether.

i. Recrystallized from ether-hexanes.

j. When accounting for recovered starting material, the yield was 92%.

Table 2.6: Examples of Some Less Usual Esters from the Precurser Carboxlic Acids

Entry	Product	(Compound Number)	Method	Reaction Time (h)	Equiv. TMSCl	Equiv. R'OH	Reaction Temp. (°C)	Yield(%)	b.p./torr Found	(m.p.) Literature	Ref.
1	$HO(CH_2)_{11}COOCH_2C_6H_5$ + $HO_2C(CH_2)_{11}OCH_2C_6H_5$	51	B a	48	2.2	3.5	22	61 14			
2	$PhCONHCH_2COOCH_2Ph$	53	B a	30	2.2	2.1	66	65	(86.5-87)	(87-89)	238
3	$HO(CH_2)_{11}COOCH_2CH_2SiMe_3$	54	B a	64	6.6	3.4	66	73 b			
4	$C_6H_5CONHCH_2COOCH_2CH_2SiMe_3$	55	B a	42	5.0	2.5	66	98			
5	$PhCONHCH_2COOC_6H_{11}$	52	B c	24	2.2	28	25	84	(101)	(105)	330
6	$C_6H_5CH_2COOEt$	56	C d	1.5	0.5 d	34	25	61		227-8	222

a. Purified by flash chromatography (16g 40-63mm silica, E. Merck, hexanes-ethyl acetate mixtures used as eluant).

b. Accounting for recovered starting material, the yield is 79%.

c. The alcohol and solvent for the reaction was cyclohexanol.

d. The reaction was promoted by silicon tetrachloride, not chlorotrimethylsilane.

allyl alcohol, for example, the conditions are mild enough to allow the desired reaction to take place without concomitant cleavage of the protecting group[332].

Whereas benzyl esters have been prepared under a wide range of acidic and basic conditions, β-trimethylsilyl esters are most often made under basic conditions; the formation of the latter has been reported using DCC in pyridine[173]. Esterification with chlorotrimethylsilane proceeds under mildly acidic conditions. This gives the synthetic chemist more choice in the conditions available for the protection of the carboxyl group in the presence of other functionalities in the molecule. This facile and inexpensive procedure thus offers some considerable advantages over traditional methods of esterification.

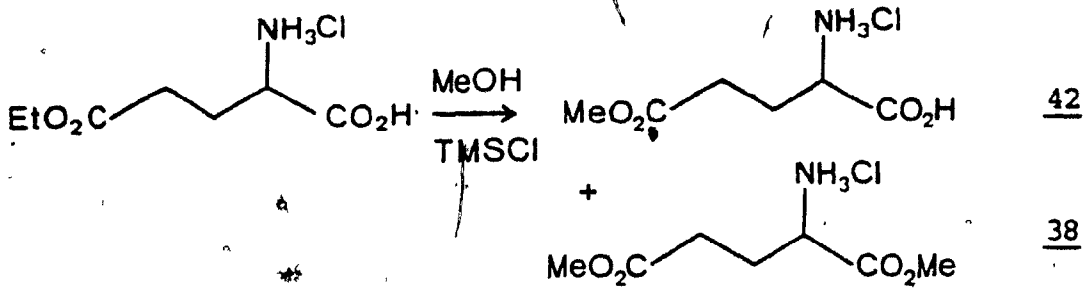
Not all esters are amenable to formation in the presence of chlorotrimethylsilane. Under a variety of conditions, for example, it proves impossible to synthesize 2,2,2-trichloroethyl esters. Also, even under forcing conditions, tertiary-butyl esters are resistant to formation from *t*-butanol. However, secondary alcohols appear to be amenable to ester formation based, in one case, on the synthesis of a cyclohexyl ester from cyclohexanol. The reasons for these results will be discussed below.

2.8.2 Transesterification

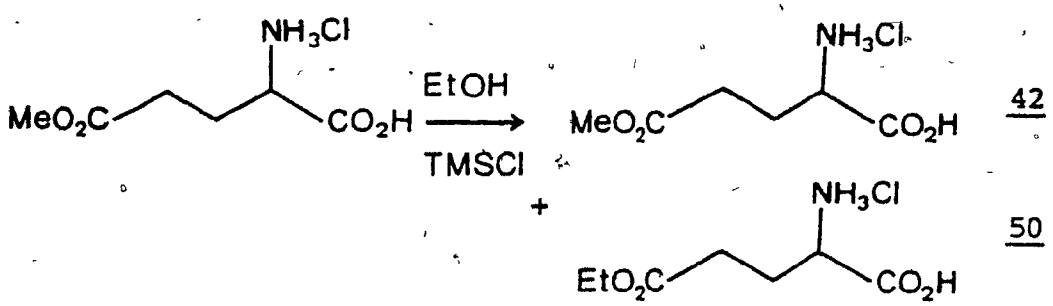
Originally, an attempt was made to di-esterify the 5-alkyl esters of glutamic acid. The aim was to achieve diprotection of the two carboxylic acids with different protecting groups. Thus, the esterification of 5-ethyl glutamate (50)(HCl salt) in methanol was undertaken using chlorotrimethylsilane. However, none of the desired 5-ethyl,1-methyl glutamate

is isolated (Scheme 2.37). Instead, an unexpected transesterification process leads to a mixture of the 5-methyl (42) and 1,5-dimethyl (38) esters. The complimentary transformation of 5-methyl glutamate·HCl (42) in ethanol with trimethylsilyl chloride leads to a mixture of the 5-methyl (42) and 5-ethyl glutamates (50) (HCl salts, Scheme 2.38). Having observed that transesterification takes place under these conditions, the generality of the reaction was investigated using a variety of alcohols.

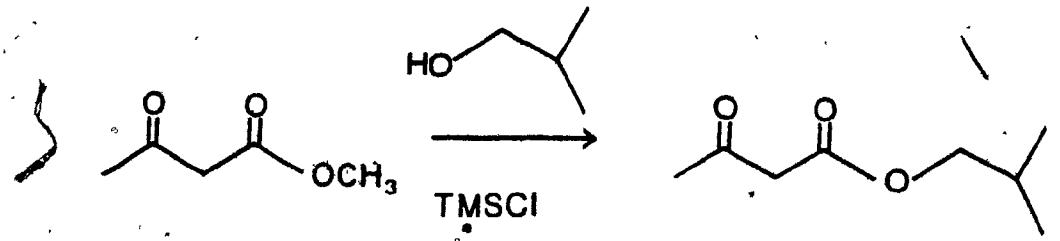
The transformations attempted were performed either in the alcohol as solvent or in another solvent with an excess of the alcohol to be transesterified. Results indicate that only those alcohols which form esters directly from carboxylic acids in the presence of chlorotrimethylsilane, such as methanol, ethanol, and *iso*-butanol (Schemes 2.37, 2.38, and 2.39), are transesterified. Less reactive alcohols which do not esterify carboxylic acids directly, such as *p*-nitrophenol (Scheme 2.40), exhibit no tendency to be transesterified.



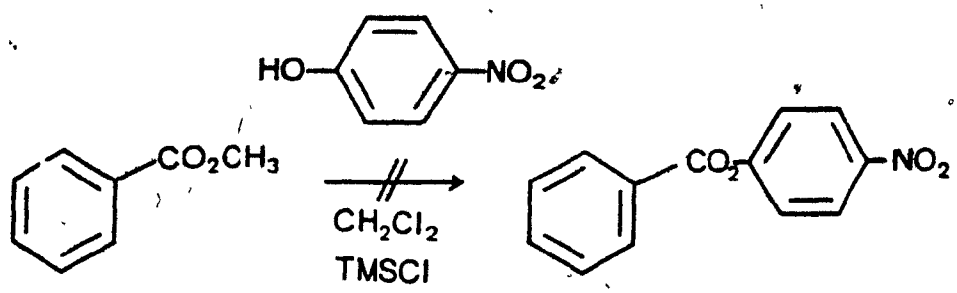
Scheme 2.37



Scheme 2.38



Scheme 2.39



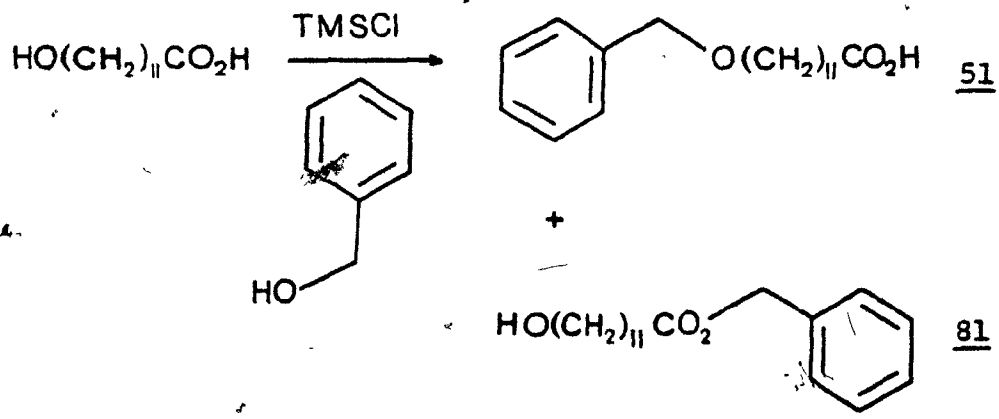
Scheme 2.40

The predictability of the results of transesterification is poor. Therefore, it appears not to have any general synthetic utility and can only be regarded as a curiosity.

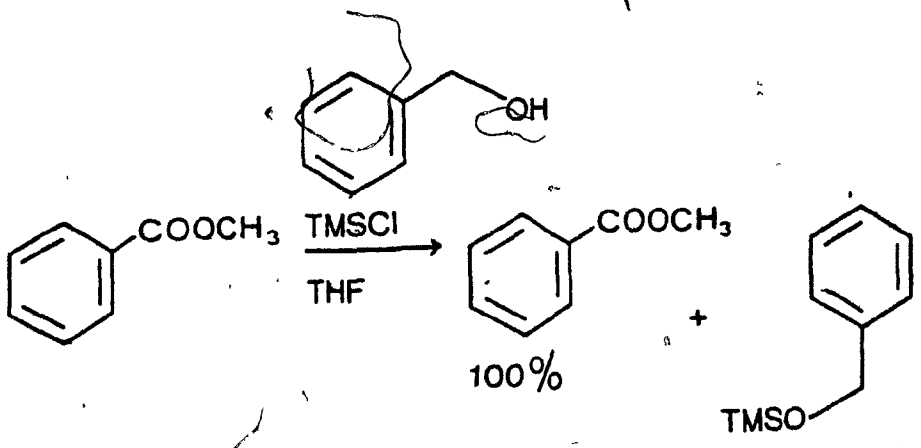
2.8.3 The Unusual Reactivity of Benzyl Alcohol

The reactivity of benzyl alcohol is different from the other alcohols used in esterification. In the esterification of 12-hydroxydodecanoic acid with benzyl alcohol, for example, both the ester (51) and ether (81) are formed in an inseparable mixture (Scheme 2.41). In addition, the attempted transesterification of methyl benzoate (39) in dry tetrahydrofuran gives after chromatography, none of the desired transesterified material, but gives instead, a mixture of the starting materials and benzyloxytrimethylsilane (82) (Scheme 2.42). As well, in an attempt to transesterify methyl phenylacetate (46) in pure benzyl alcohol, only the

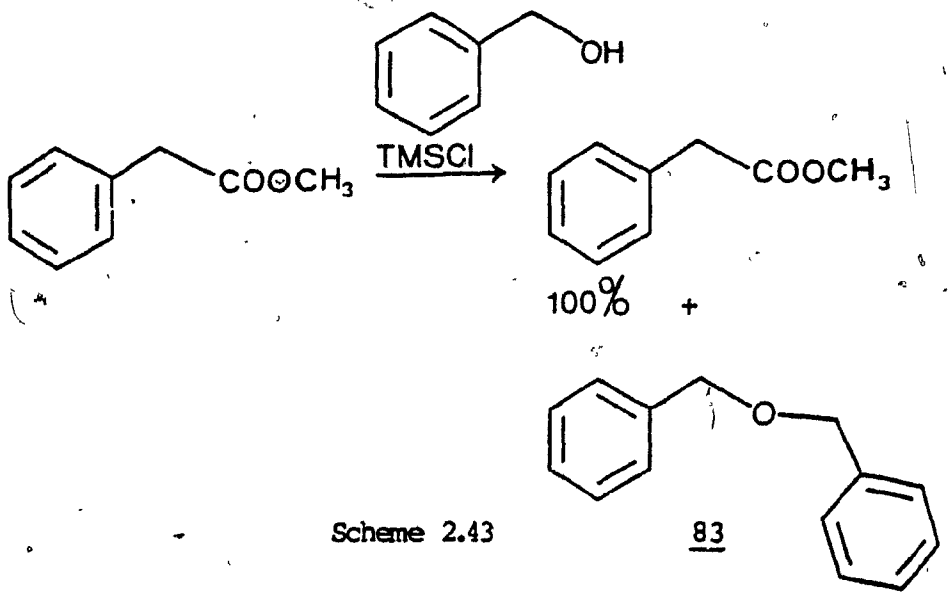
starting materials and benzyl ether (83) are isolated (Scheme 2.43).



Scheme 2.41



Scheme 2.42 82



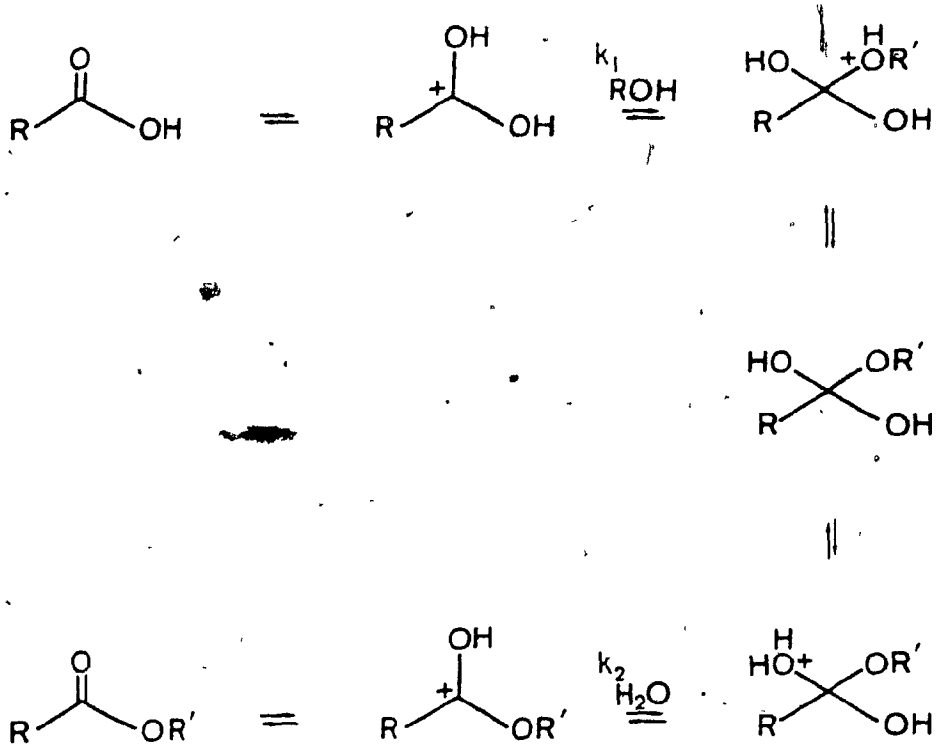
Scheme 2.43 83

This unusual facility for ether formation is not observed with other alcohols and might be ascribable to the stability of the benzylcarbonium ion.

2.9 THE MECHANISM OF ESTER FORMATION

2.9.1 Acid Catalyzed Ester Formation

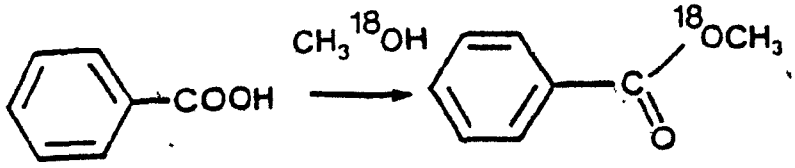
The fundamental features of the mecnanism of ester formation in mildly acidic conditions are strikingly similar to those of acetal formation. Unlike the acetal reaction, however, both ester hydrolysis and ester formation have been studied in great detail. The accepted mechanism, $A_{AC}2$, is outlined in Scheme 2.44[183].



Scheme 2.44

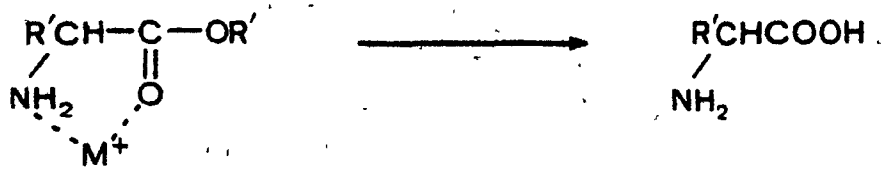
In either direction, the rate determining step is the nucleophilic addition of water (k_2, hydrolysis) or an alcohol (k_1, esterification) to a carbonium ion.

The main evidence supporting the addition-elimination mechanism is the result that ester hydrolysis is accompanied by carbonyl-oxygen exchange. This occurs in an acidic solution, and more rapidly, in basic solution[184]. In acidic media, the protonated form of the acid exists with the proton residing on the carbonyl rather than on the ether oxygen. This has been determined by both Infra-red[185], Raman[186] and ^{1}H-N.M.R. studies[187]. It is by the protonation of the carbonyl oxygen, whereby all distinction between the two oxygen atoms is lost, that isomerization can occur. In addition, it has been shown that cleavage takes place between the acyl carbon-oxygen bond rather than the alkyl carbon-oxygen bond. There is good evidence to support this. For example, the formation of methyl benzoate from $H^{18}OCH_3$ and benzoic acid gives the labelled ester (Scheme 2.45).



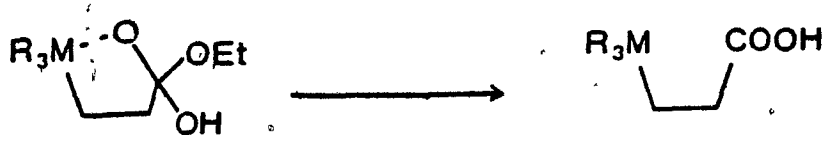
Scheme 2.45

Generally, the acidic hydrolysis or formation of esters are proton-catalyzed processes[188]. However, some exceptions to this are, the catalysis of ester hydrolysis which has been observed with Lewis acids intermolecularly[189,190,191] and by Group IV organometallic moieties intramolecularly. (Schemes 2.46 and 2.47)[192].



$M^+ = Cu^{2+}, Co^{2+}, Mn^{2+}, Ca^{2+}$.

Scheme 2.46



M = Si, Ge, Sn.

Scheme 2.47

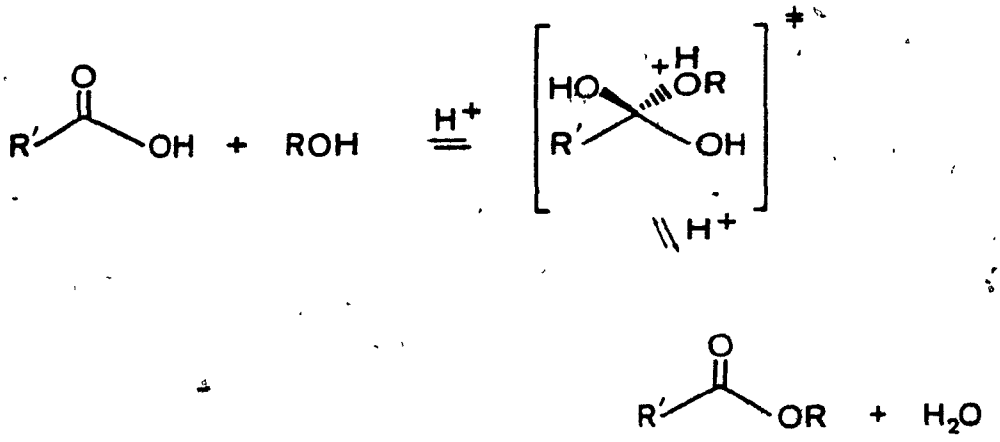
2.9.2 Factors Affecting the Rate of Ester Formation

The sensitivity of ester formation to polar groups adjacent to the acyl group is quite small. Essentially, any increase in rate of addition of the alcohol to the protonated intermediate, caused by electron withdrawing groups, is offset by the decrease in ease of protonation of the starting acid[193]. This is an important point, since the basicity both of esters and acids is relatively small. For example, the pK_a's of $C_6H_5C(OH)_2^+$ and $C_6H_5C(OH)(OCH_2CH_3)^+$ are -7.26[185] and -7.36[194], respectively.

Aromatic derivatives are generally much less reactive towards ester formation than the corresponding aliphatic compounds. This has been ascribed to the following effects; the stabilization of the initial state by delocalization and inductive electron-withdrawal by the ring[195]. In nonaromatic, conjugated carboxylic acids, lower rates of ester formation

are also observed due to a stabilization of the intermediate carbonium ion[196].

Steric effects are also extremely important in ester formation. An analysis of the transition state reveals two salient factors; the transition state is more crowded than the initial state because the central atom is close to tetrahedral, and more ordered because two molecules have combined to form one (Scheme 2.48)[197]. Therefore, the introduction of either a bulky acyl or alkyl group can dramatically increase the free energy of activation, and thus, decrease the rate of formation.



Scheme 2.47

Tables 2.7 and 2.8 give examples of the activation parameters for the formation of some selected esters. The separation of entropic and enthalpic contributions by a given group is not necessarily a simple procedure, as a group which has an effect on one usually alters the other as well. Generally, however, a bulky substituent close to the reaction centre will increase the non-bonded compression energy as the transition state is formed. This will cause an increase in $\Delta H^{\ddagger}$. At the same time, it will hinder the close approach of solvent molecules, thus minimizing

Table 2.7: Some Representative Activation Parameters For Methyl Ester Formation

Carboxylic Acid	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	Ref.
HCOOH	9.4	-27.5	199
CH_3COOH	9.4	-32.5	199
C_2H_5COOH	9.4	-33.9	199
$(CH_3)_3CCOOH$	10.8	-34.6	200
$C_6H_5CH_2COOH$	9.3	-34.5	201
$C_6H_5(CH_2)_4COOH$	9.3	-34.3	202
$C_6H_{11}COOH$	9.4	-35.7	200
$C_6H_{11}CH_2COOH$	9.9	-35.3	200
$C_6H_{11}(CH_2)_3COOH$	9.5	-33.8	200
C_6H_5COOH	15.4	-24.1	203
m-$CH_3C_6H_4COOH$	13.2	-29.8	204
p-$CH_3C_6H_4COOH$	13.8	-31.2	204

Table 2.8: Representative Activation Parameters for the Formation of Cyclohexyl Esters[205]

Substituent X in X-C_6H_4COOH	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
m-CH_3	19.4	-21.3
p-CH_3	17.9	-26.3
p-H_3CO	19.6	-22.4
o-H_3CO	17.8	-27.8
p-NO_2	18.0	-26.5
m-NO_2	17.7	-25.8
o-NO_2	16.8	-28.9
o-F	16.9	-28.3
p-Cl	17.7	-27.1
o-Cl	17.5	-27.6
o-Br	18.0	-26.5
o-I	17.0	-30.3

solvation. This steric inhibition of solvation will lead to a further increase in $\Delta H^{\ddagger}$, but as decreased solvation means less ordering of solvent molecules, a compensatory increase in $\Delta S^{\ddagger}$ will also be observed. Finally, a bulky substituent may block certain vibrational and rotational degrees of freedom, more in the transition state than the less crowded initial state, reducing $\Delta S^{\ddagger}$[198].

The principles described above are reflected in a comparison of the activation parameters for the formation of methyl acetate and methyl trimethylacetate. The increased steric bulk of the latter leads to a larger value for $\Delta H^{\ddagger}$ (9.4 and 10.8, respectively) and a correspondingly smaller value for $\Delta S^{\ddagger}$ (-32.5 and -34.6, respectively)[198,200]. The effects of steric bulk on $\Delta S^{\ddagger}$ can also be seen in the vast rate differences between the formation of methyl formate and metnyl acetate esters (Table 2.9).

Table 2.9:The Observed Rate of Formation of Methyl Esters in Methanolic HCl at 25°C ($l.mole^{-1}.sec^{-1}$)

Acid	$k_{obs} \times 10^2$	Ref.
HCOOH (in aq. HCl)	83.	199
CH_3COOH	5.93	199
CH_3CH_2COOH	5.73	199
$CH_3(CH_2)_4COOH$	2.92	199
$(CH_3)_3CCOOH$	0.194	200
$C_6H_{11}COOH$	1.18	202

In general, a polarity difference in substituents would be reflected in $\Delta H^{\ddagger}$. However, since the $\Delta H^{\ddagger}$'s for both transformations are the same (9.4, Table 2.7), the difference in the rate of formation is due entirely

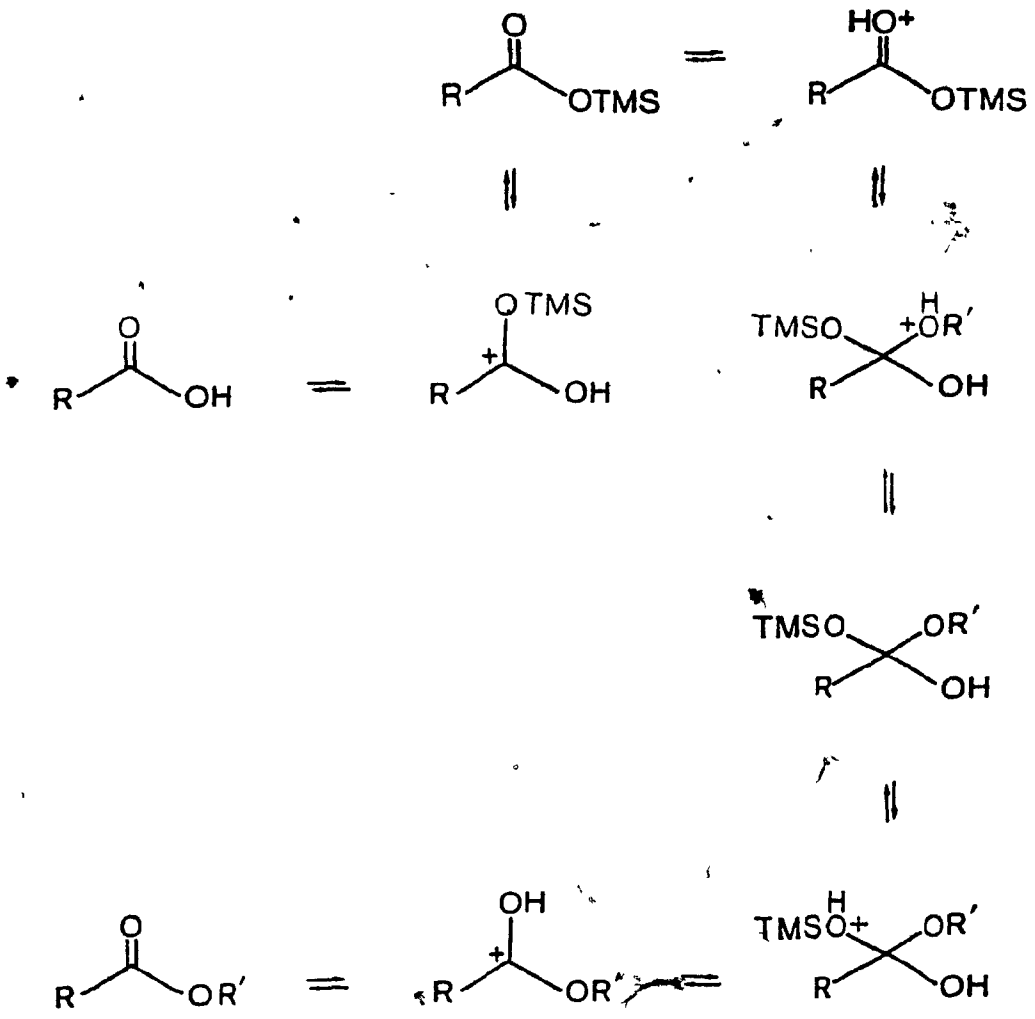
to changes in $\Delta S^{\ddagger}$[198,199] This decrease in $\Delta S^{\ddagger}$ (Table 2.7) increases with larger n-alkyl groups R' (in $R'CO_2$), until eventually a plateau is reached and is reflected in the rate of ester formation (Table 2.9)*. This must reflect the loss of degrees of freedom in the transition state with the increasing size of R'.

2.9.3 The Mechanism in the Presence of Chlorotrimethylsilane

The overall mechanism for ester formation in the presence of chlorotrimethylsilane most likely follows two different pathways. Although catalysis via the protonic route is probably also occurring to some extent*, the main pathway seems to be one in which the trimethylsilyl

* One can speculate that the protonic route is an active pathway based on the following stoichiometric considerations for the conversion of benzoylformic acid to its methyl ester. If the reaction is performed in methanol as the solvent and/or with 2 equivalents of trimethylchlorosilane, the reaction does not stop at the ester stage, but a mixture of the ester and the acetal-ester are isolated. To stop the reaction at the ester stage, 1.5 equivalents of trimethylsilyl chloride and 18 equivalents of methanol are reacted with the benzoylformic acid in tetrahydrofuran. However, two equivalents of chlorotrimethylsilane are required for the complete dehydration of one equivalent of water. If the silyl route is the sole mechanistic pathway followed, then 1.5 equivalents of chlorotrimethylsilane would allow a maximum isolated yield of 75%. Since the ester is isolated in 89% yield (Table 2.5), the protonic route must be followed to some extent.

group must play a role (Scheme 2.49). Proof for this postulation will be given below.



Scheme 2.49

To allow a comparison of the efficacy of the chlorotrimethylsilane procedure with that of the classical catalysis by hydrogen chloride and to provide evidence for the proposed silicon mechanism, the esterification of benzoic acid in methanol was followed by G.L.C.. In the former reaction procedure, 2 equivalents of trimethylchlorosilane, 1 equivalent of benzoic acid, and 95 equivalents of methanol are used. The latter reaction

procedure makes use of 2 equivalents of hydrogen chloride, 1 equivalent of benzoic acid, 1 equivalent of anhydrous $MgSO_4$ (which can adsorb 7 equivalents of water), and 95 equivalents of methanol. In both cases, the reactions are followed from time zero until 48 hours. A first-order plot of $\log(conc_{final}-conc_{init})$ *versus* time gives a straight line in both cases. The pseudo first-order rate constants are calculated to be 1.47×10^{-5} and 9.25×10^{-6} for chlorotrimethylsilane and hydrogen chloride reactions, respectively. The rate of the reaction with chlorotrimethylsilane is thus approximately 35% faster than the classical catalysis by hydrogen chloride under the conditions described.

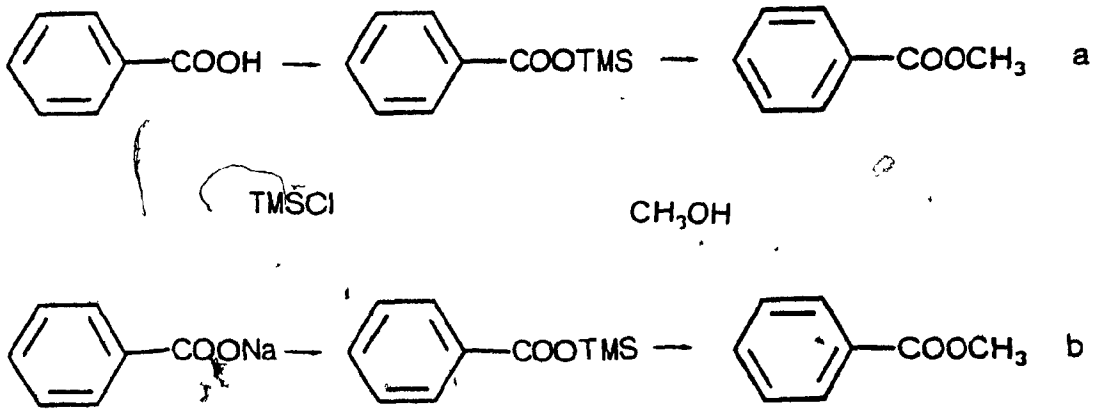
Further information supporting the proposed silicon mechanism also arises from this study. In the reaction catalyzed by hydrogen chloride, only methyl benzoate and the solvent are detected* by the G.L.C.. However, in the reaction promoted by chlorotrimethylsilane, a third peak of longer retention time than either chlorotrimethylsilane or methyl benzoate appears at a faster rate than does the methyl benzoate peak and disappears completely within 3 hours. It is reasonable to assume that this corresponds to trimethylsilyl benzoate, the intermediate in the reaction.

This postulation of the formation of a silyl ester intermediate is corroborated by the isolation of the trimethylsilyl ester of 12-hydroxydodecanoic acid (*vide infra*). In addition, although ^{1}H-N.M.R. spectroscopy is not particularly revealing with respect to the mechanism, ^{29}Si-N.M.R., using the INEPT pulse sequence (see Appendix 2) clearly

* Chlorotrimethylsilane eluted from the G.L.C. column with the same retention time as the solvent.

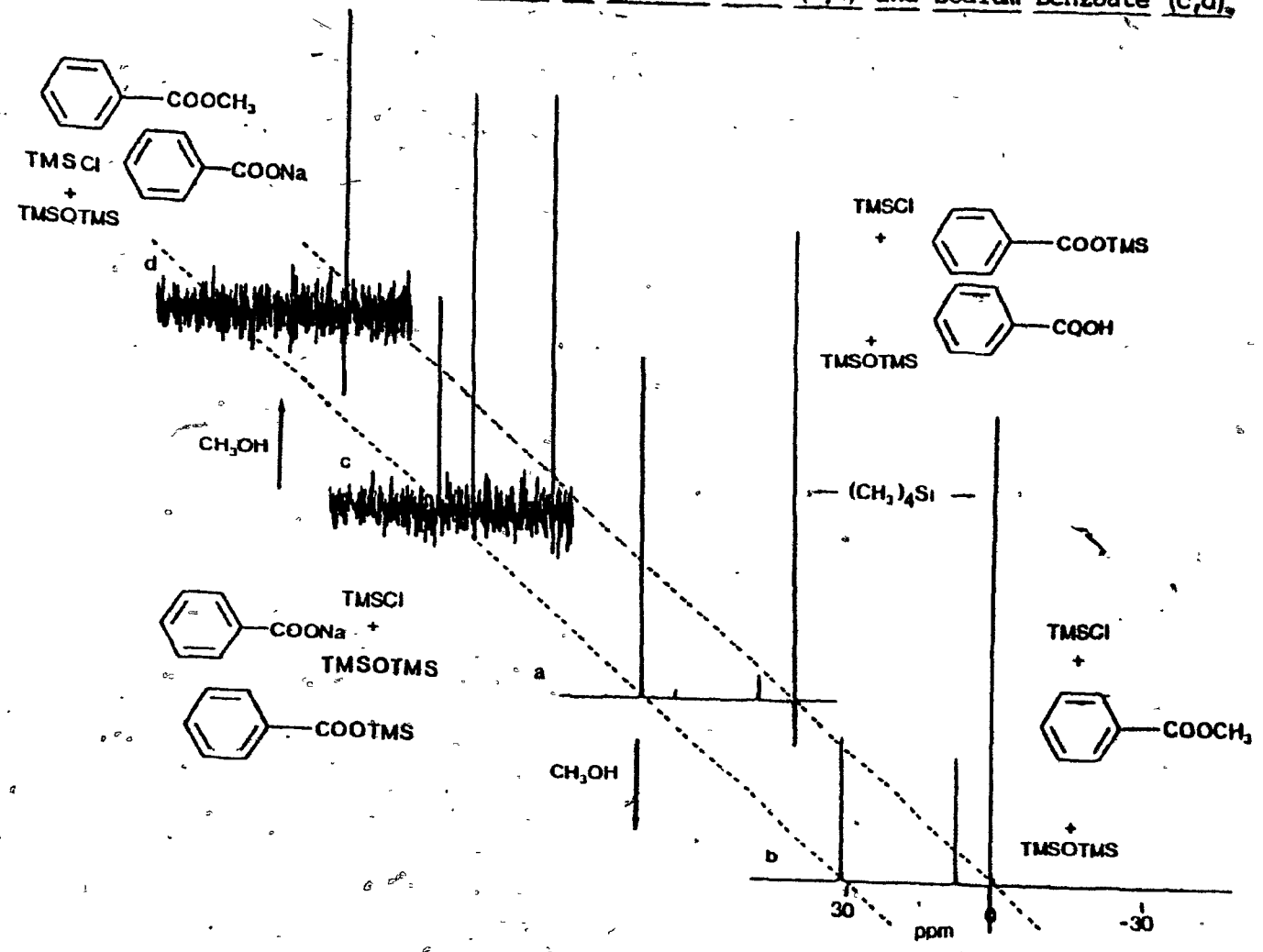
illustrates the pathway which the reaction follows. A mixture of benzoic acid and chlorotrimethylsilane displays, in the ^{29}Si-N.M.R. spectrum, three peaks; one at 31.1 ppm (trimethylchlorosilane), one at 24.4 ppm (trimethylsilyl benzoate) and a small peak at 7.1 ppm corresponding to hexamethyldisiloxane, indicating the presence of some water in the reaction mixture (Figure 2.1a). Upon the addition of methanol, the benzoate peak collapses, the trimethylsilyl chloride peak decreases in intensity (Figure 2.1b) and there is a substantial increase in the intensity of the peak observed at 7.1 ppm, the silicon end product, hexamethyldisiloxane (Scheme 2.50a).

To confirm the assignments of these peaks, a similar experiment was carried out with sodium benzoate. This clearly, if reacting at all with chlorotrimethylsilane, will form the silyl ester (Scheme 2.50b). A very large silyl ester peak (Figure 2.1c) is again observed to collapse upon the addition of methanol (Figure 2.1d). ^{1}H-N.M.R. analysis shows that the reaction product is methyl benzoate in both cases. This further supports the proposed mechanistic scheme (Scheme 2.49).



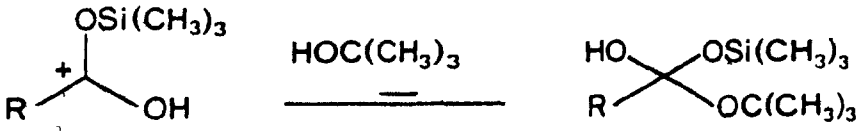
Scheme 2.50

INEPT ^{29}Si-N.M.R Spectra of the Esterification of Benzoic Acid (a,b) and Sodium Benzoate (c,d).



2.9.4 Factors Affecting the Formation of Esters with Chlorotrimethylsilane

The failure to form *t*-butyl esters in the presence of trimethylchlorosilane is easily explained. These esters are usually made with *iso*-butylene, rather than *t*-butanol under acidic conditions[206], ($A_{AC}1$) because the steric bulk of the *t*-butyl group in *t*-butanol prohibits its attack upon the carbonium ion ($A_{AC}2$). This problem would only be exacerbated by the presence of the trimethylsilyl group which would add considerably to the steric bulk of both the initial and transition states (Scheme 2.51). In addition, and perhaps more importantly, the esterification reaction would be in competition with the facile elimination of water from the *t*-butanol, and therefore, prohibit this reaction from taking place.



Scheme 2.51

In examples where the electron density on the alcoholic oxygen is lowered (Table 2.10), polar effects become quite important and the corresponding equilibrium lies further to the side of the carboxylic acid. The steric bulk of 2,2,2-trichloroethanol, for example, is comparable to that of β-trimethylsilylethanol and yet after several experiments with chlorotrimethylsilane under different conditions, no indication of the formation of an ester from the former alcohol is observed. Esters from the latter alcohol form quite readily. It must be concluded, therefore, in the case of electron poor alcohols such as 2,2,2-trichloroethanol, that the equilibrium in the presence of trimethylchlorosilane is insufficient

to allow the formation of detectable amounts of the ester.

Table 2.10:Equilibrium Constants for the Esterification of Acetic Acid[207]

R in CH_3CO_2R	K(mol/L)	ΔG^{o} *
CH_2CH_3	3.38	1660
$CH_2CH_2OCH_3$	1.42	2180
CH_2CH_2Cl	0.46	2840
$CH_2CH_2N^{+}(CH_3)_3$	0.394	2940
CH_2CF_3	0.013	4980

* The activity of water is taken as unity.

2.10 THE ACTIVATION OF CARBOXYLIC ACIDS

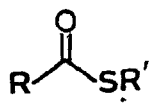
Other transformations take place at a carboxyl group which are technically esterifications, but in reality, however, are achieving quite a different purpose. Rather than protection, the carboxyl group is being activated to nucleophilic attack. The predominant use of this activation is to encourage either lactonization or the formation of an amide, especially peptides. Lactonization in particular is a difficult synthetic challenge. As there exists a large group of interesting natural products which have in common a macrocyclic lactone structure, there is a tangible interest in finding facile procedures for lactonization. Although the formation of medium-large ring lactones from the corresponding ω-hydroxy-carboxylic acids is not favoured entropically, it is often the most direct route, and therefore, the synthesis of many interesting macrocyclic compounds, such as methymycin[208,209,210], have as the ultimate step, lactonization to form the macrolide.

It is possible to synthesize small ring lactones utilizing trimethyl-

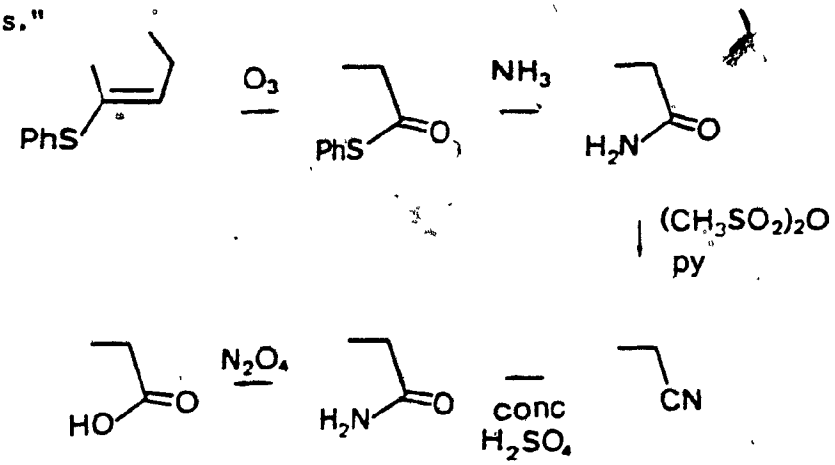
silyl chloride. For example, chlorotrimethylsilane can be used to promote the transformation of γ-hydroxybutyric acid (84) to γ-butyrolactone (85), although this conversion is not particularly challenging. Even under vigourous conditions, however, ω-hydroxy acids are not transformed into the corresponding macrolactones. For example, if 12-hydroxydodecanoic acid is refluxed with 15 equivalents of trimethylchlorosilane in anhydrous tetrahydrofuran, the only isolated products are the carboxylic acid and the trimethylsilyl 12-hydroxydodecanoate (86). Therefore, other procedures to activate the carboxyl group to nucleophilic attack must be deployed.

Both lactones and amides, can be successfully made from thioesters*. These compounds are much more reactive to nucleophiles than the corresponding oxygen esters[211], and therefore, have great synthetic utility. The following passage, written by Haslem[171], accurately depicts the establishment and importance of this area of organic chemistry.

> " Each era in the history of organic chemistry has been marked by developments which because of their originality and timeliness have had a substantial influence on subsequent research. One such masterpiece in recent times was the cobyric acid synthesis of Woodward and Eschenmoser[212]. One facet of the work of some considerable interest is the generation of the carboxyl group at position "f" in the corrin nucleus. The procedure adopted by Woodward and Eschenmoser utilises at an

* Thioesters, in the context of this thesis refer to thiol or thiolo esters, that is, esters of the form; 

early stage a phenyl thioester and exploits its enhanced reactivity towards ammonia when compared to oxygen esters, (Scheme 2.52). This work has heralded a period of unparalleled activity in which the synthetic potentialities of the thiol ester group have excited considerable interest. The use of thiol esters to selectively activate a carboxyl group towards esterification or lactonization has engendered numerous investigations and work in this area has gained particular prominence. One outcome of these developments has been the renewed attention directed generally towards thiol ester synthesis."



Scheme 2.52

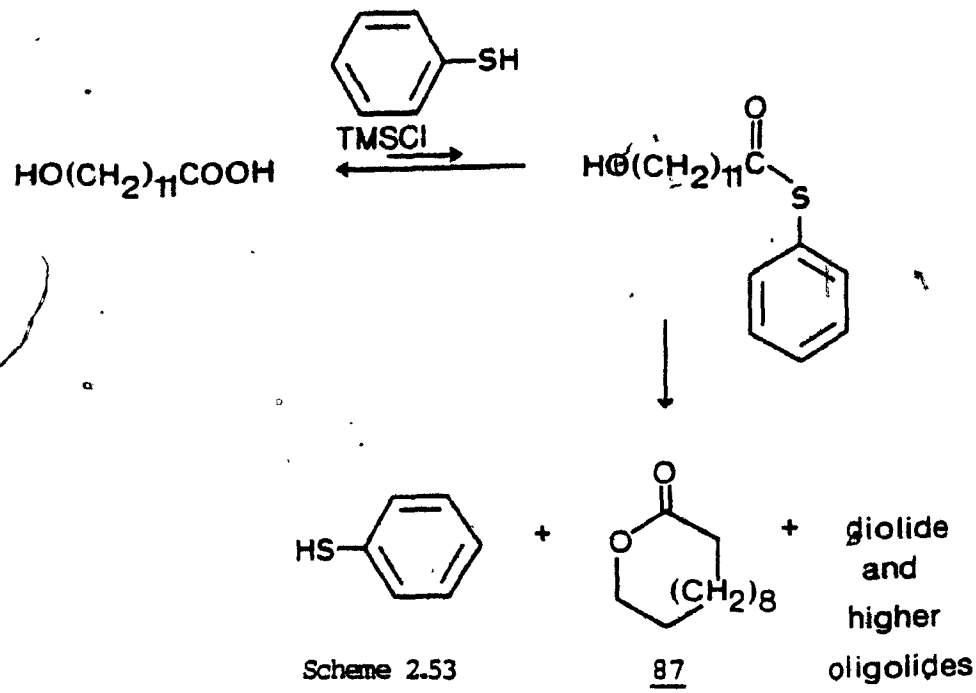
In light of the significance of thioesters in lactone formation, it was of interest to discover if trimethylchlorosilane could promote these reactions.

Thioesters may be synthesized by the exchange of a mercaptan with carboxylic esters or other carboxylic acid derivatives under equilibrating conditions[171]. However, they are not generally formed directly from carboxylic acids[213]. The equilibrium usually lies far enough to the left

as to leave the desired product inaccessible, even under vigourous conditions. The same result is observed using trimethylchlorosilane. The reaction of benzoic acid with thiophenol or benzylmercaptan in the presence of trimethylchlorosilane does not proceed, and yields only recovered starting materials. As was discovered in the case of acetalization, aromatic compounds are considerably less reactive than aliphatic compounds. Therefore, the reaction with sebacic acid (1,10-decanedioic acid) was expected to be more facile. Unfortunately, under the same conditions, none of the desired thioester is recovered.

One interesting example which indicates thioesters may be formed, even though they do not appear amenable to isolation, is the reaction of 12-hydroxydodecanoic acid with thiophenol in the presence of chlorotrimethylsilane. A remarkable observation is that the ^{1}H-N.M.R. and infra-red spectra of each of the compounds isolated after purification are identical. These compounds have been subsequently identified to be the macrolide (87), diolide (88), and higher oligolides, which are the result of the lactonization of the starting material. Unfortunately, when the reaction is repeated under conditions of very high dilution, the macrolide itself can not be solely formed. In fact, under high dilution only the starting materials are isolated. To verify the identity of these compounds, the authentic 13 membered macrolide (87) was prepared both by a slight modification of the procedure of Stoll and Rouve[214] using *p*-toluenesulfonic acid in toluene and by the *m*-chloroperbenzoic acid oxidation of cyclododecanone[215].

Although no mechanistic study was performed, it is anticipated that the reaction sequence is that shown below (Scheme 2.53).



Scheme 2.53 87

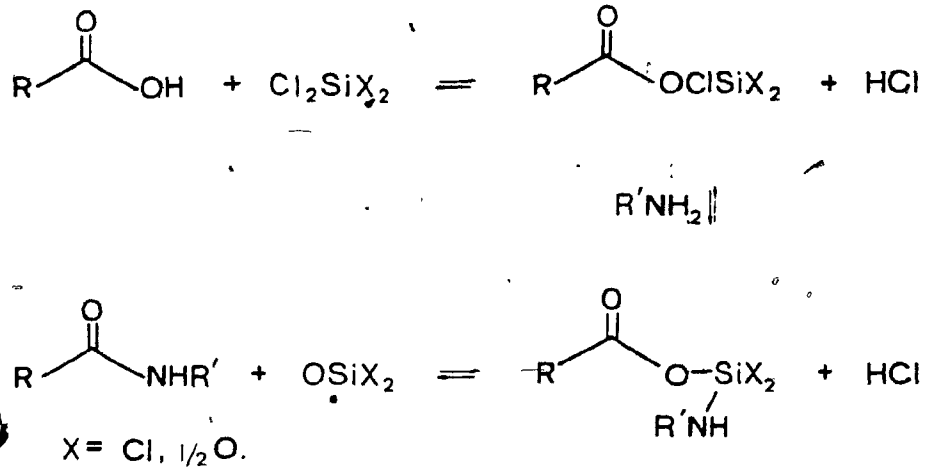
Under conditions of high concentration, traces of the thioester are formed and subsequently trapped in an intra- or inter-molecular fashion to give the macrolide or dodecanoate esters, which can subsequently lactonize. At lower concentrations, no lactones or esters are observed, indicating that any thioester formed reverted to the carboxylic acid or silyl ester before it could be trapped by an hydroxyl group. Thioesters (*vide supra*) are not easily formed from carboxylic acids and a mercaptan. The experimental results suggest, therefore, that silyl esters may be more reactive, albeit marginally, than the corresponding carboxylic acids. That is, in the presence of chlorotrimethylsilane, the thioester and subsequently the macrolide can be formed under conditions of high concentration.

If traces of the thioester were formed under these conditions, it was hoped that they could be trapped by less reactive alcohols in a manner similar to macrolide formation. However, in 2,2,2-trichloroethanol, for example, none of the desired 2,2,2-trichloroethyl phenylacetate can be detected upon the reaction of phenylacetic acid with thiophenol and

chlorotrimethylsilane. A variety of other carboxylic acids were similarly unreactive to ester formation. Either the more labile thioester never forms, the equilibrium lies very far to the side of the carboxylic acid, or the nucleophilicity of these alcohols is so low as to preclude transesterification under these conditions. This method, therefore, does not appear to provide a useful synthetic route to less stable esters.

2.11 ESTERIFICATION PROMOTED BY SILICON TETRACHLORIDE

Wong has utilized tetrachlorosilane in the synthesis of amides from amines and carboxylic acids[216]. It was determined that silicon tetrachloride is acting as a coupling reagent by forming bonds with both species. The intermediate then undergoes elimination to form the amide and one-half equivalent of "dichlorosilicon oxide", which is recycled, and subsequently forms SiO_2 (Scheme 2.54).

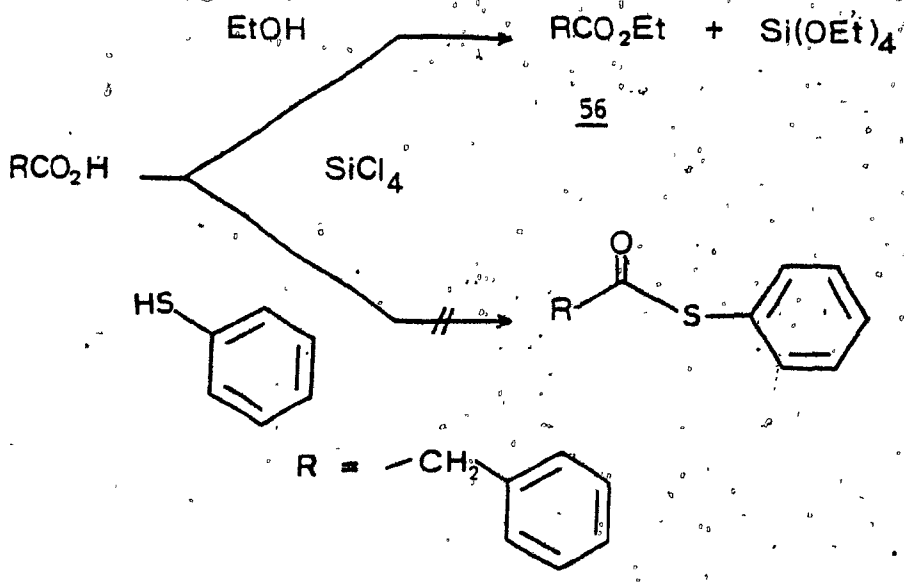


Scheme 2.54

The use of this technique as a procedure for esterification had not been

previously attempted. Since silicon tetrachloride is generally more reactive than chlorotrimethylsilane, it was predicted that the reaction would be more facile. In one example phenylacetic acid is rapidly converted to its ethyl ester (56) by the use of this reagent. However, the corresponding silicon product is not the expected silica, but rather, tetraethoxysilane (Scheme 2.55). The reaction may, therefore, be following a different pathway than the amide formation described above.

In the hope of capitalizing on the reactivity of this reagent, the synthesis of the thiobenzyl ester of phenylacetic acid has been attempted. Unfortunately, none of the ester is obtained from benzyl thiol (Scheme 2.55). Under the conditions used, it must be concluded that the reactivity of this reagent towards the promotion of esterification is not significantly greater than chlorotrimethylsilane.



Scheme 2.55

2.12 PHOSPHOROUS ESTERS

Esterification is not, of course, a procedure limited to the reaction of carboxylic acids and alcohols. Other hydroxyl groups, such as those in phosphorous and phosphonic acid compounds, also require protection as "esters". In consideration of the dramatic advances in the synthesis of nucleotides, for example, the recent total synthesis of transfer-RNA[217], techniques for the protection and deprotection of phosphorous bound hydroxyl groups are of fundamental interest. Phosphorous bound methyl esters have not, as yet, been exploited to their fullest capacity. However, this protecting group appears to offer real potential in the future as a result of its ease of formation, stability to the conditions employed for nucleotide synthesis and ease of removal[218,219,220]. The small size of the group can also be used to good advantage in both synthetic and biological testing procedures[221].

It was of interest to discover if trimethylchlorosilane could promote the formation of methyl phosphorous esters. Unfortunately, both phenylphosphonic acid and diphenyl phosphate prove to be completely resistant to methyl ester formation using methanol and chlorotrimethylsilane. In either case, only the starting materials are recovered. When diethyl phosphate is reacted under similar conditions, a complex mixture of products is isolated.

2.13 CONCLUSION

Chlorotrimethylsilane is a particularly suitable reagent for the formation of esters and acetals. While literally dozens of methods are known to effect acetal formation, few offer the advantages of low cost, simple work-up, and mild reaction conditions which the reaction with

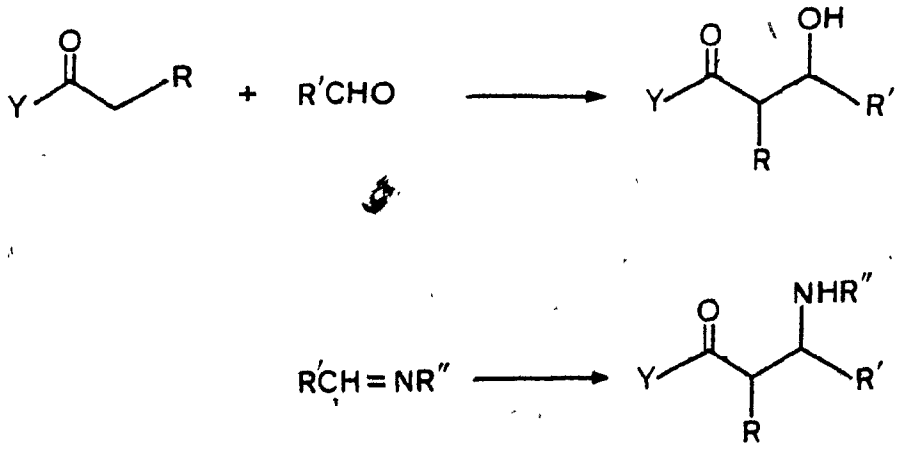
trimethylchlorosilane exhibits. Of particular interest is the selectivity that the acetalization with chlorotrimethylsilane displays; chemoselectivity for methyl acetals from activated carbonyl groups and regioselectivity for kinetic products at low temperature, or thermodynamic products at elevated temperatures, in the synthesis of cyclic acetals from butanetriol. With the formation of esters, there are some limitations. Electron poor alcohols and bulky alcohols are unreactive, as are phosphonic and phosphoric acids. The esterification procedure with chlorotrimethylsilane, however, also offers the advantages over traditional methodology of a simple reaction work-up and an inexpensive reagent. In addition, the reaction proceeds at a rapid rate, and allows the formation of the majority of synthetically useful esters viz. the methyl, ethyl, benzyl, and 2-trimethylsilylethyl esters. Moreover, the reaction conditions are quite mild. For instance, N-carbobenzoxyglycine reportedly reacts to form the allyl and crotyl esters in good yield without cleavage of the protecting group[332]. Perhaps the most impressive example of the utility of this method is the synthesis of methyl 6-aminopenicillanoate. This compound can be made in five minutes and in good yield without scission of the β-lactam bond.

3. THE REACTION OF A *bis*-SILYL ENOL ETHER WITH 1,2-DIELECTROPHILES

3.1 CARBON-CARBON BOND-FORMING REACTIONS

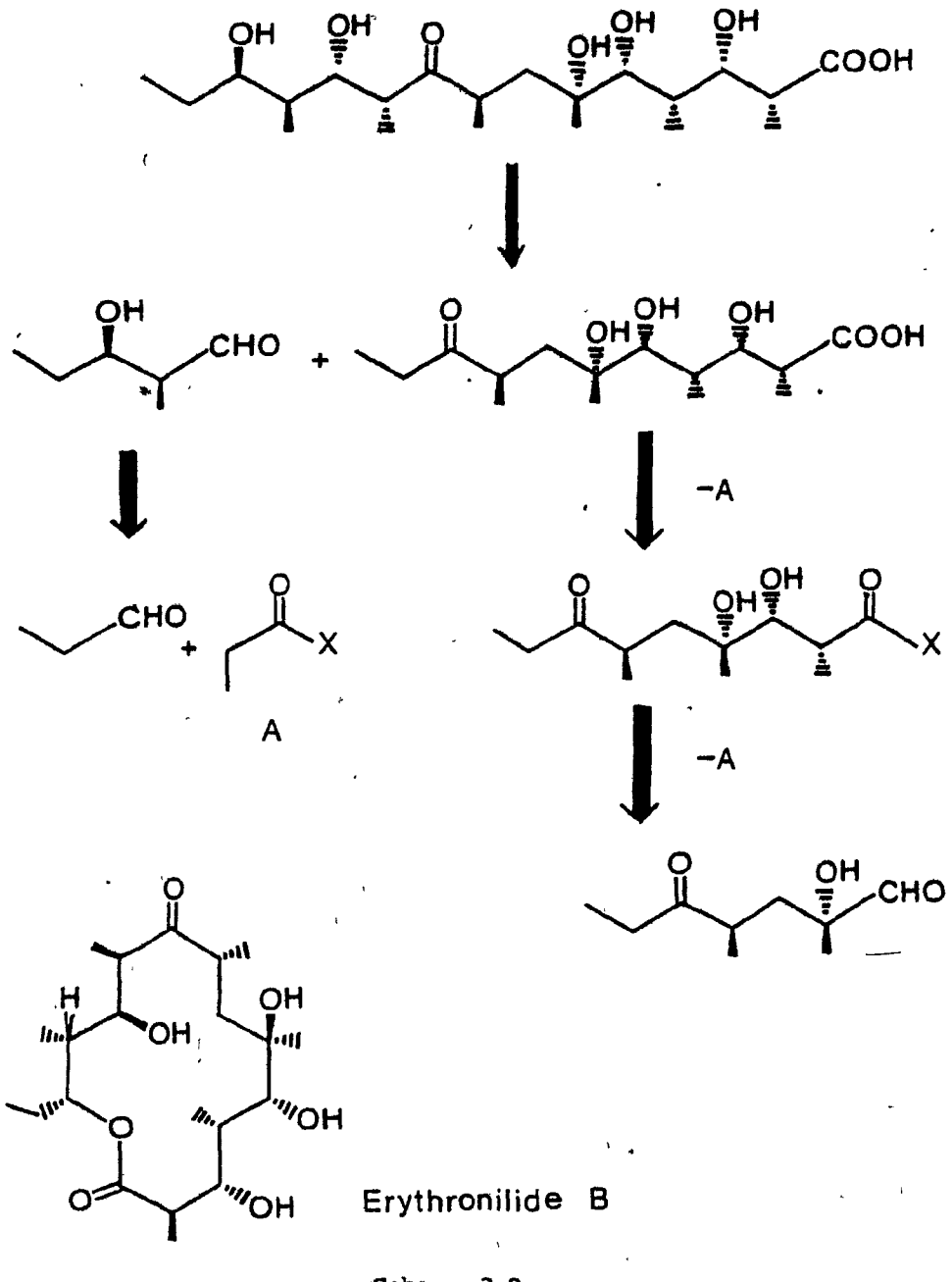
3.1.1 The Aldol Reaction

The aldol reaction, along with the related variant using a Schiff base (Scheme 3.1), is among the oldest classes of reactions in organic chemistry. It is well recognized as the most obvious means for bond creation leading to 1,3-O,O and 1,3-N,O heteroatom-heteroatom relationships in organic molecules.



Scheme 3.1

In addition, the aldol process constitutes one of the fundamental routes for carbon-carbon biosynthetic bond formation. As a result, much interest has evolved in optimizing the aldol reaction for use in synthetic organic procedures, especially in "biomimetic" syntheses. As an illustration, a retrobiosynthetic analysis of the erythronilide-B seco acid (Scheme 3.2) indicates how extensively the aldol process could be followed in the assembly of this molecule[240].

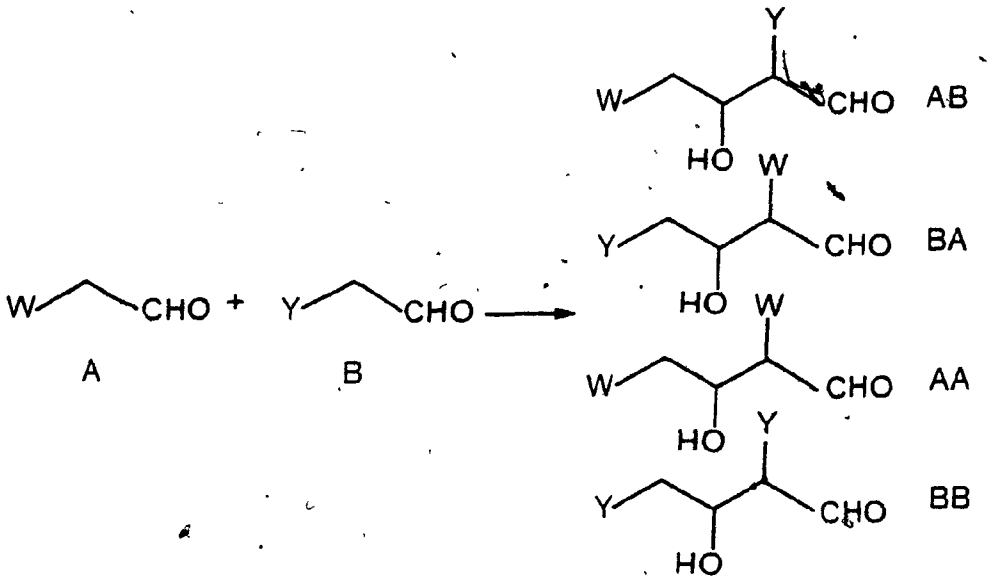


Erythronilide B

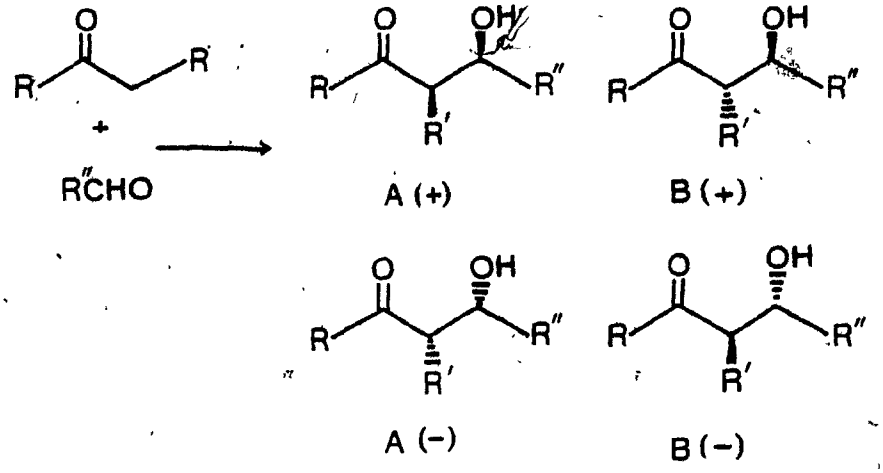
Scheme 3.2

There are many problems which arise in the utilization of the aldol reaction, although satisfactory solutions have been found for many of them. The more prominent difficulties are: (i) cross-coupling if two aldehydes are to be reacted together; that is, the reaction of A and B under aldol conditions generally results in the formation of all four

possible products, AA, AB, BA and BB (Scheme 3.3) (this problem does not arise if one of the components is a ketone), (ii) polymerization by a multiple aldol process, (iii) regioselectivity; when the enolate of a ketone is used, regioselection between the thermodynamic and kinetic enolate must be encouraged (this can usually be controlled by careful temperature regulation), and the most challenging problems, (iv) diastereoselection; assuming isolation of a single regioisomer is possible, it is then necessary to be able to select a single diastereomer from the two that can be formed (A($\pm$) *versus* B($\pm$) Scheme 3.4) and (v) enantioselection; the ability to control the absolute stereochemistry of a given diastereomer (A(+) *versus* A(-) and B(+) *versus* B(-) Scheme 3.4).



Scheme 3.3



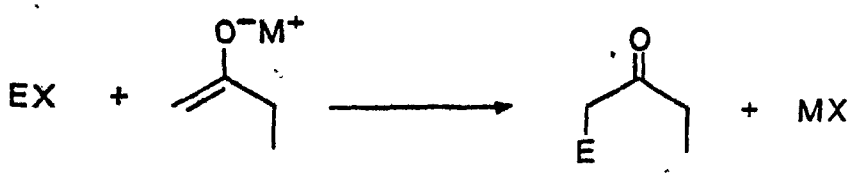
Scheme 3.4

The latter problem has been the focus of intensive research and has been recently reviewed[240].

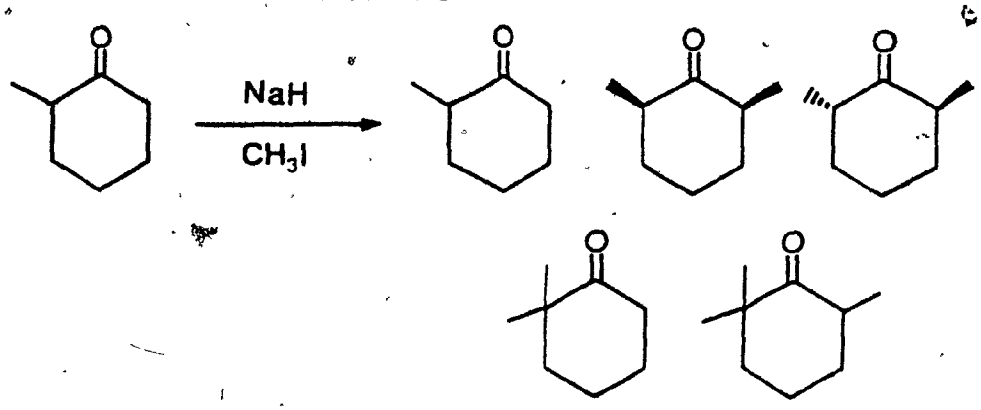
3.1.2 α-Alkylation

Another fundamental organic reaction for the formation of carbon-carbon bonds is the α-alkylation of carbonyl groups. In the case of these related "aldol-like" alkylation reactions (Scheme 3.5)*, problems also arise. The most important of these are: (i) the possibility of multiple alkylation occurring (Scheme 3.6)[241], (ii) the limited range of electrophilic components which can be used; these being limited, in general, to primary and some secondary alkyl halides or alkyl pseudo-halides, (iii) the occurrence of O-alkylation in place of C-alkylation, (iv) the possibility of competing aldol reactions, and (v) the non-regiospecific alkylation of an enolate[242].

* For the purposes of this thesis, the α-alkylation of carbonyl groups will be considered to be a special case of the aldol reaction.

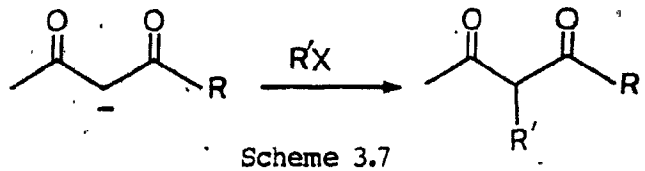


Scheme 3.5

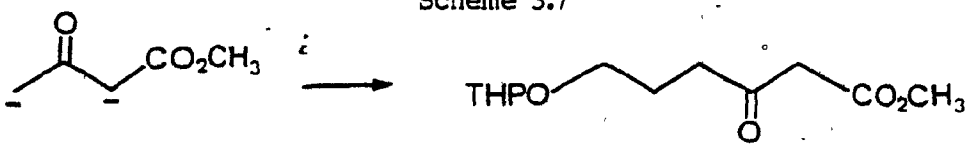


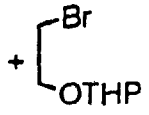
Scheme 3.6

As a result of all of these complications, the simplest procedure for alkylations of this type, treating the mixture of the carbonyl group and the group to be alkylated with a strong base, is rarely useful. The traditional solution is the use of β-dicarbonyl compounds (Scheme 3.7) which are less likely to give polyalkylation and specifically alkylate at the position between the two carbonyl groups[243]. A recent modification which also eliminates these problems entails the use of the dianion of β-keto esters[244]. In this case, the alkylation takes place specifically at the terminal anion (Scheme 3.8).



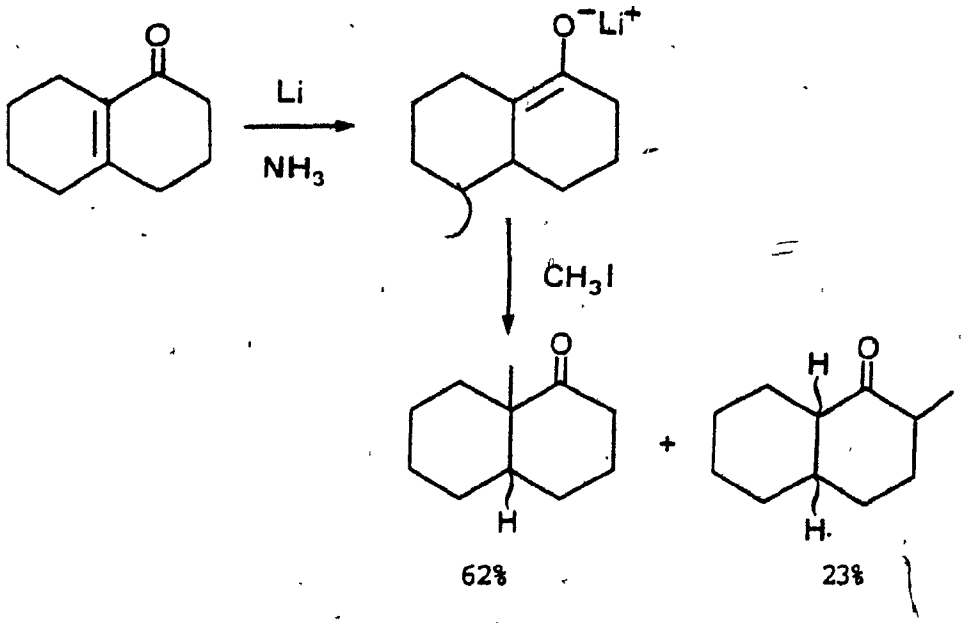
Scheme 3.7





Scheme 3.8

Several other approaches to solving these problems have been sought. Stork, having found enamines a useful but limited alternative to enolates, discovered that lithium enolates behave in a more predictable and less reactive fashion than the corresponding sodium or potassium enolates. For example, the particularly hindered enolate 91 (Scheme 3.9) is methylated to give mainly the more substituted product[245].



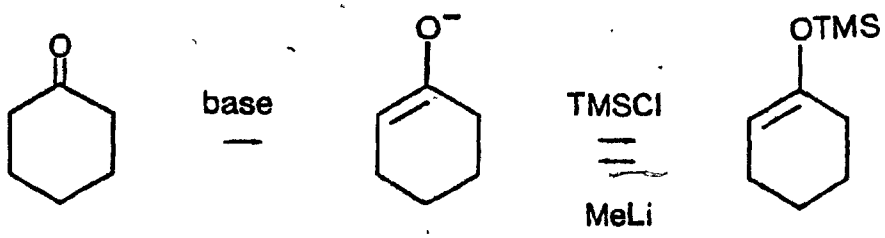
Scheme 3.9

Other less electropositive metals, like magnesium[246] and zinc[247], have also been used as enolate counterions. They give excellent results when used for controlled aldol reactions, as in the Reformatsky reaction, but usually are insufficiently reactive to allow simple alkylations to take place.

3.2 THE DEVELOPMENT OF ENOL SILYL ETHERS

Although lithium appeared to be the most useful enolate counterion, a

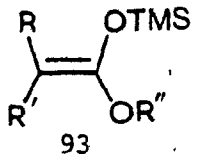
facile procedure for its introduction under non-equilibrating conditions remained elusive. It was Stork who found an appropriate means for the generation of lithium enolates from enol silyl ethers (Scheme 3.10)[27,28,248].



Scheme 3.10

In a historical context, compounds of the type 92 have been known since 1958[249]. In the last decade there has been an explosive development in the utilization of enol silyl ethers in organic synthetic transformations. Indeed, it is clear that these have been employed more often then any other organosilicon species in recent years[248], with the exception, perhaps, of silicon-based protecting groups. Three phases in the development of silyl enol ether chemistry have been noted[250]. These are: (i) the capture of enolates by silylation, isolation of the silyl enol ethers thus formed, and regeneration of the enolates to react with electrophiles under basic conditions, (ii) the reaction of silyl enol ethers directly with electrophiles under neutral or acidic (Lewis acid-catalyzed) conditions, and (iii) the use of enol silyl ethers to give products different from those obtained via the "enolate" or "enol" phases above. It is also appropriate to mention silyl ketene acetals at this juncture (silylated ester enolates 93). Their modes of reactivity are very similar to those of enol silyl ethers, making them useful synthetic

alternatives to ester enolates.

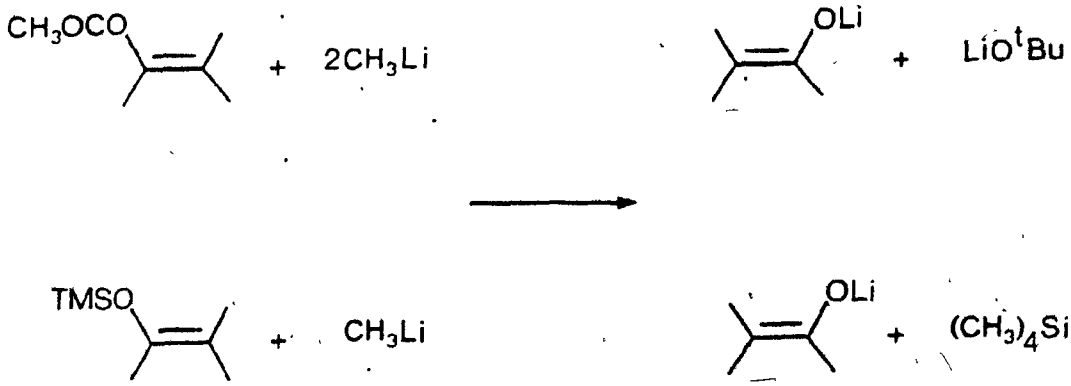


93

The use of silyl enol ethers for the formation of cyclic systems will be described shortly. In order to facilitate an understanding of the reactivity of these compounds, an outline will be given of the relevant reactions which they undergo. These will be divided into two sections; the reactions of silyl enol ethers under basic conditions (as enolates), and those under neutral and acidic conditions*.

3.3 GENERATION OF REGIOSPECIFIC ENOLATES FOR α-ALKYLATION

Traditional methods of regiospecific lithium enolate formation make use of the reaction of enol acetates with methyl lithium (Scheme 3.11)[254]. Unsatisfactory results are often observed due to the presence of the lithium *t*-butoxide formed in the reaction.

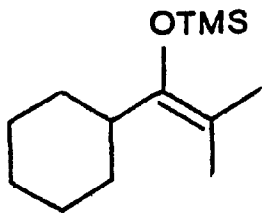
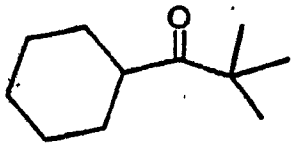
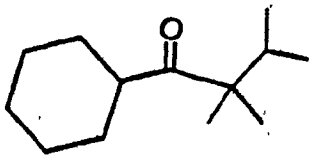
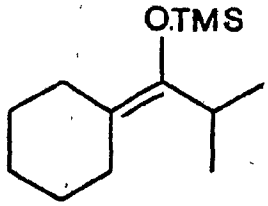
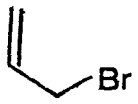
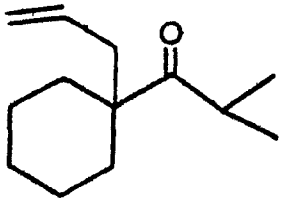


Scheme 3.11

* The syntheses of silyl enol ethers will not be discussed as they have been reviewed elsewhere[251,252,253].

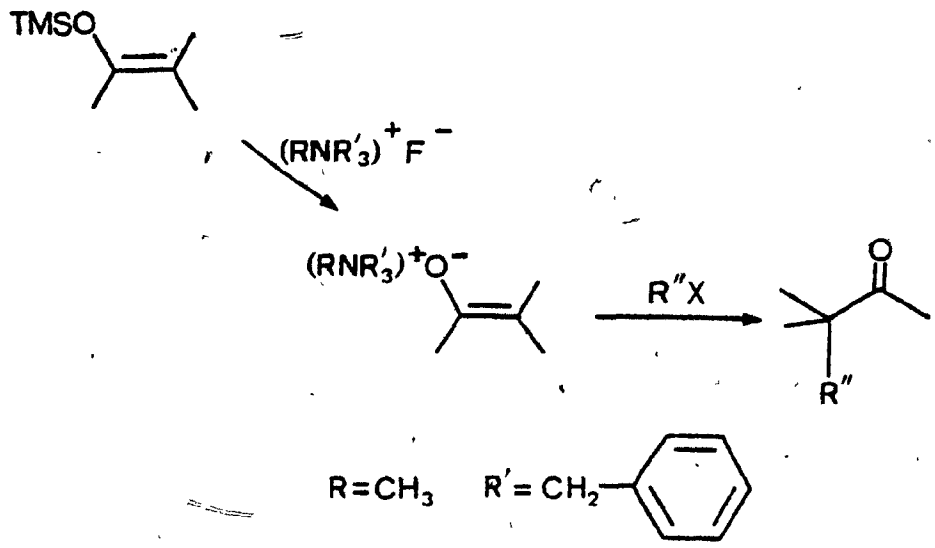
This contrasts with the case of enol silyl ethers with which the innocuous tetramethylsilane is produced (Scheme 3.11)[27,28,255]. Under the conditions used, tetramethylsilane does not exchange its hydrogen atoms, and moreover, can be used as an internal standard for ^{1}H-N.M.R. spectroscopic characterization of the reaction. These enolates can be reacted with primary, and some secondary alkyl halides and activated halogen compounds[256]. They will also undergo Michael-type alkylations with appropriately substituted vinyl ketones (Table 3.1)[257,258].

Table 3.1: Alkylations of Directed Lithium Enolates

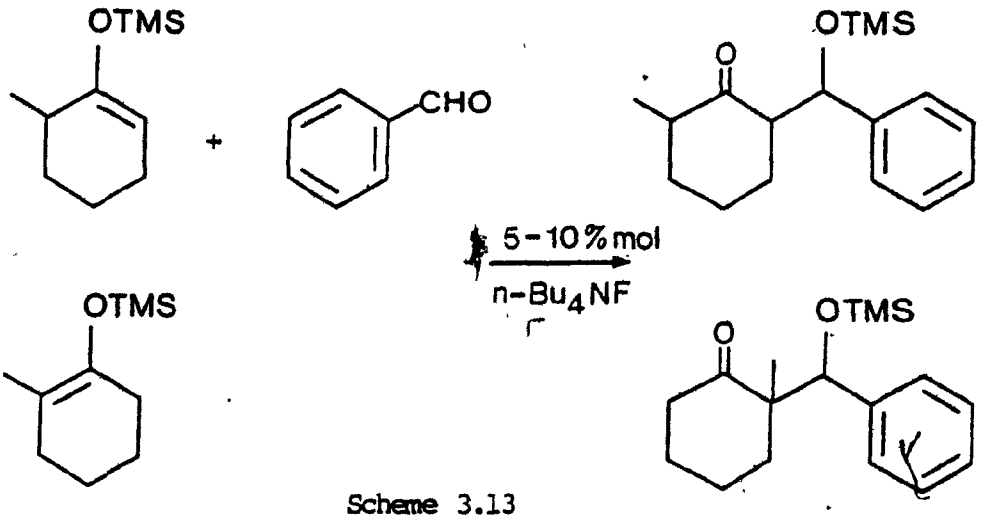
Silyl Enol Ether	Alkylating Agent	Product	Yield(%)[256]
	CH_3I		96
	$(CH_3)_2CHI$		82
			87

Lithium enolates are particularly useful when the carbonyl group is to be alkylated at the more substituted α-position (thermodynamic

enolate). When it is the less substituted α-position which is to be alkylated (kinetic enolate), the quaternary ammonium counterion gives better results[259]. Quaternary ammonium enolates are not easily accessible from enol acetates. However, because of the strong Si-F bond and the ready availability of quaternary ammonium fluoride salts, such as n-Bu_4F, these reactive intermediates are easily obtainable from silyl enol ethers (Scheme 3.12 and 3.13)[260].

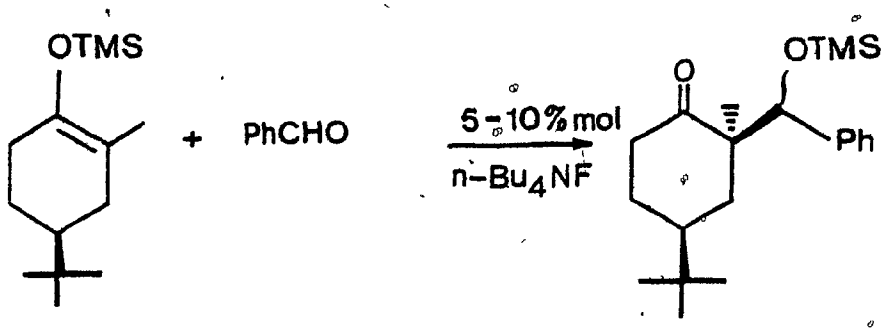


Scheme 3.12



Scheme 3.13

This latter reaction also shows high stereoselectivity; in one example, only the product derived from axial attack of the cyclic silyl enol ether is observed (Scheme 3.14)[262,263,264].

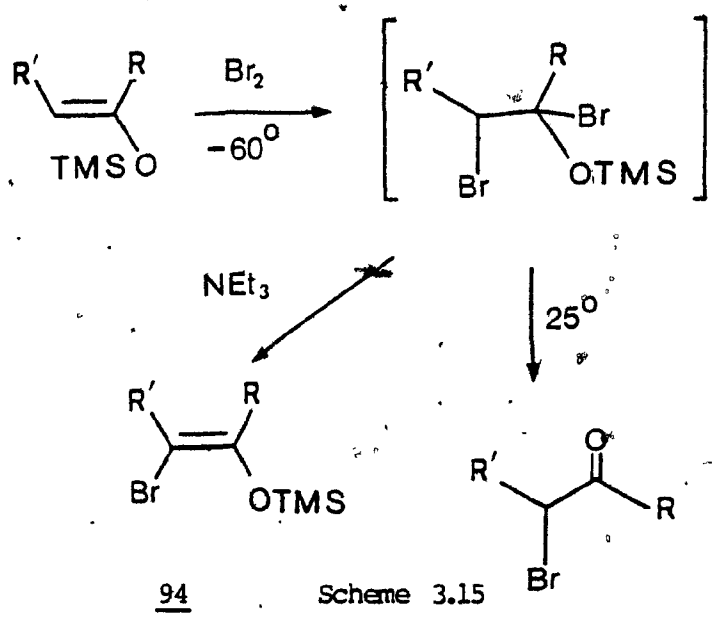


Scheme 3.14

3.4 ALKYLATION OF SILYL ENOL ETHERS UNDER NEUTRAL OR ACIDIC CONDITIONS

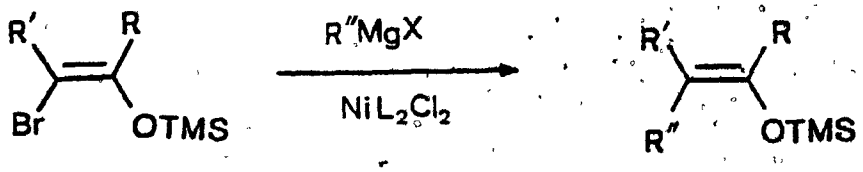
3.4.1 Non-Carbon Electrophiles

The reaction of elemental halogens with enol silyl ethers leads to α-haloketones, or under very mild conditions, α-halo silyl enol ethers with high (Z)-stereoselectivity (Scheme 3.15)[265].



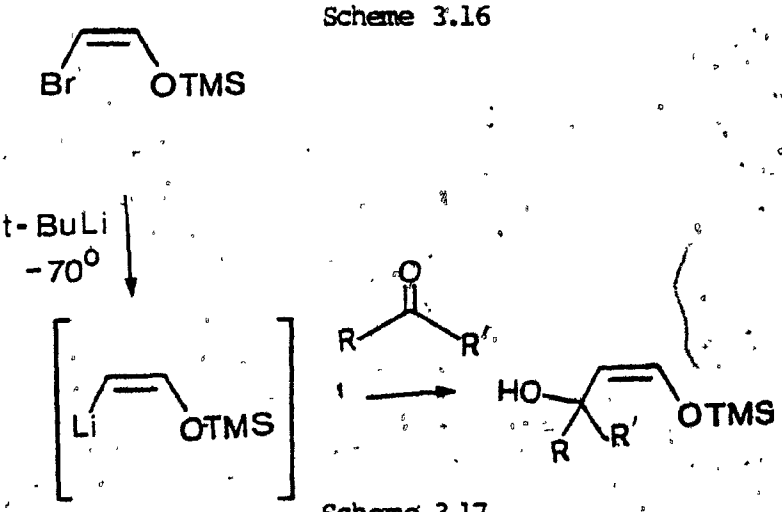
Scheme 3.15

Compounds of type 94, for example, are versatile synthetic intermediates. They can be alkylated with carbanions (Scheme 3.16), or in certain cases, the anion formed from lithium-halogen exchange can be alkylated with aldehydes or ketones (Scheme 3.17)[266].



$L_2 = ((Ph)_2P(CH_2)_3P(Ph)_2)$

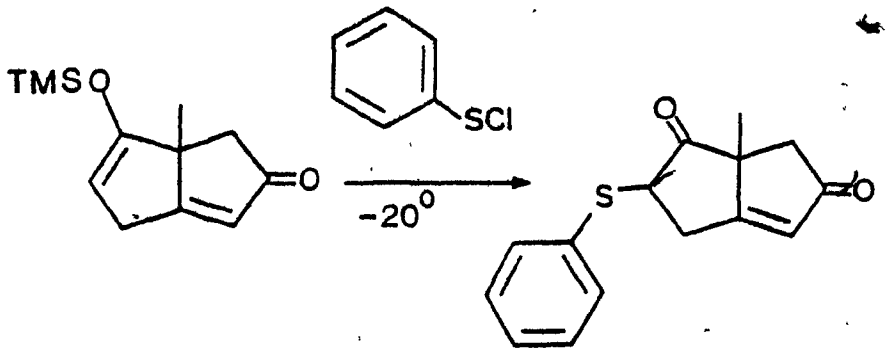
Scheme 3.16



Scheme 3.17

Halogenation of enol silyl ethers is also possible using the N-chloro or N-bromosuccinimides[253].

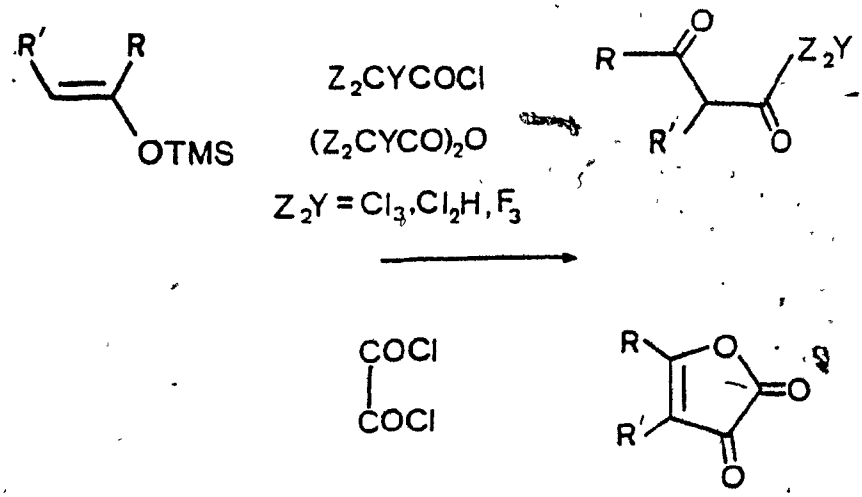
Enol silyl ethers react readily with phenylsulfenyl chloride to generate α-phenylthioketones (Scheme 3.18)[268].



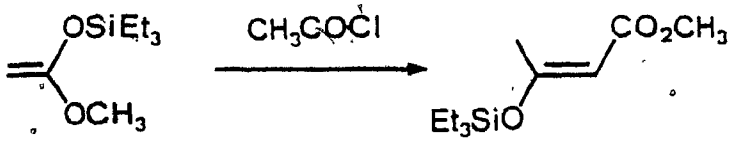
Scheme 3.18

3.4.2 Acyl Halides and Anhydrides

In the absence of any catalyst, some acyl halides are sufficiently reactive to allow the acylation of silyl enol ethers (Schemes 3.19[269,270,271,272]). Enol silyl esters also undergo acylation without the need of a catalyst (Scheme 3.20)[273].

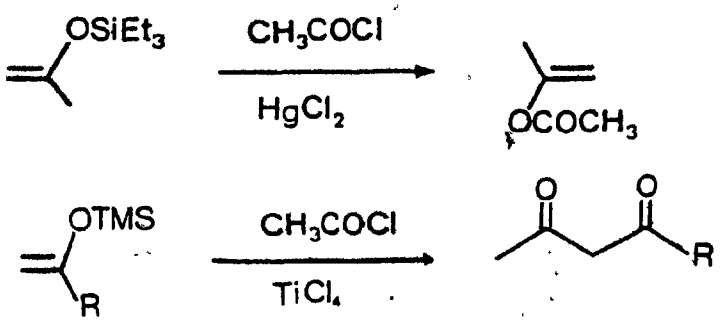


Scheme 3.19



Scheme 3.20

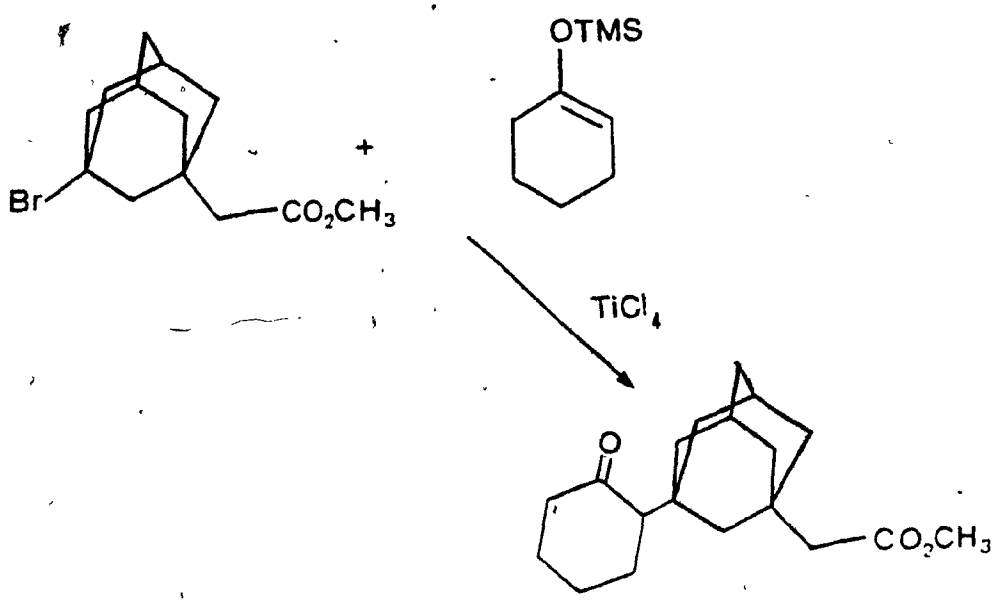
Other silyl enol ethers, however, require a Lewis acid catalyst. The most popular Lewis acids employed for acylation and other alkylations which will subsequently be described, are titanium tetrachloride ($TiCl_4$) and the zinc dihalides. These catalysts usually determine whether O-acylation[274] or C-acylation[275] (Scheme 3.21) takes place.



Scheme 3.21

3.4.3 Alkyl Halides

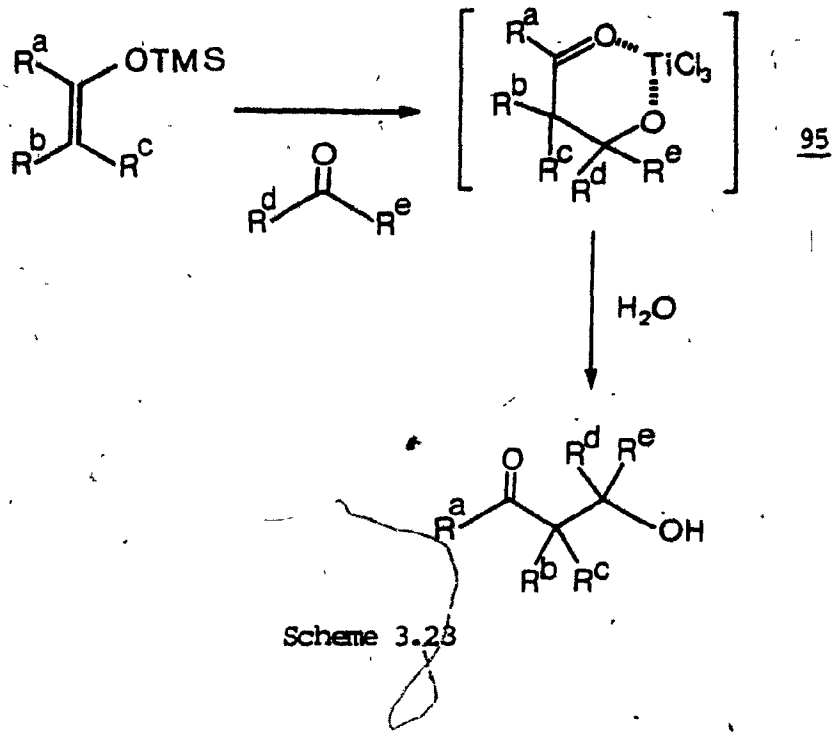
Enol silyl ethers are alkylated by tertiary, benzylic and allylic halides or acetates, those compounds which are susceptible to S_N1 reactions. Lewis acid catalysis is necessary in these alkylations (Scheme 3.22)[276]. It is interesting to note that enolates, on the other hand, are alkylated by primary, and in some cases, secondary alkyl halides, that is, those compounds susceptible to S_N2 reactions. The two methods, base catalyzed enolate α-alkylation and Lewis acid catalyzed silyl enol ether α -alkylation, are thus complementary.



Scheme 3.22

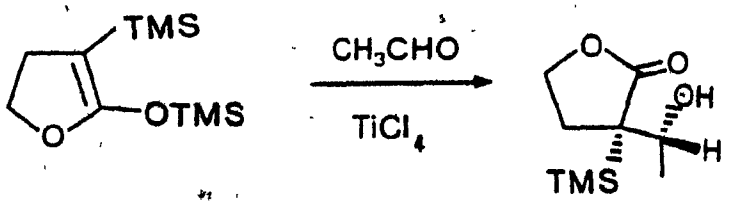
3.4.4 Ketones, Aldehydes, Ketals, Acetals and Orthoesters

Ketones and aldehydes readily alkylate silyl enol ethers and *bis*-ketene acetals in the presence of a Lewis acid catalyst. They display few of the problems which plague the aldol condensation; dimerization, polymerization, and dehydration. The Lewis acid, titanium tetrachloride for example, provides sufficient activation of the electrophile to catalyze the regiospecific and chemospecific condensation of carbonyl groups with a range of silyl enol ethers[277]. The undesirable dissociation of the aldol product is prevented by formation of the titanium chelate 95 (Scheme 3.23)[278].



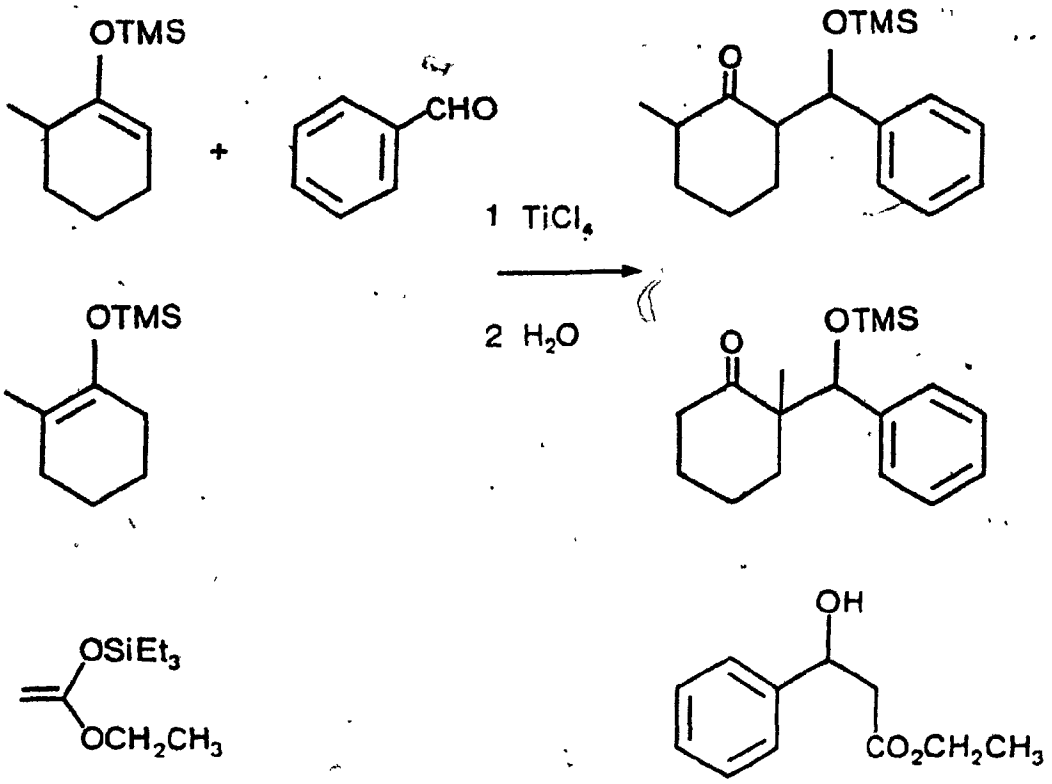
Scheme 3.23

The titanium tetrachloride is used in stoichiometric amounts and the aldol product is obtained cleanly and in high yield[30,279]. Moreover, the reaction displays considerable diastereoselectivity presumably because the transition state is cyclical 95, (Scheme 3.24; only one diastereomer 96 was isolated)[280].



Scheme 3.24 96

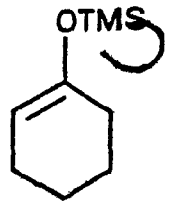
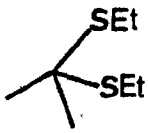
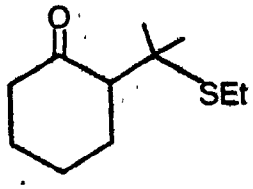
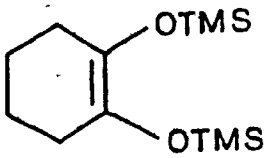
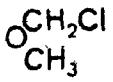
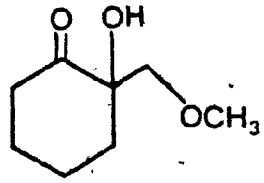
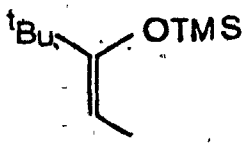
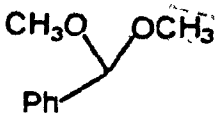
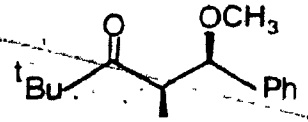
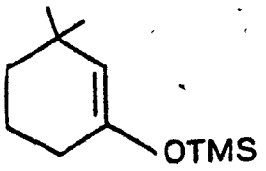
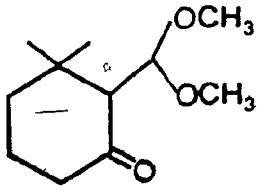
The overall order of reactivity of the electrophiles towards enol silyl ethers is; aldehydes (-78°C) > ketones (0°C) >> esters, where the numbers in parentheses refer to the thermal reaction conditions normally used[278]. Silyl ketene acetals undergo the reaction in the same manner (Scheme 3.25)[281].



Scheme 3.25

The remarkable difference between the silyl enol ether alkylation and the aldol condensation lies in the classes of electrophiles which can be utilized. The aldol reaction is essentially limited to ketones and aldehydes. However, as well as ketones and aldehydes, acetals, ketals, orthoesters, dithioketals and acetals, α-halophenylsulfides and chloromethylmethyl ethers, are sufficiently reactive to alkylate silyl enol ethers (Table 3.2).

Table 3.2: Examples of Electrophiles Which Alkylate Enol Silyl Ethers

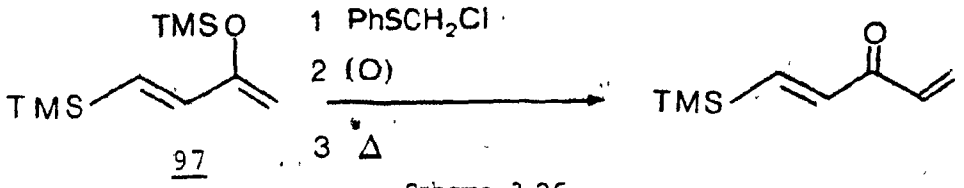
Enol Silyl Ether	Electrophile	Lewis Acid		Yield(%)	Ref.
		$SnCl_4$		80	283
		Zn-Cu $(CH_3)_2CHI$		67	284
		TfOTMS	 95% erythro	94	285
	$HC(OCH_3)_3$	$TiCl_4$		82	286

This broad range of electrophiles allows a wide choice in the preparation of an overall synthetic scheme.

3.5 SILYL DIENOL ETHERS (SILOXYBUTADIENES) AND *bis*-SILYL ENOL ETHERS

3.5.1 Siloxybutadienes

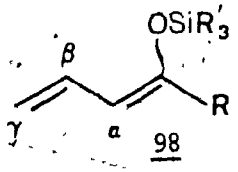
With 2-siloxybutadienes, for example 97, alkylation is observed only at the C1-position (Scheme 3.26)[278,288]. Essentially, these compounds react in the same manner as non-conjugated silyl enol ethers.



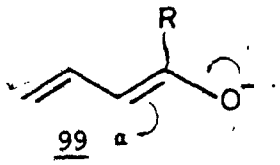
97

Scheme 3.26

On the other hand, 1-siloxybutadienes, such as 98, have the opportunity to be alkylated at either the α- or γ-positions. Mukaiyama has shown that compounds such as 98 react with electrophiles preferentially at the γ-position[289,290,291]. Dienolate anions such as 99, however, react with electrophiles at the α-position under kinetically controlled conditions[292]. Therefore, the use of silyl dienol ethers presents a simple solution to the long standing problem of achieving γ-alkylation.



98



99

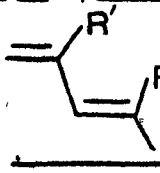
The relative ease of α-alkylation *versus* γ-alkylation has been the focus of extensive study by Fleming[243,292,293,294]. It is clear that both the type of electrophile and the substituents on the butadiene affect the extent of regioselectivity. However, the role which substituents play at the α- or γ-position remains uncertain. Electrophiles have been

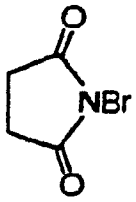
observed to display the following characteristics: (i) halogens and pseudohalogens react almost exclusively at the γ-position, (ii) the more stable the carbonium ion (formally) derived from treatment of a carbon electrophile with the Lewis acid, the less α-alkylation is observed[295], and (iii) "positive oxygen" electrophiles, such as *m*-chloroperbenzoic acid, add exclusively at the α-position[294]. The type of butadiene also affects the regioselectivity. For example, with aldehyde and ketone derived compounds, such as 98 (R=H, alkyl not C_6H_5), reactions normally take place at the γ-position. Ester derived compounds such as 98 (R=O-alkyl), on the other hand, show considerable variation in reactivity; γ-selectivity can be enhanced by electron donating β-substituents or by increasing the size of the ester alkyl group. Changing the silyl group has the most profound effect of all; increasing electron withdrawal encourages γ-alkylation. Some representative results of the extent of γ-alkylation under a variety of conditions are given in Table 3.3[292].

3.5.2 1,3-*bis*-Trimethylsiloxybutadienes

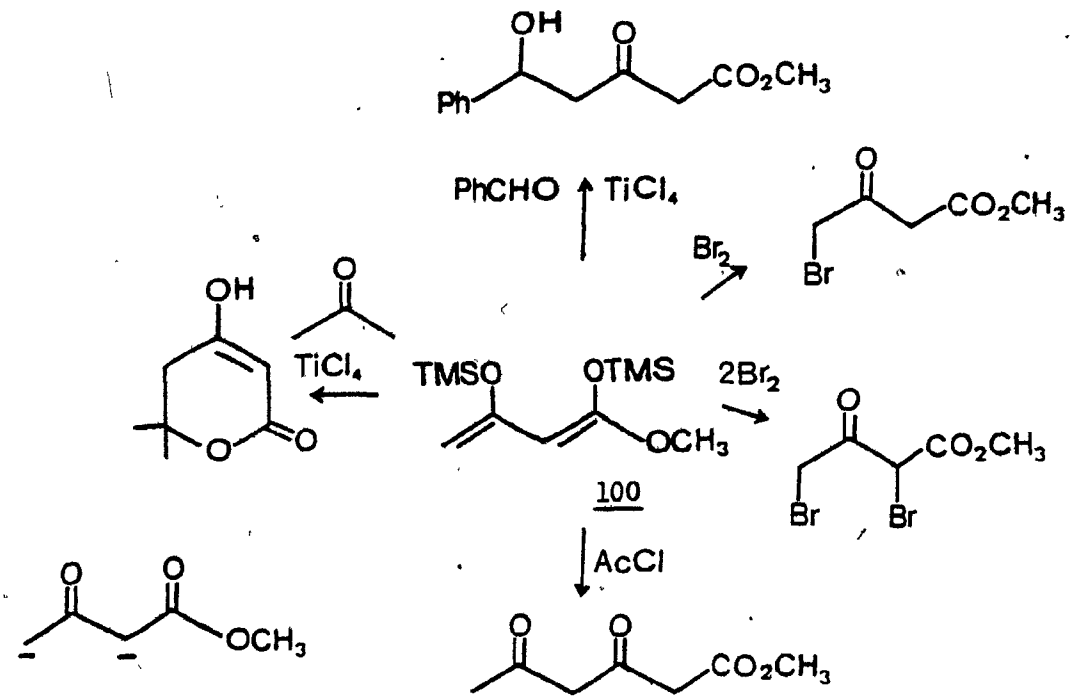
1,3-*bis*-Trimethylsiloxybutadienes react analogously to 1-siloxybutadienes. Following monoalkylation, however, the remaining enol silyl ether may also react to form dialkylated products. One of the most studied compounds of this type is 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3 butadiene, 100. The γ-position is the more easily alkylated, although dialkylation occurs readily. Some simple reactions of this compound are shown in Scheme 3.27[297].

Table 3.3: Regioselectivity in the Reaction of 1-(trimethylsiloxy)-butadienes with Electrophiles, Expressed as the Proportion (%) of γ-Adduct Obtained[292]



		R = Ph, R′ = H	R = OCH$_3$, R′ = CH$_3$	R = OCH(i-C$_3$H$_7$)$_2$, R′ = CH$_3$
Electrophile				
PhSCl		100	100	100
		100		
PhSCH$_2$Cl	a	45	65	85
PhSCH(Cl)(CH$_2$)$_2$CH$_3$	a	66	84	100
PhCHO	b	100		
HC(OCH$_3$)$_3$		100 [a]		100 [c]
(CH$_3$)$_2$C(OCH$_3$)$_2$	b	100		
CH$_3$CH(OEt)$_2$	a	60		100
^{t}BuCl	b	0		
CH$_3$COCl		NR [d]		100 [c]
PhCH(Br)CH$_3$	a	NR [d]		78

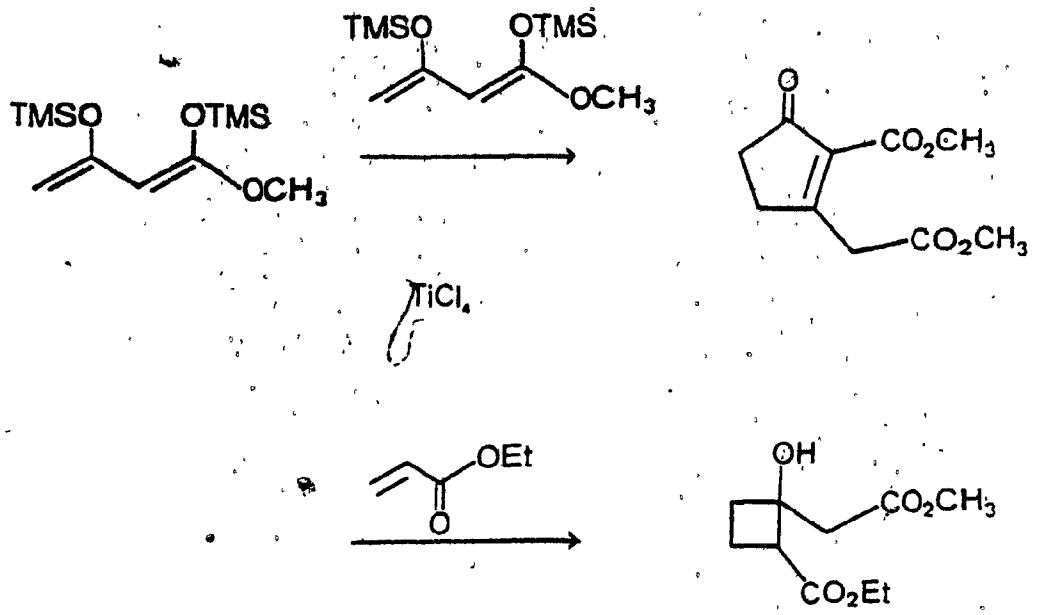
Lewis acid
a $ZnBr_2$
b $TiCl_4$
c catalytic amount of $ZnBr_2$
d reaction fails



101

Scheme 3.27

It is interesting to compare the reactivity of the dianion 101, formed under basic conditions, with the *bis*-silyl enol ether 100. The dianion acts as a hard nucleophile and attacks α , β-unsaturated carbonyl systems in a 1,2-fashion[298]. The *bis*-silyl enol ether, on the other hand, acts as a soft nucleophile and adds conjugatively to α, β-unsaturated substrates under mild conditions (Scheme 3.28)[297].



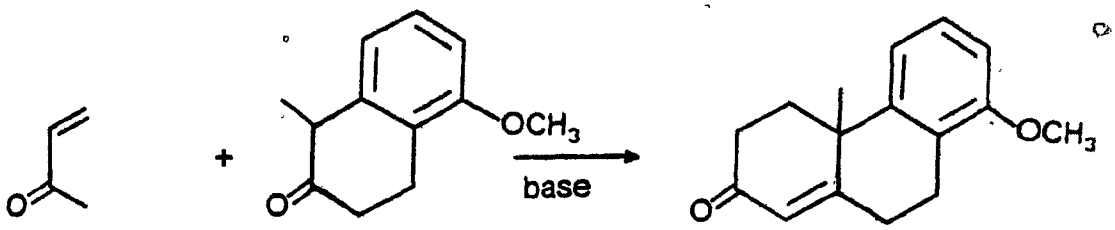
Scheme 3.28

3.6 RING FORMATION

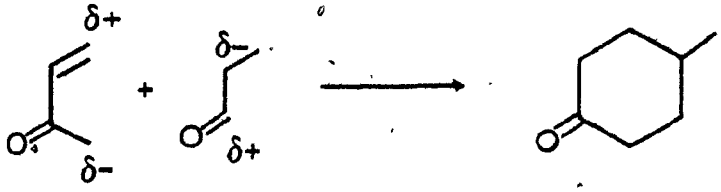
3.6.1 The Synthesis of Six-Membered Rings

The formation of cyclic compounds is a challenge of some consequence to the synthetic organic chemist. Many of the natural products of interest as synthetic targets contain at least one ring system and many are polycyclic in nature. Methods for ring formation, therefore, have been intensively sought for some time. During the era when steroids presented many of the most difficult synthetic challenges, it was the construction of 6-membered rings which were the focal point of much research. One reaction which has been extensively used is the Robinson annelation (Scheme 3.29)[299]. The regiochemistry of this reaction is essentially controlled by the direction of polarization within each

fragment, represented schematically in Scheme 3.30.

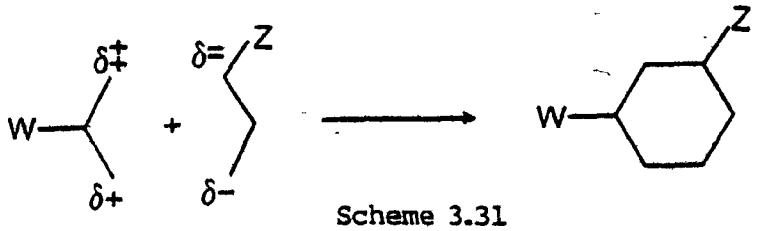


Scheme 3.29



Scheme 3.30

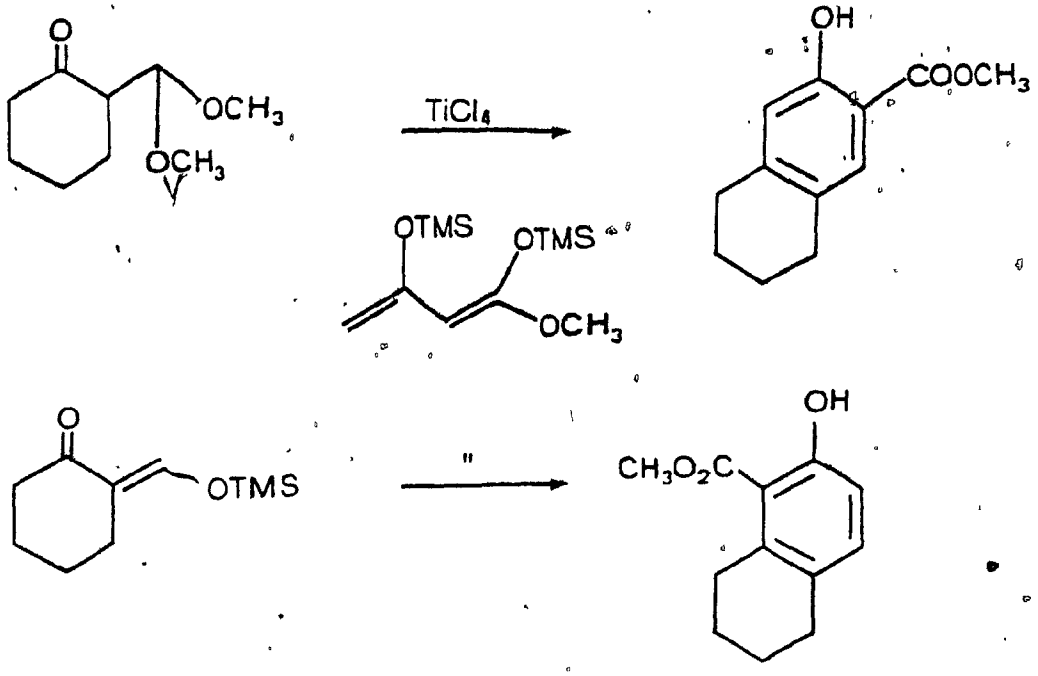
While this and other traditional ring-forming reactions are very useful, synthetic targets exist for which they can not be suitably employed. Recently, a new approach to ring formation was described[300]. The reaction involves the condensation of two 3-carbon units; one with two nucleophilic sites and the other with two electrophilic sites. The regiochemistry of this reaction is controlled by the differential reactivities at these sites (Scheme 3.31).



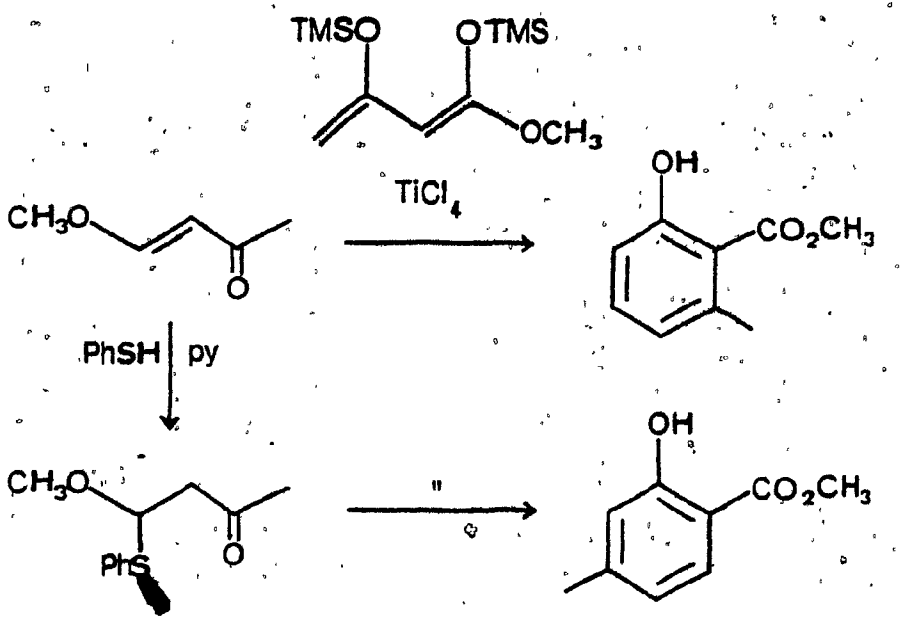
Scheme 3.31

One dinucleophilic fragment which can be used is the *bis*-silyl enol ether 100. As has been described (*vide supra*), this compound shows greater reactivity at the γ-position than at the α-position, so that

either monoalkylation (γ-position) or dialkylation (α- and γ-position) can be selected. Using a variety of β-dicarbonyl equivalents, with titanium tetrachloride catalysis, a general route to methyl salicylates is available. The regioselectivity is controlled by a propitious choice of carbonyl equivalents (the dielectrophilic fragment), which is governed by the order of reactivity for the electrophilic components under titanium tetrachloride catalysis; conjugate (γ-) position of an enone > ketone > monothioacetal, acetal[300,301]. In consideration of these relative reactivities, reactions can be designed to give products with completely predictable regiochemistry (Schemes 3.32 and 3.33).

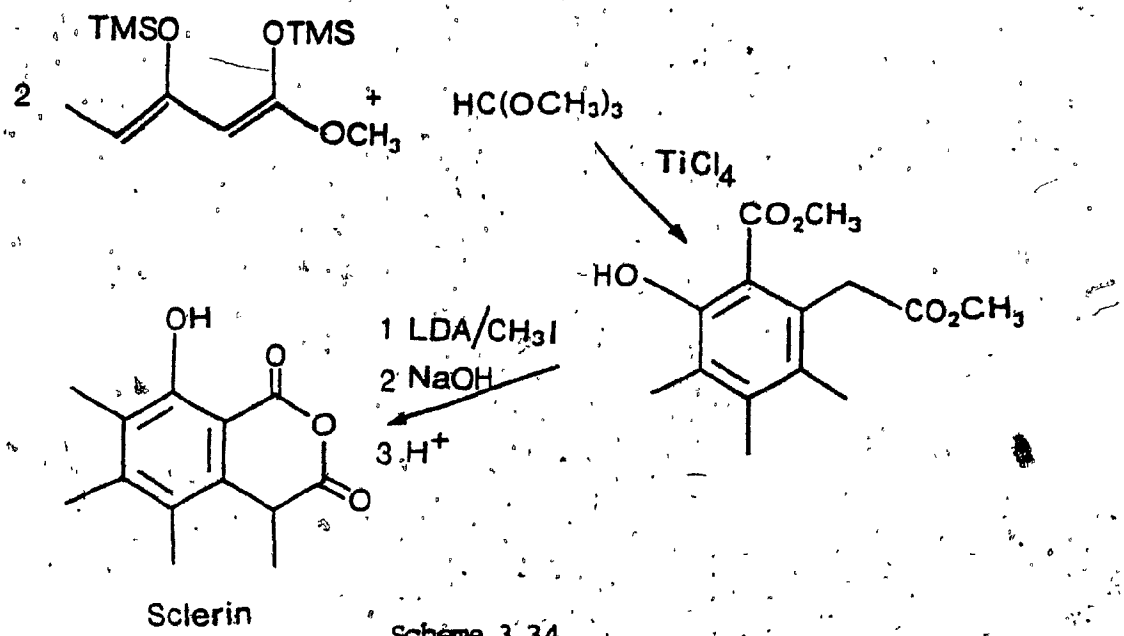


Scheme 3.32



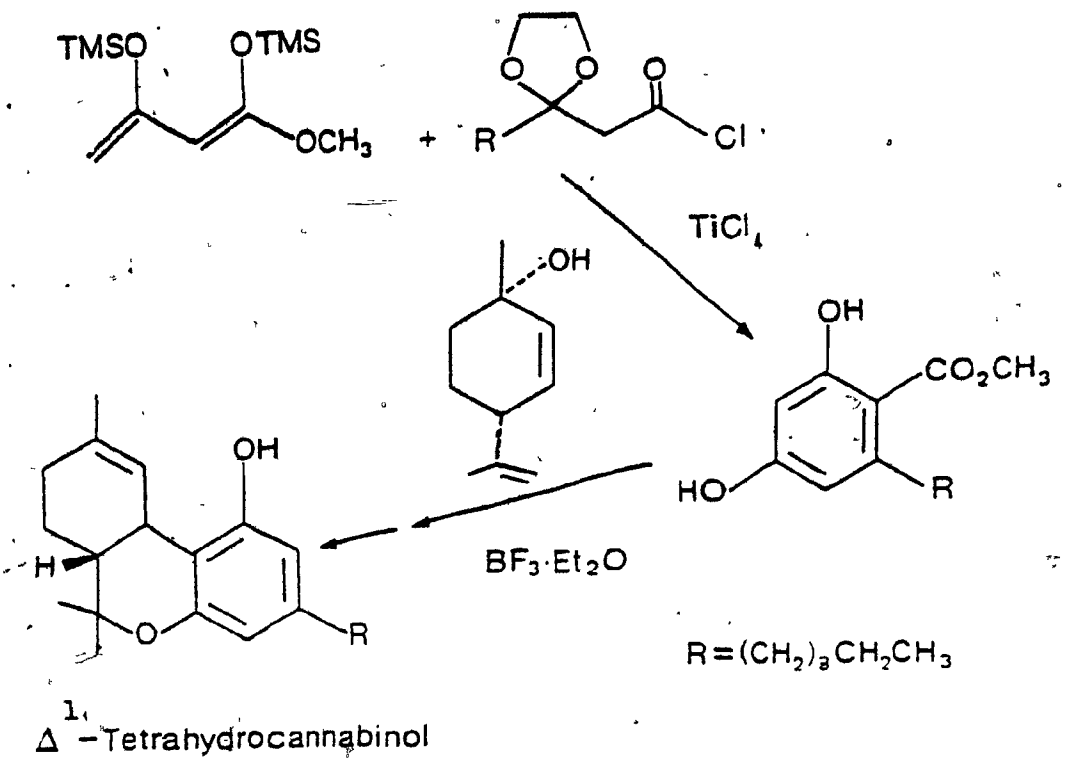
Scheme 3.33

The use of 100, a masked form of methyl acetoacetate, is of particular interest because the acetoacetate unit is one of the fundamental building blocks in the biogenesis of natural products. Two examples of very short regioselective syntheses of natural products are given in Schemes 3.34[303] and 3.35[301].



Sclerin

Scheme 3.34

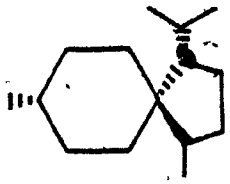


Scheme 3.35

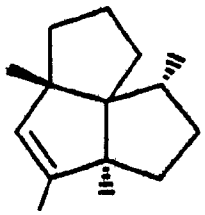
These examples serve to show the utility of this reaction scheme in the synthesis of complex aromatic systems not easily obtained by other routes.

To some extent, the cyclization reaction to form 6-membered aromatic rings proceeds successfully because of their intrinsically stable nature. Whether the use of this reaction could be extended to the synthesis of less stable rings of other sizes, however, remained to be determined. The construction of 5-membered rings has provided at least as great or perhaps a greater challenge to the synthetic organic chemists than the 6-membered ring. The 5-membered ring systems, cyclopentane, cyclopentene, and cyclopentanone, for example, are observed in a myriad of natural products which have been chosen as synthetic targets; such as the acoranes 102[304], isocomene 103[305] and the prostaglandins ($PGF_{2\alpha}$) 104[306]. It is the latter group of compounds which has captured the imagination of synthetic organic

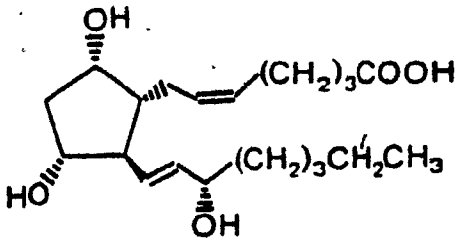
chemists over the last decade.



102



103

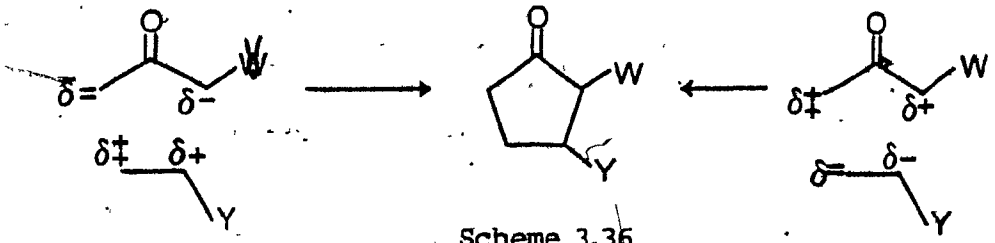


104

An account of the attempts to make 5-membered ring systems of this type, using the cyclization strategy described above, will be the focus of the remainder of this chapter.

3.6.2 The Synthesis of Five Membered Rings

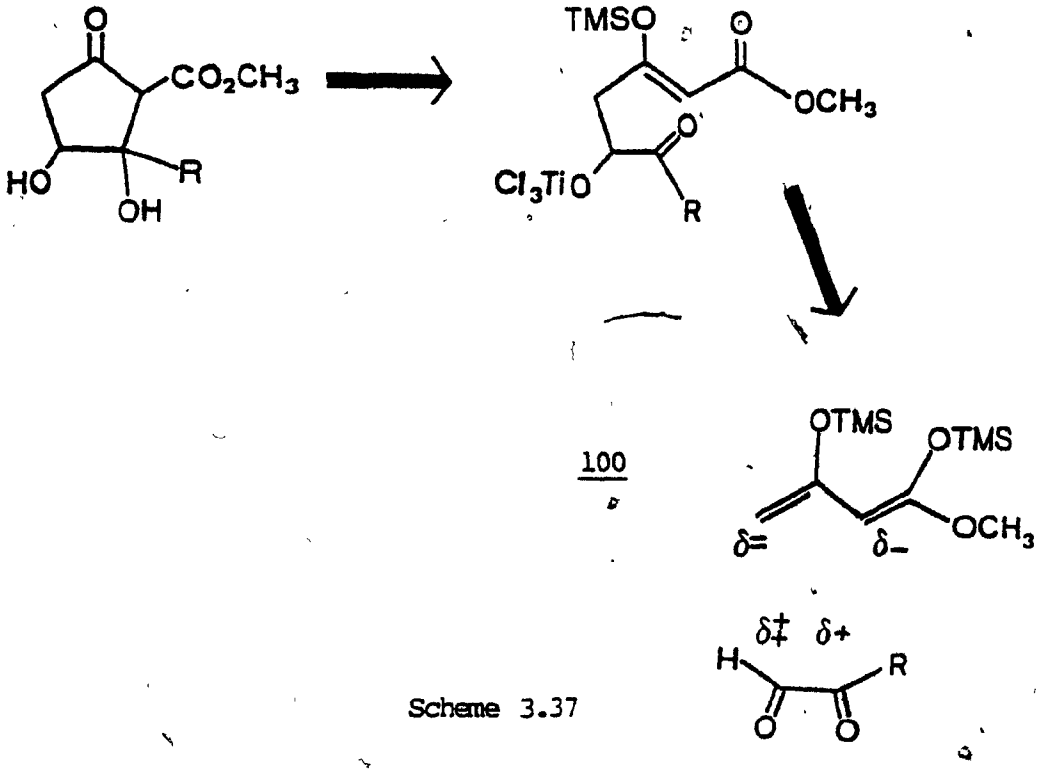
The six membered ring cyclization utilizes a 3-carbon + 3-carbon condensation. The corresponding cyclopentenone system would thus theoretically involve a 3-carbon + 2-carbon system (Scheme 3.36).



Scheme 3.36

From an retrosynthetic analysis, the synthesis of a 2-carbon dielectrophile, a masked 1,2-dicarbonyl unit, appears to be simpler than that of a 1,2-dinucleophilic unit. Therefore, the reaction chosen to be initially studied involved 100, a compound whose reactivity is well known, with a series of 1,2-dicarbonyl units (Scheme 3.37). The purpose of the study

was to examine the relative reactivities of various dicarbonyl equivalents when in a 1,2-relationship and also to examine the possibility of using this approach for the construction of five membered rings.



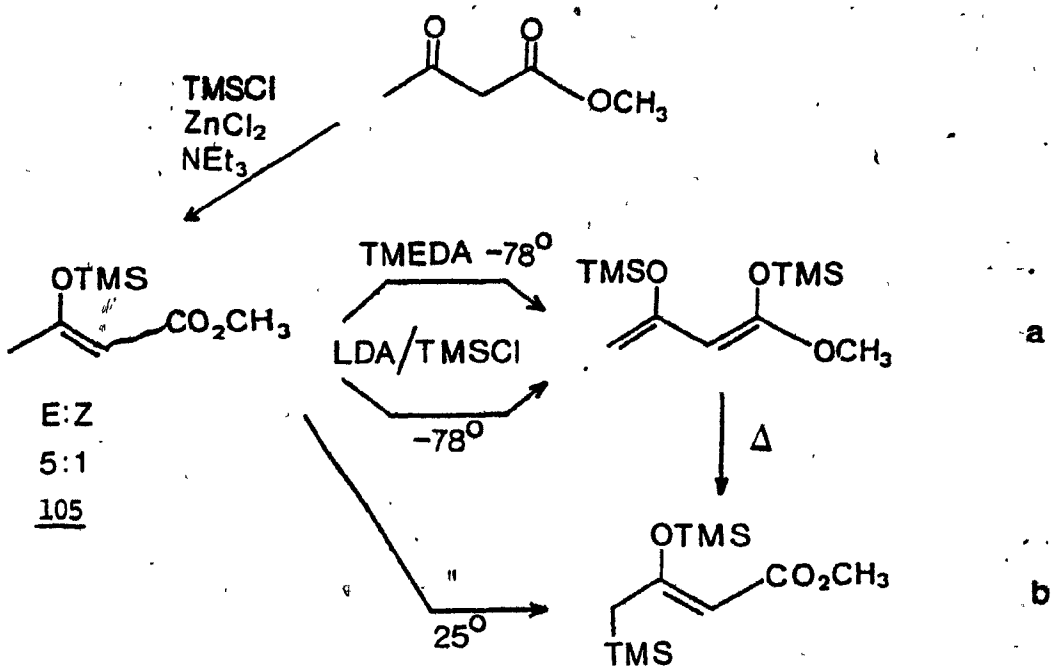
100

Scheme 3.37

3.7 SYNTHESIS OF THE ELECTROPHILIC AND NUCLEOPHILIC COMPONENTS

3.7.1 Nucleophilic Components

1.3-*bis*-Trimethylsiloxy-1-methoxy-1,3-butadiene 100, the dinucleophilic component of the cyclization reaction, can be synthesized in excellent yield. Because the direct silylation of the dianion of methyl acetacetate leads to C-O-*bis*-silylation[307], the reaction is normally done in a two step process (Scheme 3.38a)[300].



Scheme 3.38

The first step is based on work by Danishefsky[308] and Dunoguès[309] where the silyl group is introduced in basic media with zinc chloride catalysis 105. The second step, using lithium di-*iso*-propylamide, chlorotrimethylsilane and tetramethylethylenediamine (TMEDA) as a lithium chelating agent[300], proceeds readily to give a single isomer, based on the observation of only two trimethylsilyl peaks in either the ^{1}H- or ^{29}Si-N.M.R. spectra.

Problems can arise, however, during the removal of TMEDA in the work-up procedure after the second step. First, the compound cannot be purified by chromatography on silica gel or alumina as this leads to extensive degradation. Second, contrary to reports in the literature[307,310], it is observed that elevated temperatures (>0°C) lead to partial decomposition or rearrangement of the molecule, and thus,

distillation to give the product in good yield is difficult. As a result, the TMEDA must be removed over a long period of time (6-14 hours) under high vacuum at room temperature. Even under these conditions some decomposition occurs.

The stereochemistry of 100 was initially assigned to be (E) based on work by Ireland[311]. It was discovered during the course of work with this compound, and by others[310], that a novel 1,5-thermal silicon migration is a main pathway for the decomposition of 100 (Scheme 3.38b). In light of this rearrangement, it can be concluded that 100 exists in the (Z) isomeric form. However, the existence of an equilibrium between the (E) and (Z) isomers cannot be excluded.

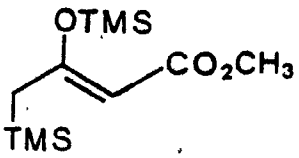
In the absence of TMEDA, excellent yields of a bis-silyl enol ether are obtained at all temperatures below 0°C (Table 3.4). Even without purification, only one compound is isolated. This product is identical to that synthesized in the presence of TMEDA, based on ^{1}H- or ^{29}Si-N.M.R. studies. Moreover, it can be isolated within one hour and with much less concomitant decomposition. At 0°C or greater, significant amounts of rearranged and polymeric products are obtained.

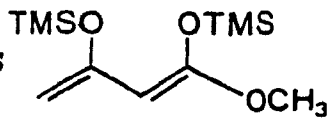
3.7.2 Electrophilic Components

Procedures for the synthesis of 1,2-dielectrophilic compounds, such as 106 where R=C_6H_5, are well known. Therefore, dielectrophiles of this type were chosen to be used in the cyclization reaction to form 5-membered rings. The scheme for the synthesis of some selected electrophiles is given in Scheme 3.39.

Table 3.4: Reaction Efficiency in the Absence of TMEDA

Relative proportion of silylated compounds in the formation of 100 at various temperatures#





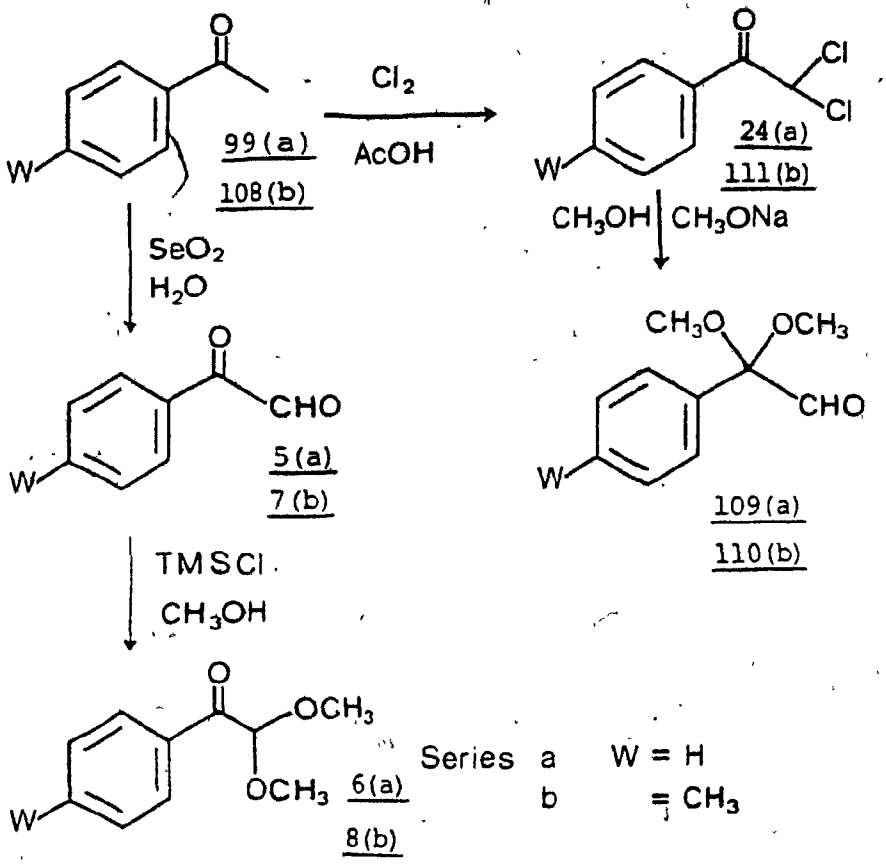
Temperature	Conditions	TMSOTMS	100	100-x
25	No temperature control, compounds rapidly mixed.	x*	—	100-x
25	Temperature controlled using H_2O bath, compounds mixed slowly.	3	57	21**
0	Rapidly mixed.	15	85	—
0	Slowly mixed.	6.5	80	9
-23	CCl_4/CO_2	15	85	—
-42	CH_3CN/CO_2	11	89	—
-78	CH_3COCH_3/CO_2	10	90	—
-78	CH_3COCH_3/CO_2 + TMEDA.	10	90	—
-110	ether/CO_2	13	87	—

The % of the enolic compounds is based on the integration of the vinylic hydrogens. The non-enolic components were evaluated using the integration of the TMS peaks.

* Since TMSOTMS peak is under the C-TMS peak, the relative % is difficult to determine. The major (>90%) portion is the C-silylated compound.

** The relative amount of the starting material (105) is 9%.

Although TMSOTMS is present in all spectra, this compound can be easily removed by pumping at high vacuum. For example, the first entry at 0°C, after 2 hours pumping, the relative % of TMSOTMS dropped from 6.5% to 1.5%.



Scheme 3.39

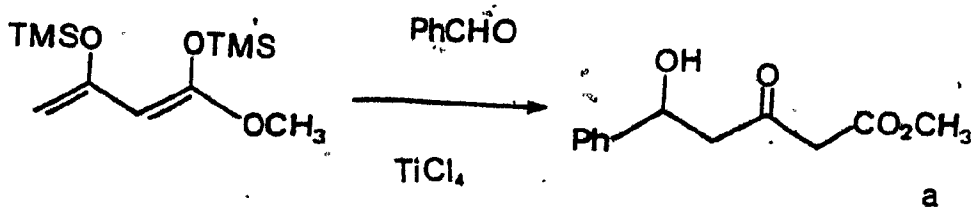
α,α -Dichloroacetophenone 24 is readily synthesized by the direct chlorination of acetophenone in acetic acid[312]. It is isolated in a yield of 93% after distillation. Treatment of 24 with sodium methoxide in methanol under an inert atmosphere, leads to a 81% yield of 2,2-dimethoxyphenylacetaldehyde, 109. The conversion of 109 to phenylglyoxal 5 has been described by Trost[72]. However, as only fair yields are obtained using this procedure, the direct synthesis from acetophenone 99 can be used. This involves oxidation with selenium dioxide to give the glyoxal 5 in 84% yield after distillation. This compound readily sets to a stiff gel, probably as a result of polymerization. Because of the difficulty in

handling polymers of this type, the glyoxal is converted to the dimethyl-acetal 6. It can be made in 83% yield using chlorotrimethylsilane in methanol. These procedures can be equally applied to the *p*-methyl derivatives to give comparable yields (Scheme 3.39, series b). The starting material *p*-methylacetophenone 108 can be synthesized in 73% yield by the Friedal-Crafts reaction of toluene with acetic anhydride[316].

3.8 CONDENSATIONS

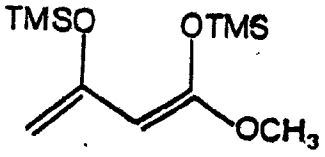
3.8.1 Monoalkylation

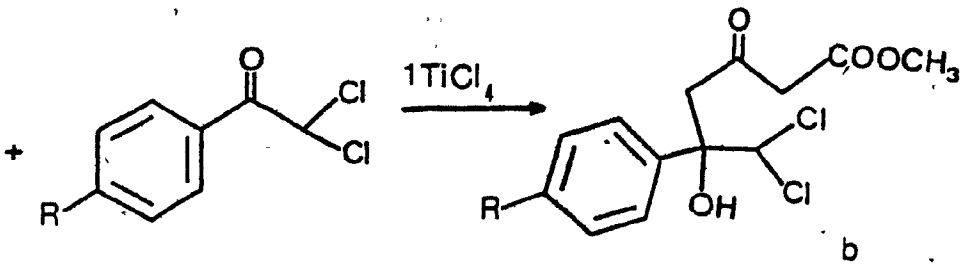
The *bis*-silyl enol ether 100 can be reacted to give a series of mono-alkylated products with catalysis by one equivalent of titanium tetra-chloride (Scheme 3.40). These reactions must be quenched with basic media to neutralize the HCl formed after the hydrolysis of $TiCl_4$. Normally, the use of aqueous sodium bicarbonate solutions leaves emulsions of titanium dioxide which are difficult to separate from the organic components of the reactions. Alternate work-up procedures can be used, such as, Amberlyst A21 weakly basic resin and *iso*-propanol, or ~10 equivalents of water in the presence of excess solid K_2CO_3 or $NaHCO_3$. However, while the latter two procedures avoid the formation of emulsions, the reaction products and yields are inconsistent. Therefore, an aqueous work-up followed by extraction with ether is considered the best choice of the neutralization procedures attempted.



a

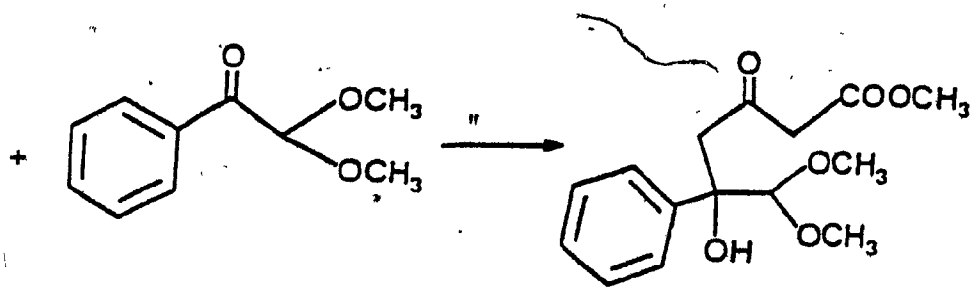
112





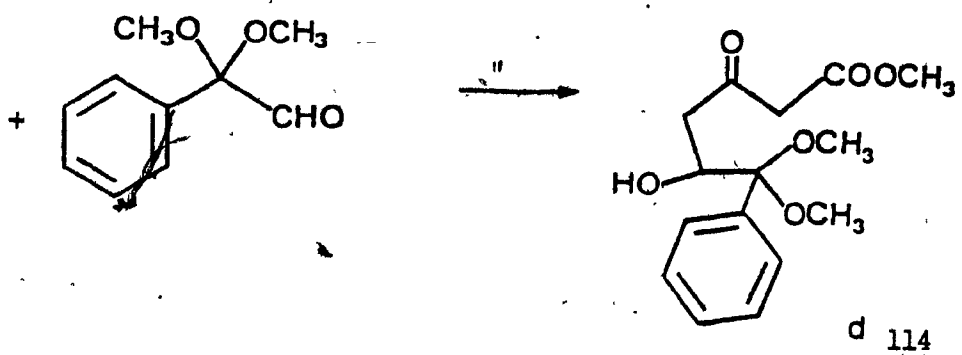
b

115,116



c

113



d 114

Scheme 3.40

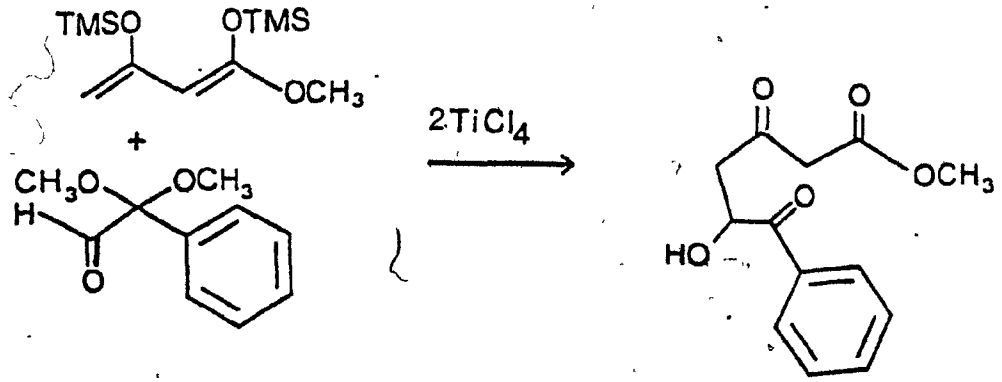
The crude reaction mixtures after work-up (Scheme 3.40) consist of a major product with traces of other compounds. ^{1}H-N.M.R. spectra of the crude mixtures show the desired monoalkylated products 112, 113, 114, 115 or 116, in yields in excess of 70%. The purification of these compounds, however, leads to some difficulties. For example attempted separation of 116 on mesh chromatography gives none of the purified material (the yield of the crude starting material was 55%, based on ^{1}H-N.M.R.). This is due to the crude material undergoing a very efficient retro-aldol reaction in the presence of the T.L.C. silica gel. The use of flash chromatography gives improved yields for 115 and the other compounds, however, some decomposition on the column always accompanies these separations. Modifications of the chromatographic procedure, such as the deactivation of the silica gel with methanol, triethylamine, or water, do not lead to improved yields.

As can be seen, all these reactions give γ-alkylation products; no evidence of α-alkylation is observed. Moreover, all of the electrophiles react, exclusively at the more reactive carbonyl position. It should be noted that the *bis*-silyl enol ether 100 formed in the absence of TMEDA (Scheme 3.40a) reacts in the same manner as that formed in the presence of TMEDA (Scheme 3.27), confirming that the two synthetic products are the same[297].

3.8.2 Dialkylation

The Lewis acid catalyst which is employed in the aldol reaction does not act as a true catalyst in that molar equivalents are required for the reaction to proceed. Each carbon-carbon bond formed results in the

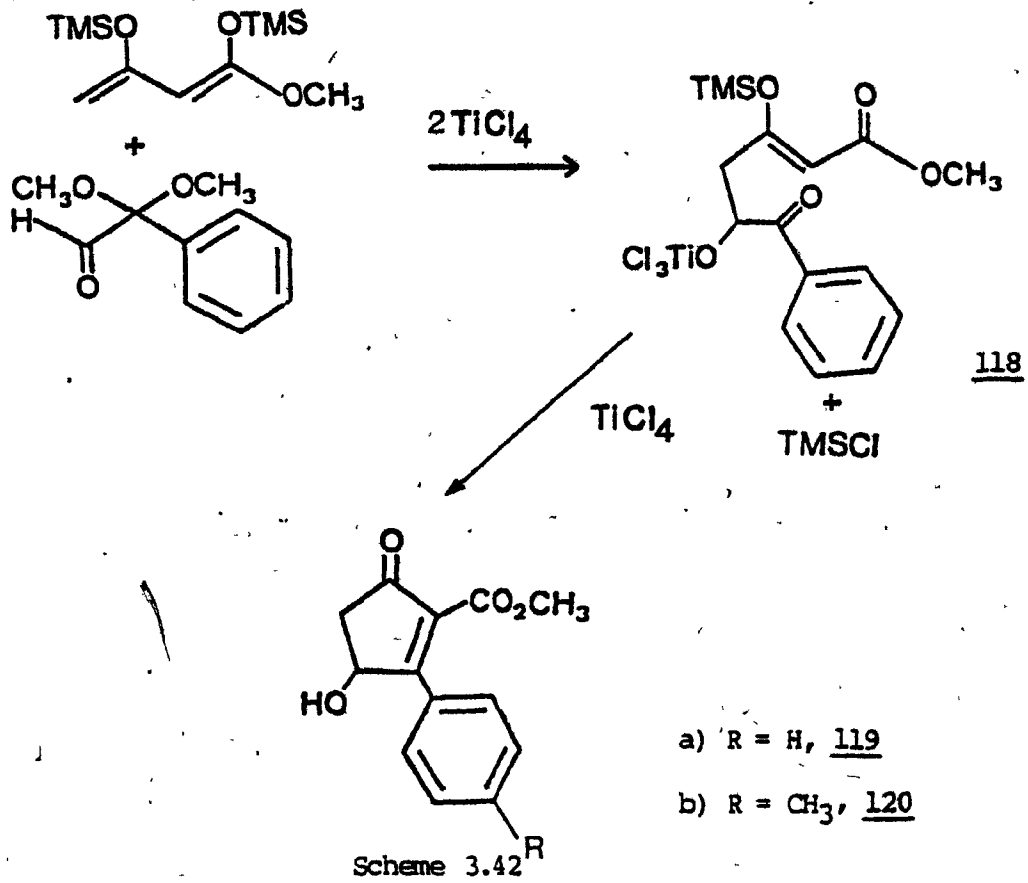
concomitant formation of an oxygen-titanium bond. It was expected, therefore, that the use of two equivalents of $TiCl_4$ with the 1,2-dielectrophiles (reactions 3.40 b, c, and d), would lead to cyclic dialkylated products. However, under these conditions, reactions 3.40b and 3.40c gave the same monoalkylated products. Although dialkylation does not occur in reaction 3.40d, an interesting deketalization at the benzylic position accompanies the monoalkylation (Scheme 3.41). This deketalization does not occur with unactivated acetals, such as 117 (Scheme 3.44). As the work-up for the reaction makes use of basic media, conditions under which the hydrolysis of ketals does not occur, this deketalization might be promoted by titanium tetrachloride.



Scheme 3.41

In light of these results, it is reasonable to conclude that α-alkylation of the presumed silyl enol ether intermediate 118 (Scheme 3.44) takes place much less readily than alkylation at the γ-position of 100. The dichloroalkyl group, dimethylacetal or dimethylketal, are not sufficiently electrophilic for α-alkylation to occur. It is obvious that a more potent electrophile is required if dialkylation is to be achieved. In reaction 3.41, however, a more potent electrophile, the benzylic ketone,

is generated *in situ*. One should be able to take advantage of this situation by using more $TiCl_4$. Indeed, when three equivalents of titanium tetrachloride are used, α -alkylation can occur to generate the cyclic system (Scheme 3.42).



a) R = H, 119

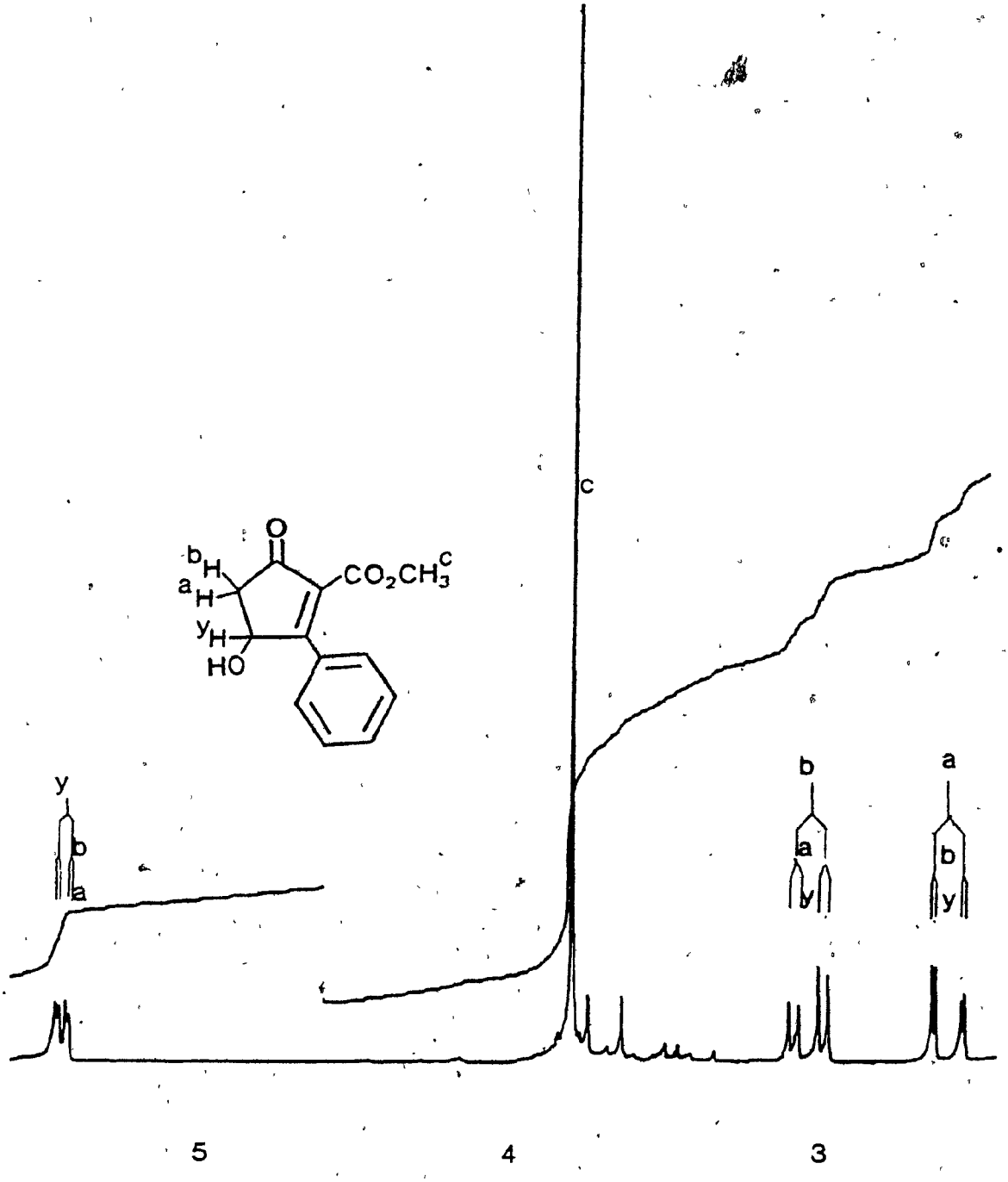
b) R = CH_3, 120

Scheme 3.42

These cyclopentenones can be easily identified due to the very recognizable ABX system in the ^{1}H-N.M.R. spectrum. A portion of the 200 MHz spectrum of 119 is shown in Figure 3.1 (the aromatic region and the region below 2.5 ppm have been omitted).

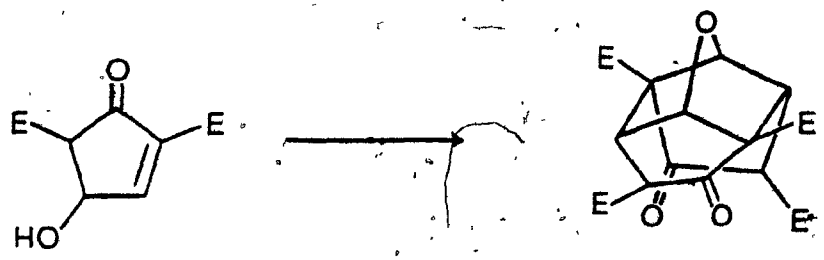
Concentration and temperature regulation play very important roles in the reaction. After much experimental trial and error, the optimum reaction sequence is as follows: one hour at -78°C, warming to 0°C over 15 minutes (ice bath), and then the quenching of the reaction. If the

200 MHz ^{1}H-N.M.R. Spectrum of the Indicated Hydroxycyclopentenone

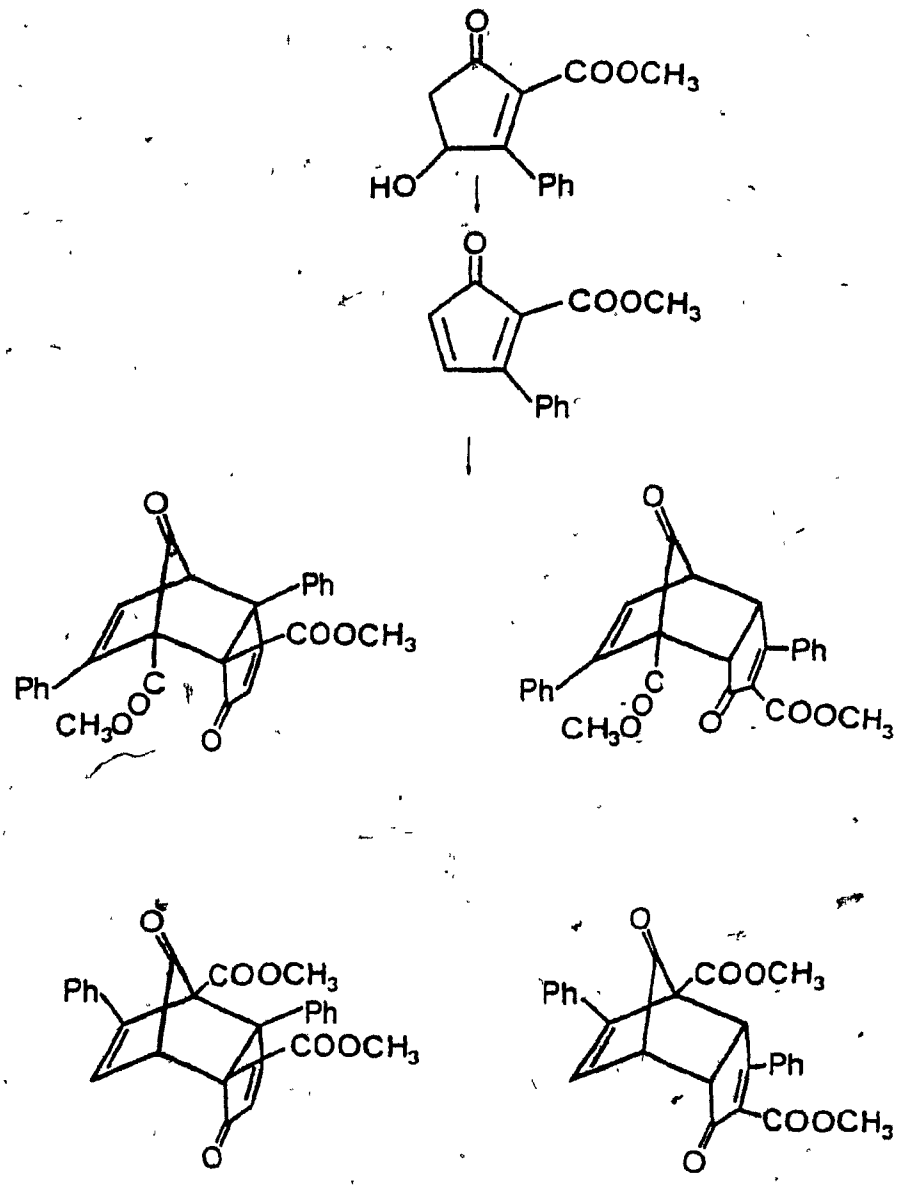


concentration of either the enol silyl ether, or the electrophile are greater or lower than 0.1 M, then much lower yields of the desired cyclopentenone are realized. If this regime is not followed, complex reaction mixtures result from either excessive reaction time or thermal conditions, and monoalkylated products result from either insufficient reaction times or thermal conditions.

The yields of the reactions 3.42a and b are relatively high (70–80%), based on the ^{1}H-N.M.R. analysis of the unchromatographed material. However, substantial decomposition of the products occurs on the silica gel column. Although deactivation by methanol, of the silica gel, improves the isolated yields, they remain moderate; 35% and 48% for 119 and 120, respectively. The occurrence of decomposition on the column is most likely a reflection of the intrinsic instability of the cyclopentenone system. There is ready elimination of water from cyclopentenones leading to cyclopentadienones. These compounds then readily undergo Diels-Alder and other processes to give a complex series of products and polymers (Scheme 3.43).



$E = CO_2CH_3$



+ exo isomers

Scheme 3.43

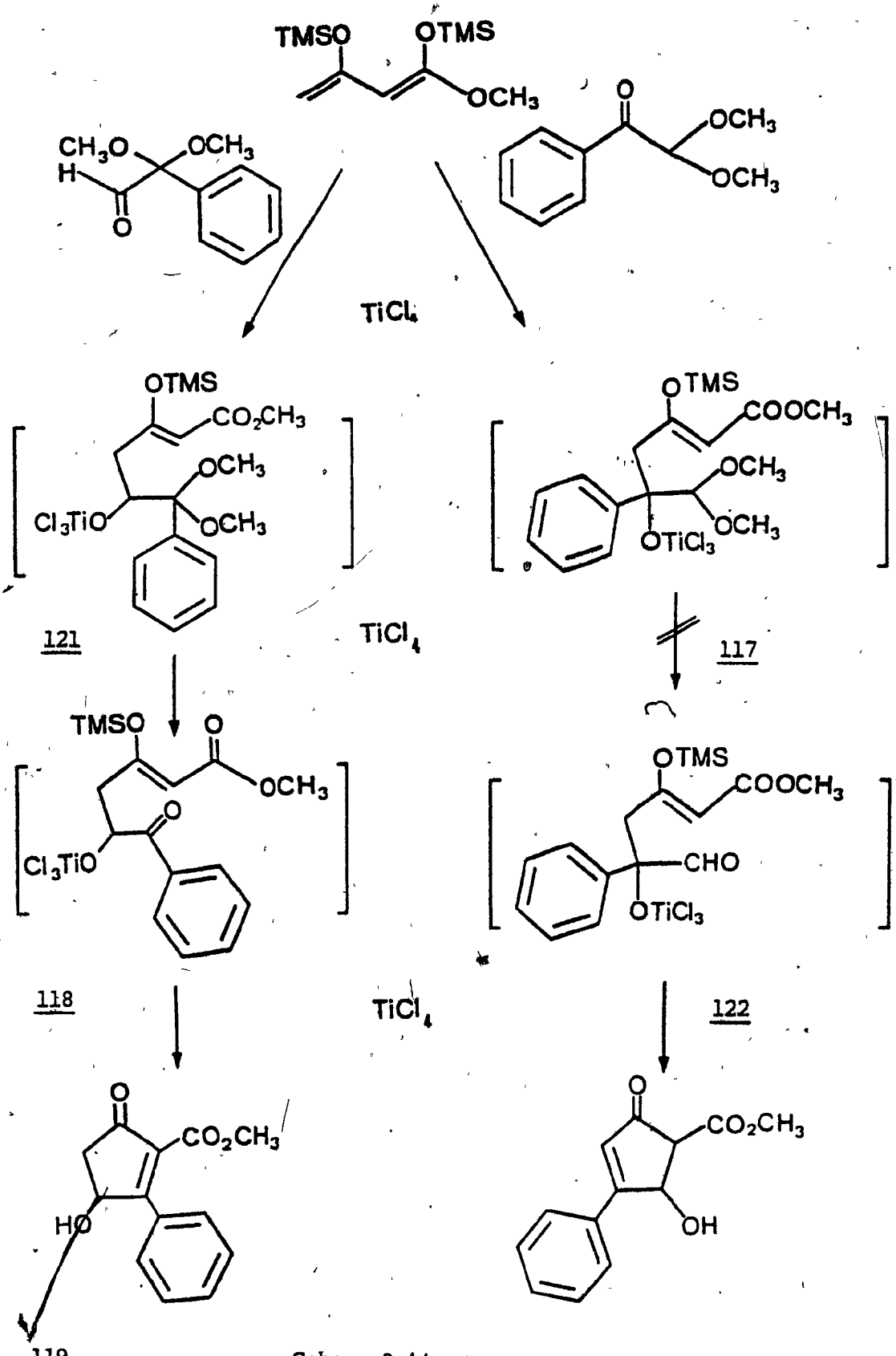
3.8.3 Controlling the Regioselectivity of Ring Formation

It was initially hoped that both possible regioisomers could be selectively formed in the cyclization reaction. However, since deacetalization only occurs with the benzylic ketal 121 --> 118, just one regioisomer is accessible (Scheme 3.44). It had been anticipated that the

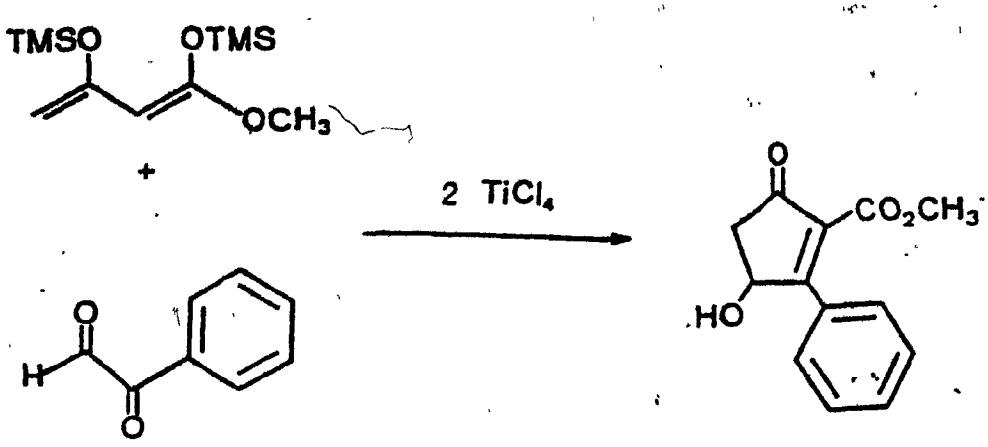
electrophilicity of the two carbonyl groups of 5 would be similar and that the use of this reagent would lead to a mixture of both possible regioisomeric compounds. It is surprising to discover, however, that the same regioisomer 119 can also be formed from the α-ketoaldehyde 5 (Scheme 3.45).

The reaction with this electrophile is regioselective indicating, under these conditions at least, that aldehydes are more reactive electrophiles than ketones, even activated benzylic ketones. The hydroxycyclopentenone which is isolated has the same substitution pattern as the synthetically challenging prostaglandins skeleton. It is possible, therefore, that other simple ketoaldehydes could be used for the generation of prostanoids by this simple reaction sequence. It should follow that one of the regioisomeric cyclopentenones is available from any keto-aldehyde (Scheme 3.46). These keto-aldehydes are very easy to generate* from a variety of precursers[317,318,319,320].

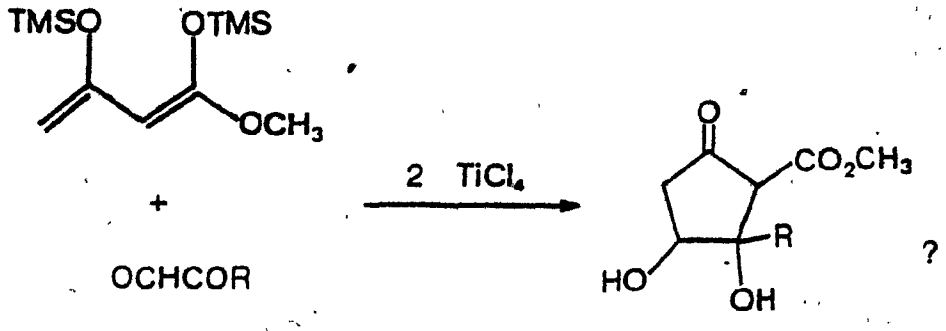
* It should be noted that these ketoaldehydes are difficult compounds to handle as polymerization readily occurs.


TMSO
OTMS
OCH3
CH3O
OCH3
H
O
OCH3
OCH3
TiCl4
OTMS
CO2CH3
OCH3
Cl3TiO
OCH3
121
TiCl4
OTMS
COOCH3
OCH3
OTiCl3
OCH3
117
TMSO
O
OCH3
O
Cl3TiO
118
TiCl4
OTMS
COOCH3
CHO
OTiCl3
122
O
CO2CH3
HO
119
O
CO2CH3
OH

Scheme 3.44

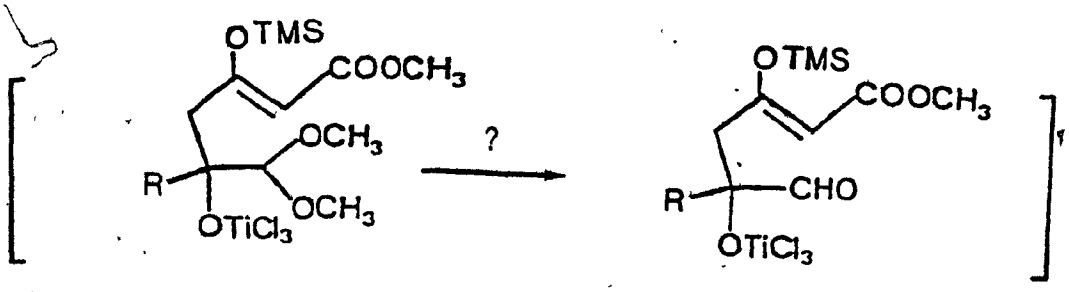


Scheme 3.45



Scheme 3.46

The other regioisomeric hydroxycyclopentenone, however, is not nearly as accessible. If cyclization was to occur, a deacetalization step would have to be implemented in between the alkylations of the two silyl enol ethers (Scheme 3.47).



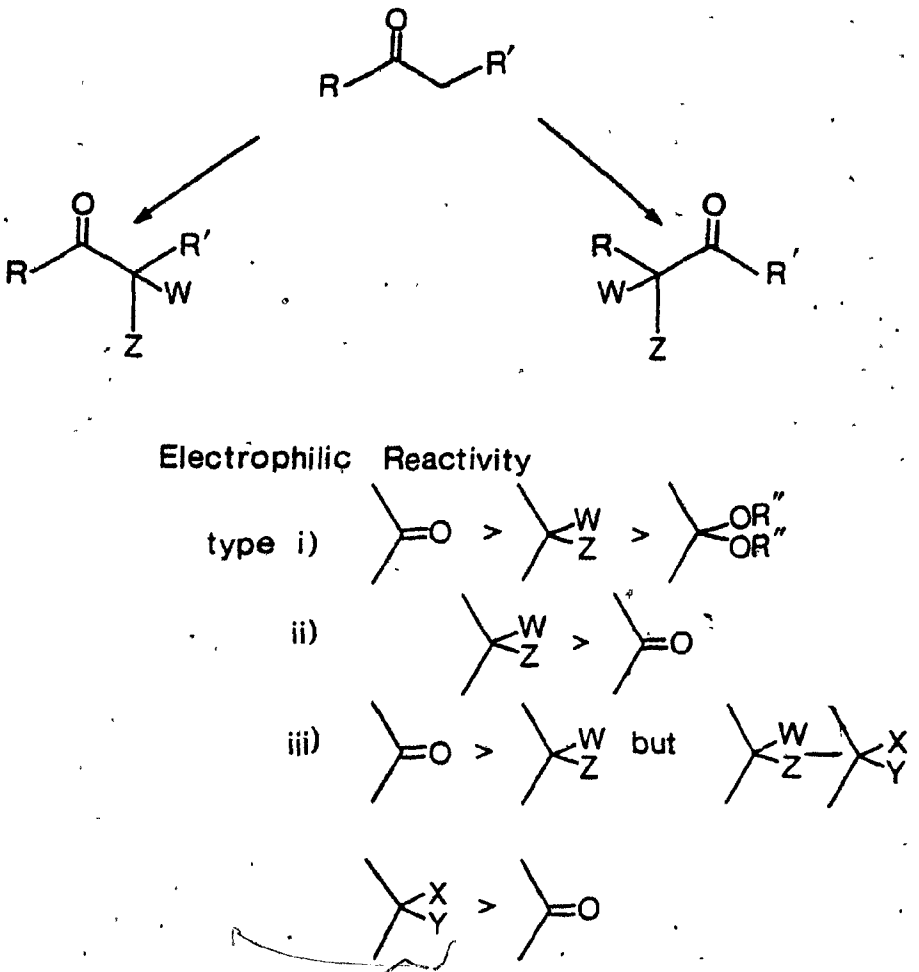
117 , Scheme 3.47 122

To be synthetically useful, this must occur in "one-pot" sequential procedure. Further constraints exist in that the reagent for deacetalization must not react with the enol silyl ether. This is a difficult challenge as most acidic deacetalization catalysts, such as aqueous acid or trimethylsilyl iodide, react with the enol silyl ether directly. In one experiment, for example, the attempted deacetalization of the intermediate 117 (R=Me) with iodotrimethylsilane leads to a complex tar. These difficulties in the deacetalization process are exacerbated by the need to keep the reaction at low temperatures to prevent self-condensation.

The simplest solution to this problem would be to find a reactive electrophile with one of the following properties: (i) less reactivity than a ketone but substantially more than an acetal, (ii) greater reactivity than a ketone, or (iii) less reactivity than a ketone, but must be transformable into a reactive electrophile under conditions which do not affect silyl enol ethers. To be of synthetic use, these hypothetical compounds must be easily synthesized from a carbonyl group (Scheme 3.48). In addition, it must be possible to control the regiochemistry of their formation.

3.8.4 Approaches to Finding Alternate Electrophiles

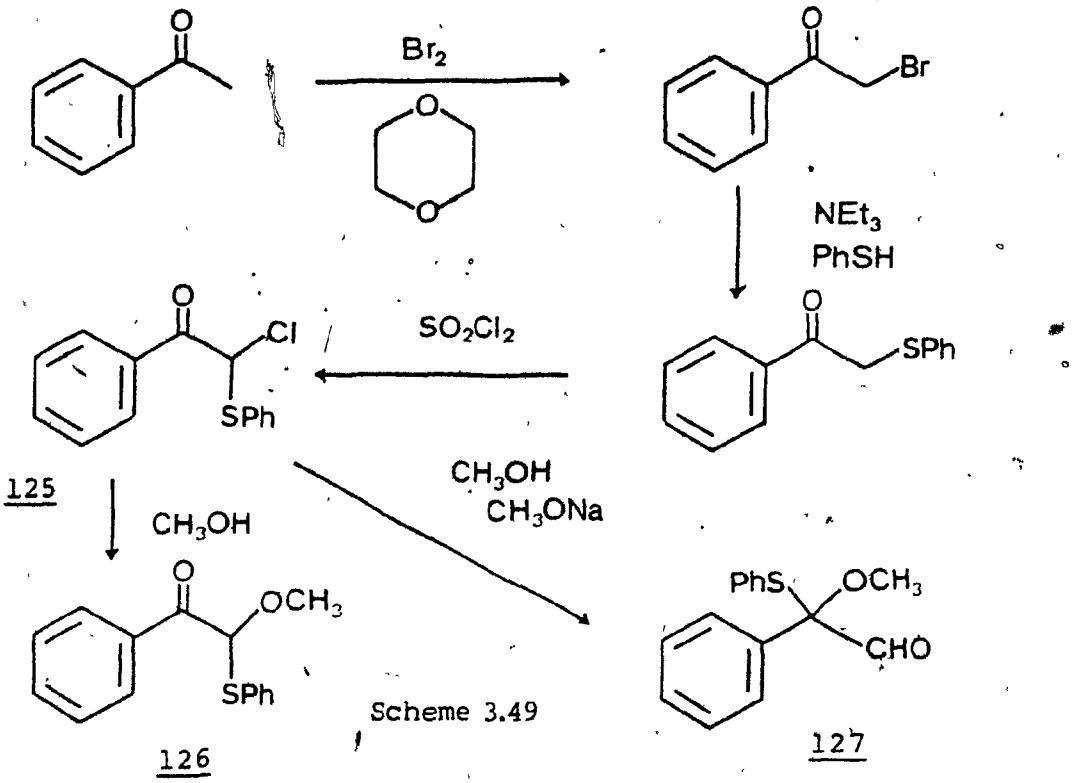
Some attempts have been made to find electrophiles which fulfil the requirements listed above. A possible alternative electrophile exhibiting the necessary properties of type (i) compound are the hemithioacetals. They are less reactive than ketones[297] and the possibility exists that their reactivity is intermediate to acetals or ketals and ketones (type i). They can be synthesized from a methyl ketone or aldehyde to generate



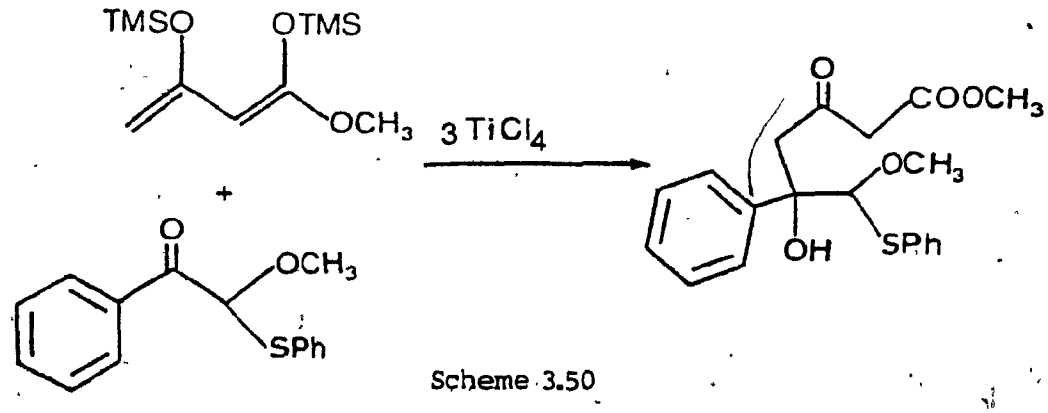
Scheme 3.48

both possible regioisomers of the α-carbonylhemithioacetal.

A synthesis of α-ketohemithioacetals involves the following steps (Scheme 3.49). In the first step, the bromination[321] of acetophenone proceeds readily in 55% yield. It is surprising to note that the bromination of phenylacetaldehyde under identical conditions, which would have eventually led to the same products, gives only a complex tar. Next is the introduction of the thiophenyl group which, using a modification of the method of Duhamel[322] is achieved with thiophenol and triethylamine in cold hexanes to give the product 124 in 99% yield. Chlorination with sulfuryl chloride[323] gives the α-chloro phenylsulfide 125 in 99% yield.



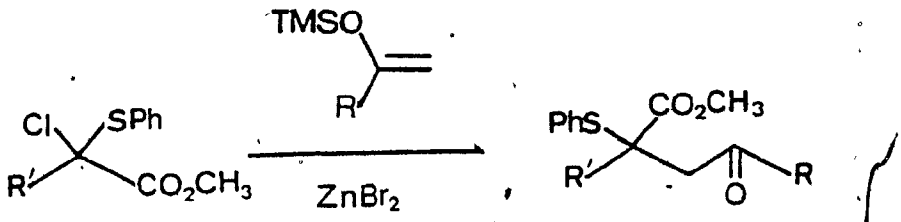
Methanolysis of 125 leads to 126 in 87% yield[324], while treatment of 125 with one equivalent of sodium methoxide in methanol at 0°C leads to 127 in a 77% yield[324]. The yields of the overall reaction sequences are quite high 40% and 42% from acetophenone for 126 and 127, respectively. Unfortunately when the condensation of the hemithioacetal 126 with the *bis*-silyl enol ether 100 was attempted, catalyzed by three equivalents of $TiCl_4$, the desired cyclopentenone is not formed, only the monoalkylated product is isolated (Scheme 3.50).



Scheme 3.50

This indicates that the hemithioacetal is insufficiently electrophilic to allow the formation of 5-membered rings under the conditions used. Moreover, it is also unreactive towards the deacetalization step which would have allowed the formation of a more potent electrophile.

A second electrophile of type (ii) is an intermediate in the synthesis of hemithioacetals, the α-chlorobenzyl phenylsulfide 125. Compounds of this type can be used as electrophiles for the α-alkylation of carbonyl groups (*vide supra*). Recently, the successful use of methyl α-chloro-α-phenylthioacetate for condensations with silyl enol ethers has been described (Scheme 3.51)[325,326].

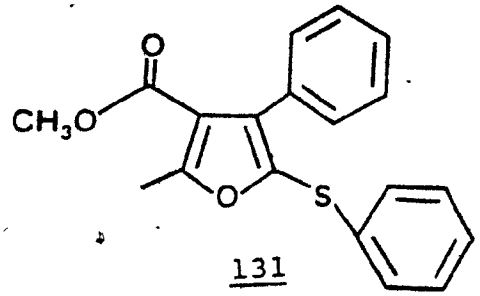


Scheme 3.51

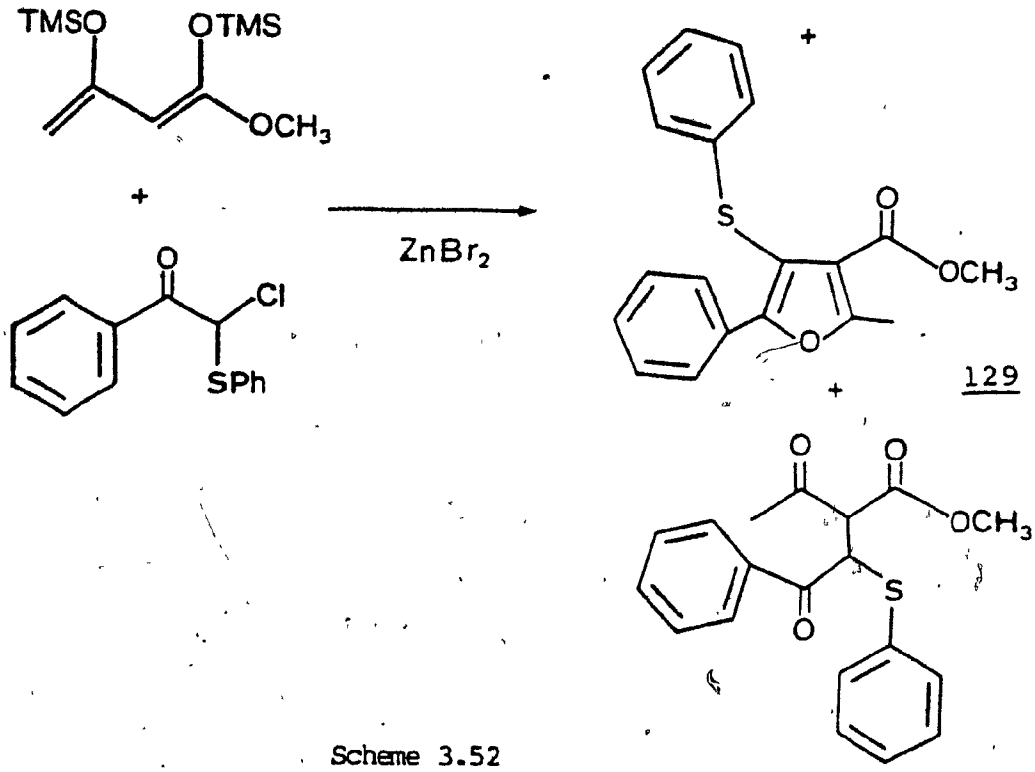
When the corresponding reaction of 100 with the phenyl ketone 125 is attempted, with zinc bromide as catalyst, none of the desired cyclization products are isolated. Instead, the formation of substituted furans, for which there is some precedent in the literature[258], and monoalkylated products are observed (Scheme 3.52). It can be seen that the furan 129 and the inseparable pair of diastereomers 130 arise from α-alkylation of 100 at the carbon bearing chlorine in electrophile 125. The other furan 131 also arises from α-attack, but at the phenyl ketone centre. This is the only electrophile in the context of this thesis in which α-alkylation of this type has been observed. This may arise in either or both of two ways. First, traces of the γ-alkylation products might be formed,

leading to a furan and concomitant formation of a hydroxylic species (such as trimethylsilanol). These hydroxylic species could hydrolyse 100 to the monosilyl enol ether, which would then undergo α-alkylation to give the furans 129, 131, and the monoalkylated products 130. Again, formation of these furans would be accompanied by the production of hydroxylic species and further hydrolysis of 100 could occur. On the other hand, Fleming has noted that of all the electrophiles which he has tested (Table 3.3) the α -chloro phenylsulfides give the greatest proportion of α-alkylation. This electrophile may simply be one for which the α-/γ-alkylation ratio is very high. It is possible that the alkylation which takes place first is the γ-alkylation, and that a subsequent rearrangement to the α-product takes place. However, it does seem unlikely that there would be enough of a thermodynamic advantage in the formation of the α-alkylated product to justify such a rearrangement, and therefore, this possibility appears remote.

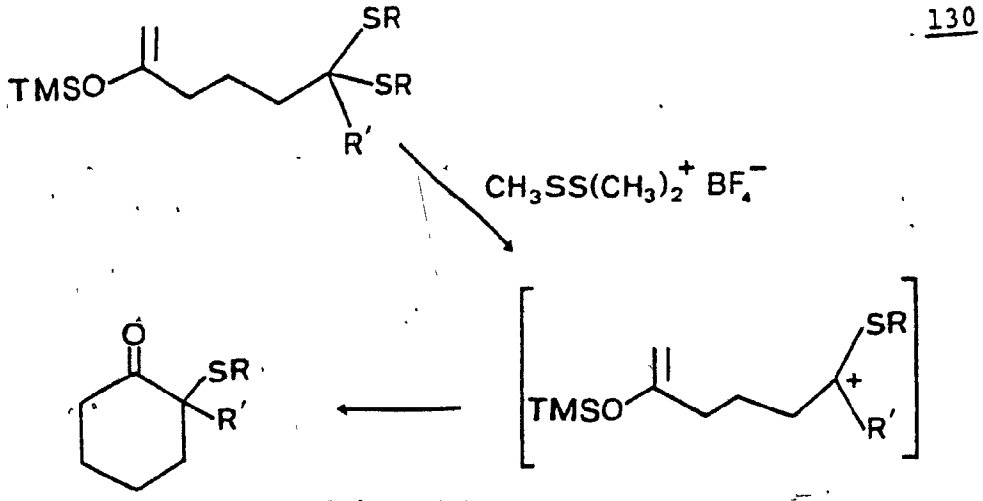
Attempts to utilize electrophiles of type (i), hemithioacetals, or type (ii), α-keto-α-chloro phenylsulfides, do not appear to be suitable for the synthesis of 5-membered rings. Electrophiles of the type (iii), those which can be deblocked in the presence of an enol silyl ether, have recently been described by Trost[282]. Dithioketals can be transformed into carbonium ions in the presence of a silyl enol ether (Scheme 3.53)[327].



131

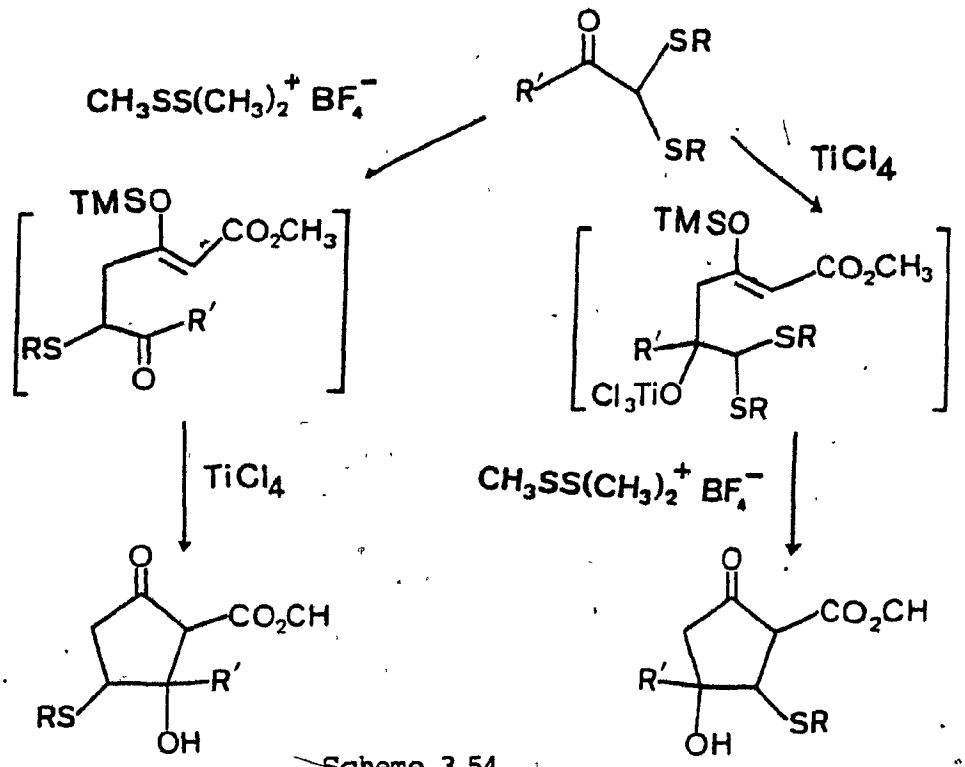


Scheme 3.52



Scheme 3.53

It seems possible, therefore, that a procedure of this type would allow the formation of cyclopentenones as well (Scheme 3.54).



Scheme 3.54

This proposed scheme could allow the synthesis of both regioisomers from a single carbonyl group, and as a result this type of electrophile offers real potential, although experimental work in this area has yet to be done.

3.8.5 Modification of the Lewis Acid Catalyst

Another way in which the reactivity of the electrophile could be increased is the manipulation of the Lewis acid catalyst. If a more oxophilic catalyst could be found, then it is possible that the electrophiles described could be used to give the desired cyclization products

directly. Both stannic chloride and the zinc dihalides have been used as Lewis acid catalysts, but both are less reactive than $TiCl_4$. It was hoped, therefore, that changing the ligands on the titanium would lead to improved electrophilic reactivity. Unfortunately, some preliminary experiments show that solutions of this kind are difficult to find. For example, the cyclopentadienyl substituted titanium species (Cp_2TiCl_2) is far less reactive then titanium tetrachloride itself; no reaction was observed in the condensation of benzaldehyde with methyl 3-trimethylsiloxy-but-2-enoate at 115°C over a 48 hour period.

3.8.6 The Relative Reactivity of Electrophiles Towards 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene Under Acid Catalyzed Conditions

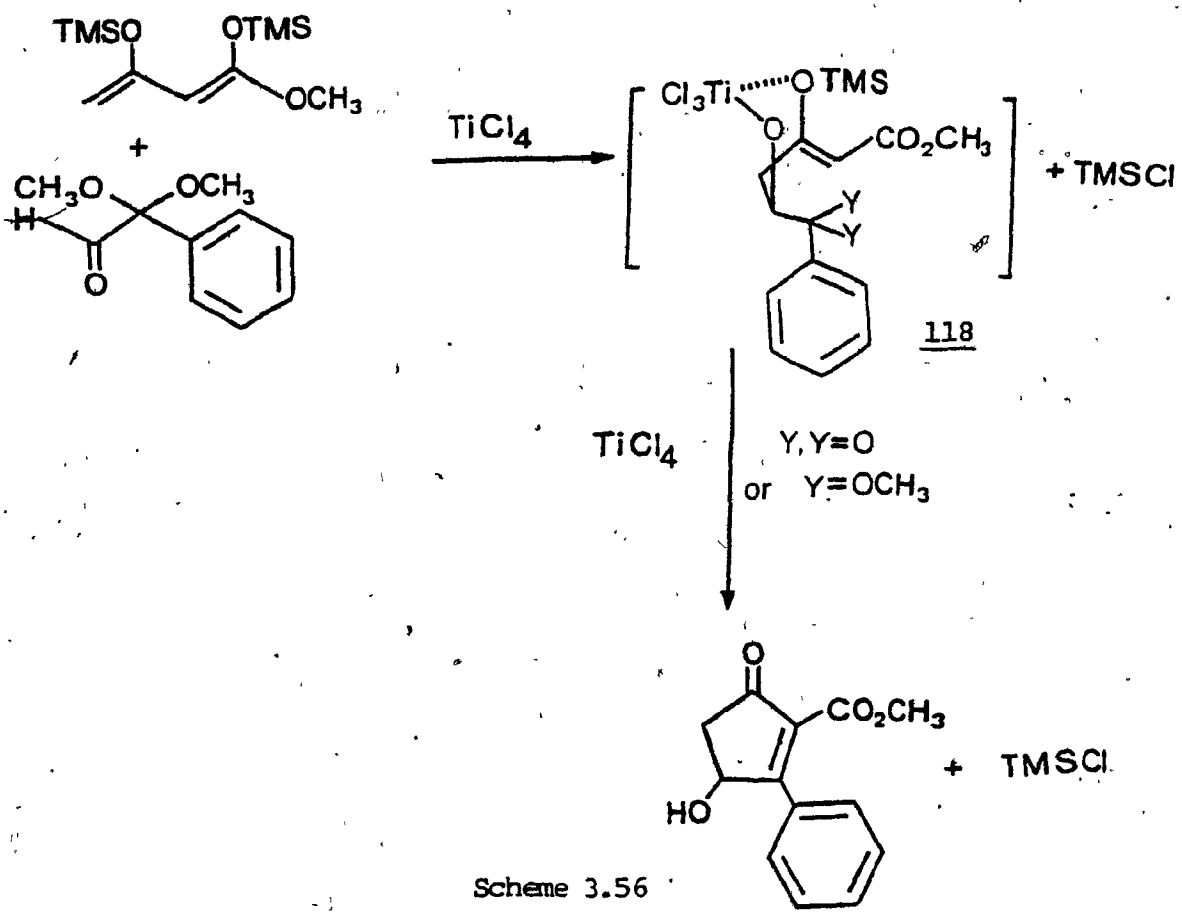
The work described has involved the use of one silyl enol ether 100 in condensation reactions with a series of electrophiles. While it is not possible to state that the order of electrophilic reactivity will be the same for other silyl enol ethers, it can serve as a guideline. The relative reactivities of the electrophiles has been found to be the following (Scheme 3.55).

$$RR'C(Cl)SC_6H_5 > ArCOCHO > ArCOCHO > RC(OCH_3)_2, RC(OCH_3)SC_6H_5 > RCHCl_2$$

Scheme 3.55

3.9 MECHANISM

The mechanism of the reactions of silyl enol ethers with electrophiles under titanium tetrachloride catalysis, have been postulated[277,328] to proceed via a cyclic transition state (Scheme 3.56).



Scheme 3.56

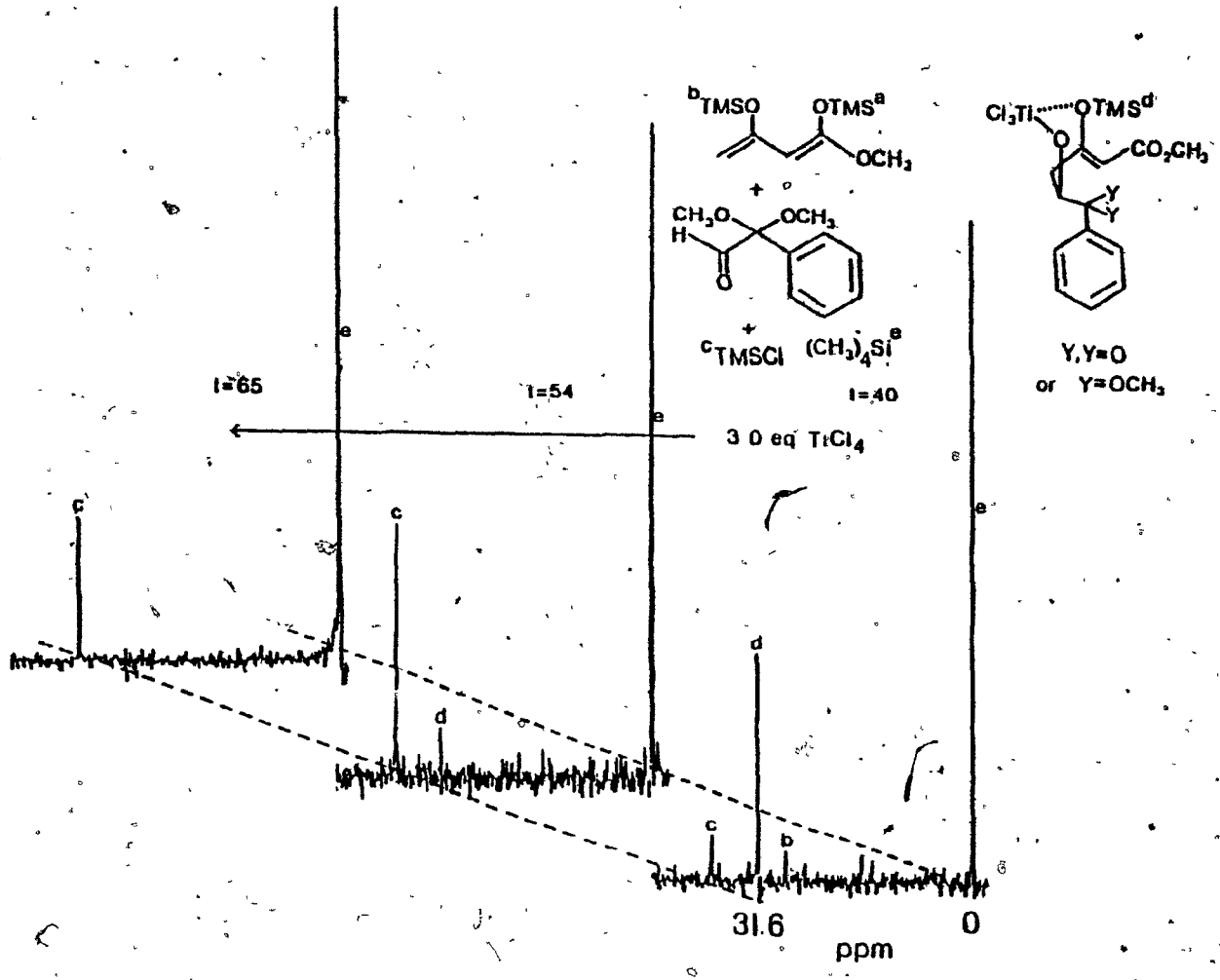
Support for this rests upon the occurrence of diastereoselection during alkylation which must arise from a relatively rigid transition state. No direct spectroscopic evidence has been reported to confirm this postulate.

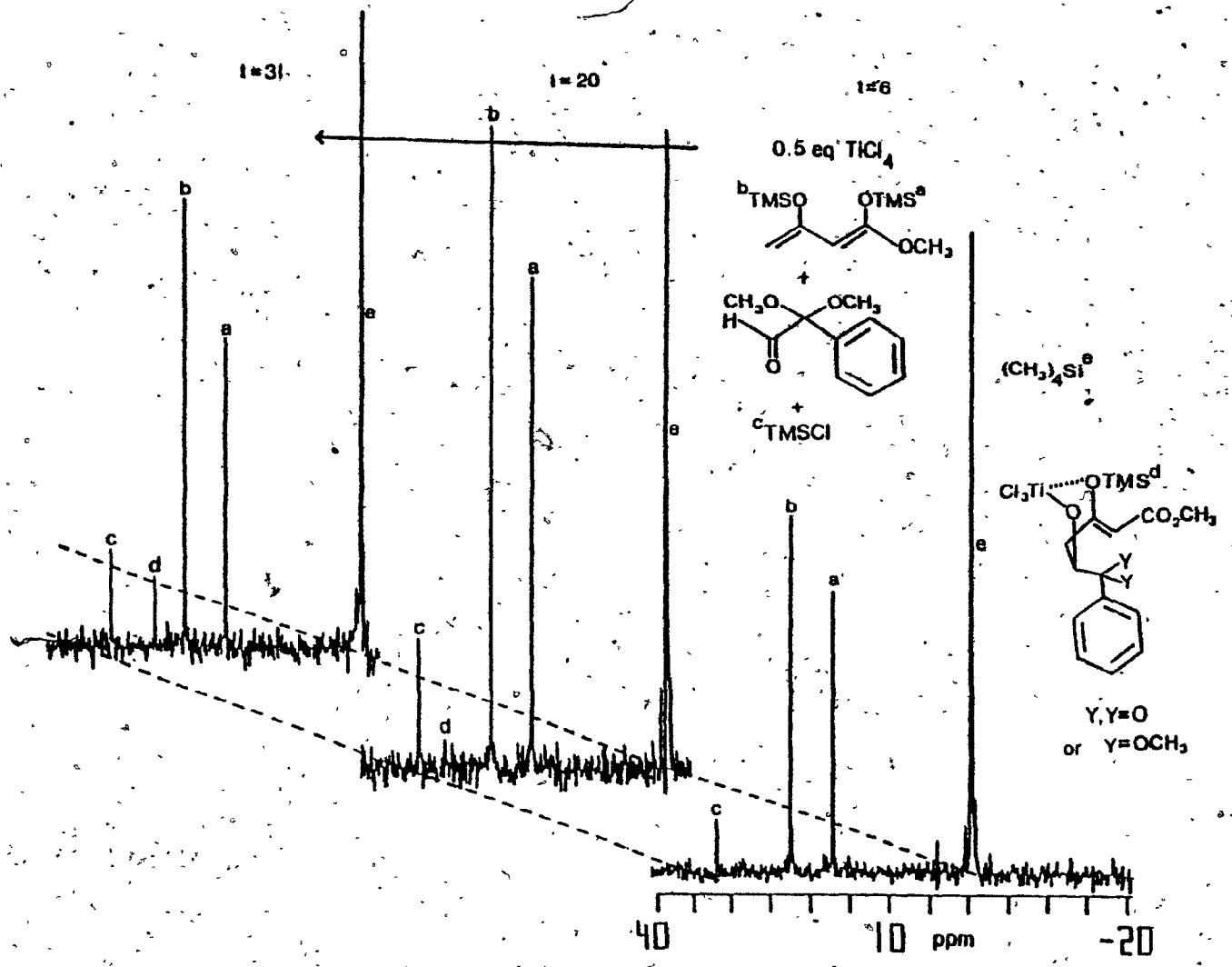
In order to clarify the mechanism of the 3-carbon + 2-carbon cyclization reaction, ^{29}Si-N.M.R. using the INEPT pulse sequence was used (see Appendix 2). Data accumulations of only seven minutes are required

for each of the six spectra taken, when using the INEPT pulse sequence. The concentration of the reactants are necessarily high, and therefore, the direct mechanistic correlation with the preparative scale reaction cannot be necessarily inferred. The reaction is performed at -50°C in two stages (at lower temperatures, precipitates form which greatly distort the spectra); to an equimolar mixture of the *bis*-silyl enol ether and 2,2-dimethoxyphenylacetaldehyde, in methylene chloride, is added 0.5 equivalents of titanium tetrachloride. After three spectra are taken at approximately 10 minute intervals, the remaining 2.5 equivalents of titanium tetrachloride is added to complete the reaction and then a further three spectra are taken. The results are shown in Figure 3.1. The starting *bis*-silyl enol ether shows two peaks; the enol silyl ether (22.5 ppm) and the enol silyl ester (17.1 ppm). It should be noted that these peaks are slightly downfield from the corresponding peaks in the absence of $TiCl_4$; the resonances in that case are 21.8 and 16.2 ppm, respectively. Upon addition of titanium tetrachloride, the enol ester peak begins to decrease in intensity and is accompanied by the formation of some chlorotrimethylsilane. There is also the formation of a new peak at 26.1 ppm which is believed to correspond to the chelated monosilyl enol ether 118 (Scheme 3.56). With the addition of the remainder of the titanium tetrachloride, the enol ester and enol ether peaks both collapse, leaving peaks corresponding to the trimethylchlorosilane and the monosilyl intermediate 118. After one hour, the reaction is complete and the only remaining silicon containing product observed is the chlorotrimethylsilane (31.6 ppm). It should also be noted that the silyl peak observed at 26.1 ppm, must be bound to an oxygen atom chelated to a titanium moiety either inter-, or more likely, intramolecularly. The unchelated monosilyl enol

INEPT ^{29}Si-N.M.R Spectra Following the Condensation Reaction of the Indicated Enol Silyl Ether and Electrophile to Determine the Mechanism

(t refers to the time halfway through an aquisition)




t=31
t=20
t=6
0.5 eq TiCl4
bTMSO
OTMS a
OCH3
CH3O
H
OCH3
O
+
cTMSCl
(CH3)4Si e
Cl3Ti
OTMSd
O
CO2CH3
Y
Y
Y,Y=O
or Y=OCH3
a
b
c
d
e
40
10
ppm
-20

ether 97 displays a peak in the ^{29}Si-N.M.R. at 20.09 ppm ((E) isomer, the minor (Z) isomer (15%) displays a peak at 19.93 ppm), considerably upfield of the peak observed from 118. A downfield shift of this sort is a result of deshielding of the silyl oxygen atom by the chelating titanium moiety.

This spectral data confirms the sequential nature of the reaction, shows that it is the silyl enol ester which reacts first through the γ-position, that titanium directly coordinates, probably in an intramolecular fashion, to the oxygen upon which the silyl group of the silyl enol ether resides, and finally, that trimethylsilyl chloride is the only silicon containing product of the reaction.

3.10. CONCLUSION

The utility of silyl enol ethers in organic synthesis is rapidly becoming widespread. In order to further evaluate the utility of these compounds a wide variety of dielectrophiles in a 1,2-relationship were synthesized. The relative reactivity of these electrophiles towards 1,3-bis-trimethylsiloxy-1-methoxy-1,3-butadiene under $TiCl_4$ catalysis was determined. It has been shown that γ-alkylation is the preferred mode of reactivity for this compound (with the exception of α-chloro phenylsulfides which react predominantly at the α-position). In addition, an order of electrophilic reactivity towards silyl enol ethers has been established based on the the reactivity of these 1,2-dielectrophiles. In certain cases, it has been determined that dialkylation can occur leading to hydroxycyclopentenones. These compounds are of interest because their substitution pattern is the same as that for the prostaglandins.

The mechanism of the dialkylation reaction has been shown to proceed

via an intermediate bound to the titanium catalyst. The enol ester reacts first at the γ-position to form the chelated intermediate. This intermediate silyl enol ether then reacts at the α-position to give the cyclic product. It is hoped that the experimental work on the chemistry of enol silyl ethers has served to indicate just what versatile reagents they are. Moreover, it is hoped that this mechanistic and synthetic work will further facilitate the use of silyl enol ethers in synthetic organic chemistry.

Appendix 1:Chromatography

A Comparison of the Relative Efficiency of Flash, Mesh, and High Pressure Liquid Chromatography

One of the more tedious and time consuming tasks in the organic synthetic laboratory is the purification of compounds. It is also one of the most important procedures. The time which is required to spend on this problem, however, is minute compared to the situation only five years ago. This can be credited largely to Still[79] who reported a new chromatographic technique, flash chromatography. Flash chromatography incorporates features from both gravity feed column chromatography and high pressure liquid chromatography, thus allowing the advantages of both techniques to be exploited. The advantage of the former technique is essentially the ability to do large scale separations, while the latter technique exhibits the merits of speed and high efficiency.

Flash chromatography is a medium pressure column technique which uses a smaller silica gel particle size (40-63 microns) for higher chromatographic efficiency while maintaining reasonable flow rates. The technique allows the easy separation of quantities of material from 1 mg to 1 g and may be further scaled-up in some cases. Another very important element of this technique is the direct correlation of the separation of compounds on a T.L.C. plate (0.2 mm thick, aluminum backed) to that on the column. For the separation of only two components, compounds whose R_f differ by 0.1 or more can be easily separated. Its utility can be further expanded for the separation of multi-component mixtures by using step-gradient elution. As can be seen from the experimental section, this technique was extensively used.

Another technique which has been exploited to achieve good separations is mesh chromatography[80]. This is a similar technique to flash chromatography but differs in the mesh of the silica gel used. To compensate for the higher density of the packing of the smaller particles (T.L.C. grade silica gel), less silica gel is required. Therefore, this procedure belongs to the family of short column chromatography techniques. Mesh chromatography allows the separation of two compounds with an R_f difference of 0.07 or greater. It is inadequate, however, for the separation of multi-component mixtures with or without step-gradient elution. One disadvantage of this procedure is the poor correlation of the separation of compounds on the column with that on a T.L.C. plate.

Both mesh and flash chromatography are extremely simple to set up, to run, and require very inexpensive equipment. There are limitations, however, in the amount of material which may be separated and the efficiency of the separation. For large scale separations, the Waters Prep 500A H.P.L.C. can be utilized. This instrument allows flow rates of 50-500 mL/min through a radially compressed column (6.25 cm internal diameter, 30 cm in length) with an internal volume of 500 mL. This large scale equipment is particularly useful for such problems as the removal of benzyl alcohol from a mixture of benzyl alcohol, benzyl ether and methyl benzoate (see ester experimental section). The removal is accomplished by trapping the benzyl alcohol on the column with a non-polar eluent leaving the etheric compounds free to elute. Subsequently, the benzyl alcohol can be washed from the column with methanol. Although this is not truly a chromatographic procedure as much as a filtration, it is a very useful separation technique.

It is also possible to use the Prep 500A for separations which

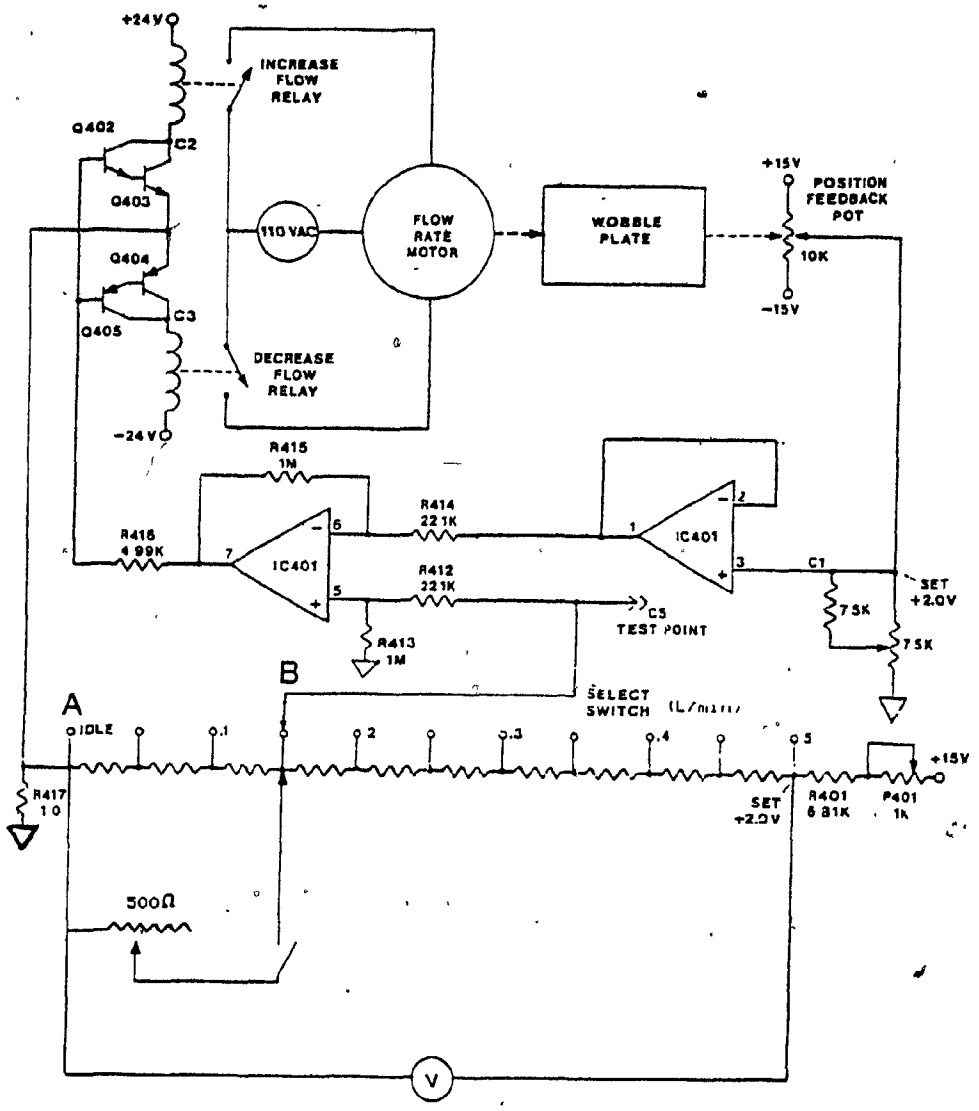
required high chromatographic efficiency. The columns supplied by Waters, however, are far too large, and expensive in the use of solvents, to use for the efficient separation of small quantities of material. Therefore, a 2.5 x 30 cm stainless steel column obtained from Waters can be adapted for use in this context. Unfortunately, the silica gel supplied by Waters gives poor results when packed in this smaller column. However, by using a different silica gel (43-60 microns, Merck kieselgel) and the dry packing technique of flash chromatography, the separations can be improved.

Further modifications of the equipment were required before efficient separations could be achieved. From chromatographic theory[329], the reduction in flow rate and/or particle size of the packing material improves the separation of the components of the mixture at the expense of separation time and column loading, respectively. In consideration of this theory, a flow rate of 25 mL/min was found to be optimum in terms of resolution, efficiency and time. However, the instrument only allows flow rates of up to 500 mL/min in 50 mL/min increments. The ideal flow rate, therefore, was unattainable.

The flow rate controller was modified to make this optimum flow rate accessible. The flow rate of a Waters Prep 500A Liquid Chromatograph[333] is controlled by a feedback mechanism which compares the existing flow rate, represented by a voltage across the flow rate transducer, with the newly selected flow rate, represented by a voltage taken from the flow rate switch (a voltage divider). If a difference exists between the two voltages, the flow rate will be incremented or decremented until the new flow rate is established. Flow rates other than those provided by the manufacturer are obtainable by modifying the flow rate switch. This can

be done by adding a 500-Ω variable resistor between the idle point (see Figure 4.1, position A) and the third position of the flow rate switch (position B). This permits a smaller voltage change to be selected by the comparator, and thus, control of the flow rate from 12-100 mL/min is

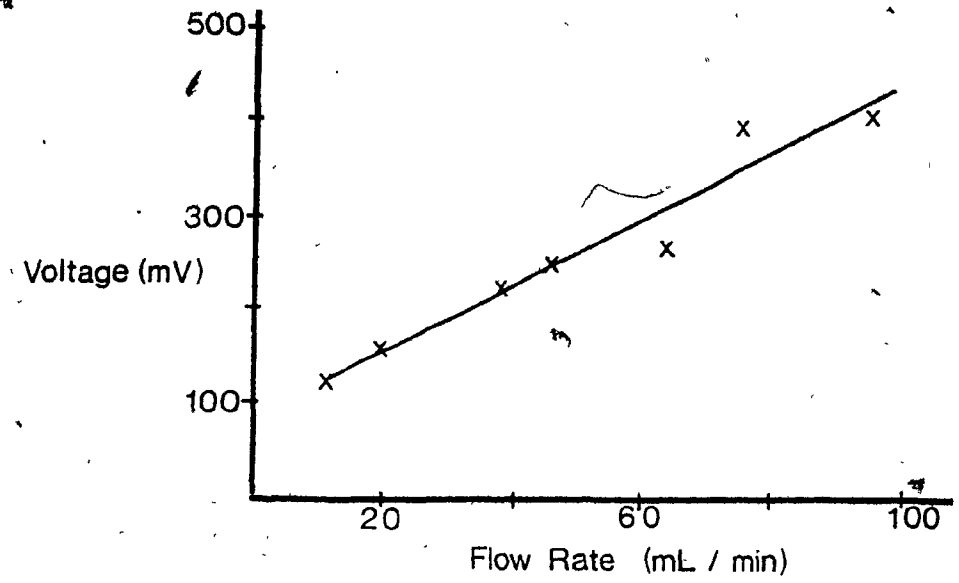
Figure 4.1:A Circuit Diagram of the Modified Waters Prep 500A Liquid Chromatograph*



* This modified version of the original Waters diagram is reproduced with permission.

possible. A calibration curve can then be constructed (Figure 4.2) by plotting the voltage applied to the comparator (or the values on the variable resistor dial) *versus* the flow rate. This curve is linear with an intercept of 12 mL/min which represents the minimum voltage difference that the comparator can detect.

Figure 4.2:A Plot of the Measured Voltage Across the Flow Rate Switch *versus* the Observed Flow Rate



A comparison of the efficacy of the modified H.P.L.C. and flash chromatography was carried out by separating a 1:1 mixture of methyl and propyl *p*-hydroxybenzoates. An oversized column (2.5 cm internal diameter, packed with 15 cm of silica gel (vertical column height)) was used for the flash chromatography to allow a better separation. Table 4.1 shows the quantities of materials submitted to the column as a mixture and isolated as pure compounds after chromatography. The purity was ascertained by both T.L.C. and ^{1}H-N.M.R.. It can be clearly seen that the H.P.L.C. gave

a remarkably efficient separation, especially in consideration of the small structural difference between the two compounds*. The separation with flash chromatography was not nearly so successful.

Several advantages exist in the use of the Waters H.P.L.C.. One can selectively "shave" purified material from the column and recycle the remaining mixed materials. It is also possible to use more sensitive or selective detectors such as the ultraviolet detector. One disadvantage, however, is the difficulty in choosing a solvent system. For flash chromatography, one simply chooses the solvent system for which the intermediate position between the two compounds to be separated, corresponds to a "mobility" on T.L.C. of R_f=0.33. The mobility on T.L.C. which corresponds to a good H.P.L.C. separation is R_f=0.07. As it is difficult to accurately measure such low R_f's, choosing an appropriate solvent system involves much trial and error.

In conclusion, it can be said that the modified H.P.L.C. is extremely efficient for difficult separations. It will separate compounds whose R_f differs by 0.05 or more. This simple and inexpensive modification also fills the gap between the analytical and "preparative" liquid chromatographs by allowing improved separation capability in the 50-500 mg sample range. It is not appropriate, however, for routine separations in light of the difficulty in choosing the solvent system.

* Although the H.P.L.C. permits recycling, that is, passing the mixture through the column more than one time via internal tubing, this was not utilized so that a fair comparison between the techniques could be made.

Table 4.1:A Comparison of the Separation Capabilities of Flash Chromatography and the Modified Waters Prep 500A H.P.L.C.

Technique (Eluent)	Propyl ester (mg) on column	Propyl ester (mg) off column	Recovery* %	Methyl ester (mg) on column	Methyl ester (mg) off column	Recovery* %
H.P.L.C. (9:1 hexanes-ethyl acetate)	66.5	66.0	99	66.5	64.0	96
Flash (4:1 hexanes-ethyl acetate)	74.0	45.0	61	75.0	20.1	26

* The mixture of the two compounds was placed on the column in a small quantity of the eluent solution. The separation procedure followed was that of Still[79] and Waters[333], respectively. With the H.P.L.C., however, the suggested packing and flow rates were modified. The fractions were spotted on T.L.C. (Kieselgel 60 F_{254} aluminum-backed plates from E. Merck), eluted in the solvent system used for the preparative separation and developed in a sulfuric acid-based developer. Fractions containing a single compound on the basis of the T.L.C. were combined, the solvent removed under reduced pressure and an ^{1}H-N.M.R. spectrum taken of the residue. The spectra in all cases confirmed the presence of a single product, either the methyl or propyl -hydroxybenzoate.

Appendix 2:Nuclear Magnetic Resonance Spectroscopy Using The INEPT* Pulse Sequence

Nuclear Magnetic Resonance has become the single most important technique for the identification of organic molecules. To a certain extent, this is due to the very high sensitivity, short relaxation times, and large natural abundance of protons which are observed in the magnetic resonance experiment. However, the attainment of comparable chemical information from carbon, nitrogen, and silicon nuclei, has been limited by low abundance, long relaxation times, low sensitivity, and in the case of silicon and nitrogen, has also been hampered by a negative gyromagnetic ratio. The latter three problems can be circumvented by the use of a technique termed "insensitive nuclei enhanced by polarization transfer" or INEPT[336].

This method makes use of a multi-pulse sequence whereby the nuclear spin polarization of protons (large Boltzman population difference and short relaxation times) is transferred to the insensitive nuclei (I)** to which they are coupled (I=^{13}C[336], ^{15}N[337], ^{29}Si[338]). It has not only been applied to spectral enhancement but in addition, to spectral simpli-

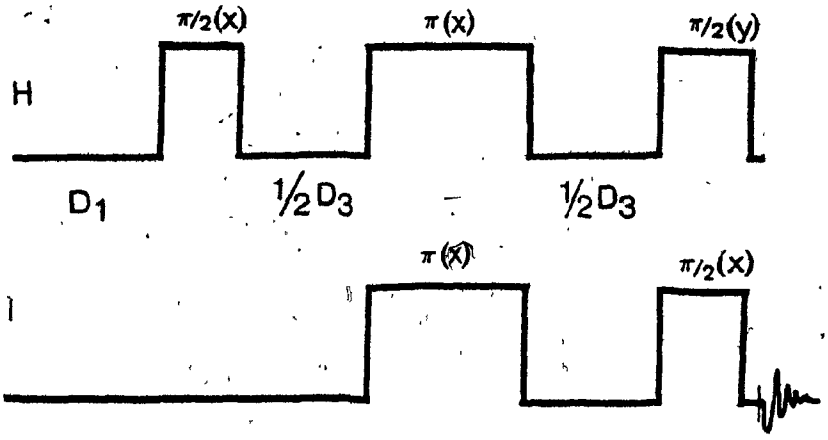
* This treatment of the INEPT pulse sequence is in no way intended to be a mathematically rigourous, but rather a simplified "hand-waving" explanation which, it is hoped, will allow an understanding of and outline the utility of the INEPT pulse sequence. For a mathematical treatment the reader is referred to the references 334-344.

** I refers to insensitive nuclei, H to a proton.

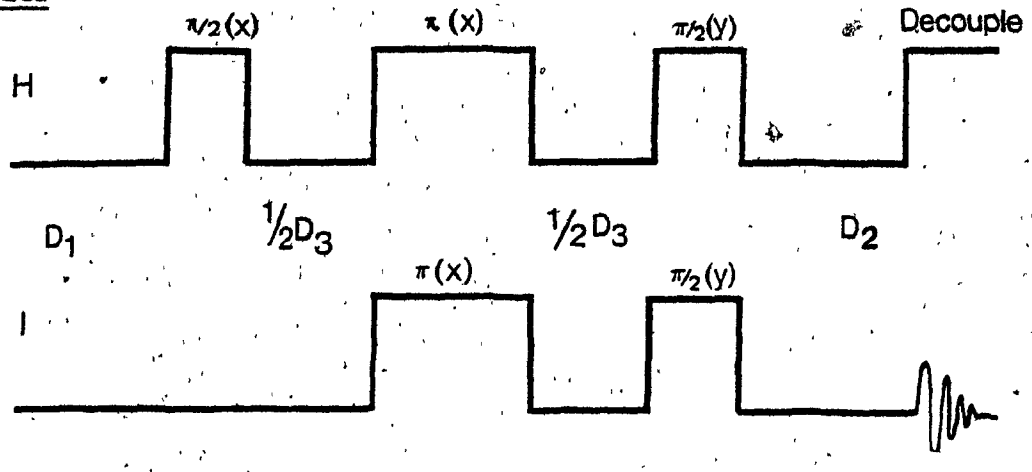
fication[339,340] and two-dimensional ^{1}H-N.M.R.[341].

The multi-pulse sequence can be modified to give coupled or decoupled spectra. Representations of the two pulse sequences are given below.

Coupled



Decoupled

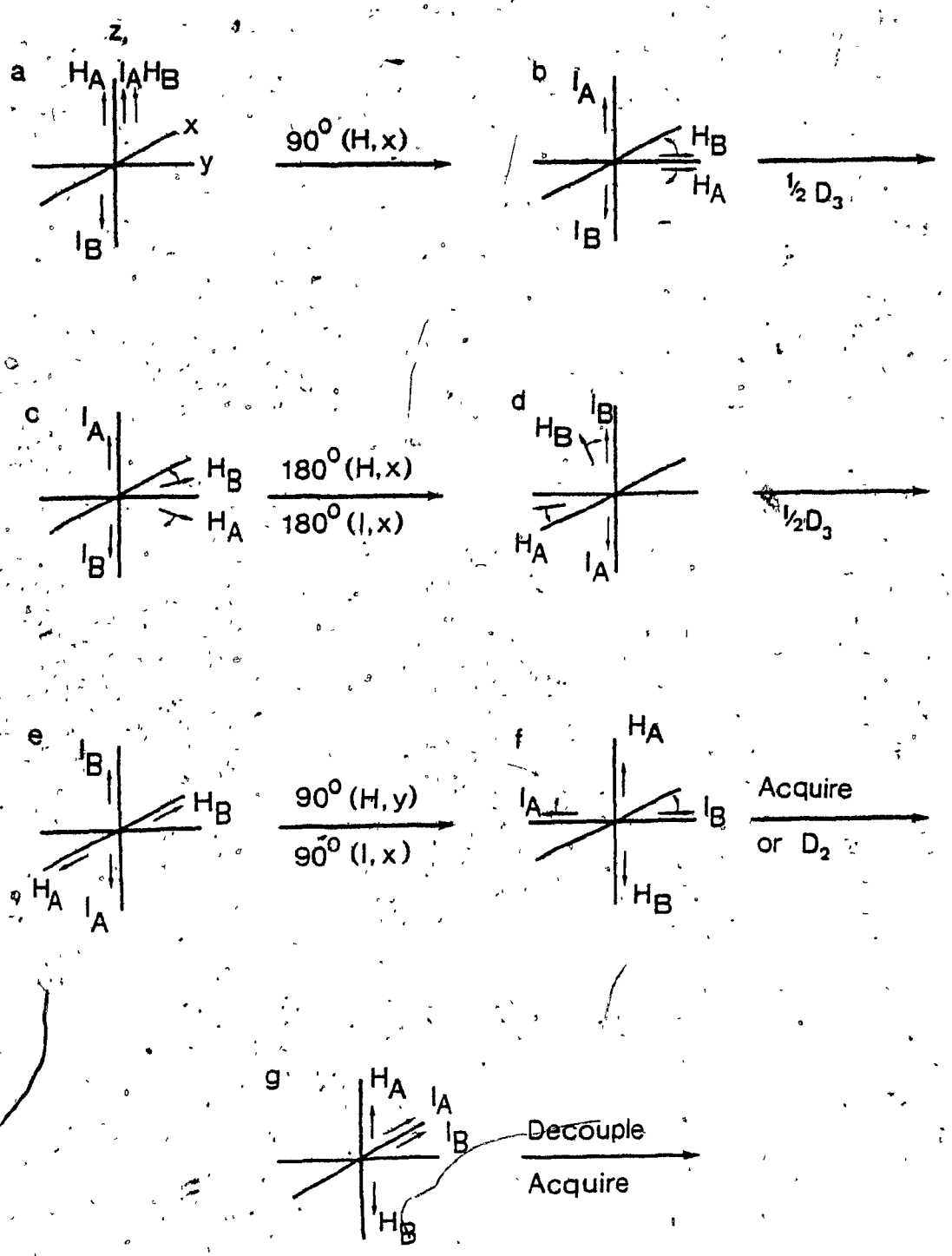


The H $\pi/2(x)$ refers to a pulse along the x-axis of appropriate length in microseconds to rotate the H magnetization vector from its original position parallel to the z-axis onto the x-y plane. D_3 and D_2 represent delay periods in milliseconds during which the magnetization vectors are allowed to precess. The understanding of the pulse sequence is simplified if one realizes that the H $\pi(x)$ and I $\pi(x)$ are simply refocusing pulses[342] placed at the midpoint of a free precession (D_2 or D_3) in order to observe

only the precession due to H-I coupling.

Bendall, Pegg, and Doddrell[343,344] have shown that the results of these pulse sequences can be analyzed using the Heisenberg vector approach. Utilizing a doubly rotating frame of reference, the polarization of I and H in an IH system can be followed simultaneously (Scheme 4.1). H_A and H_B represent the net proton magnetization vector, that is, the excess polarization aligned along the +z-axis, I_A and I_B refer to the I atoms, half in the +z and half in the -z direction, which are coupled to H_A and H_B respectively. The net initial magnetization of I will be ignored for the purpose of this discussion.

The initial state of the system, in the presence of magnetic field is represented in Scheme 4.1a. An H $\pi/2(x)$ pulse rotates the H magnetization vector onto the y-axis (Scheme 4.1b) where H_A and H_B begin to precess due to coupling to I_A and I_B. After a delay of period $1/2D_3=1/(4J_{HI})$, H_A and H_B have diverged 90^o (Scheme 4.1c). At this point, the H $\pi(x)$ and I $\pi(x)$ refocusing pulses are employed (Scheme 4.1d). The 180^o H pulse refocuses all H precessions while the 180^o I pulse serves to reverse the directions of I_A and I_B allowing the maintenance of coupling information. After an additional time delay of $1/2D_3$, H_A and H_B are aligned in opposite directions along the x-axis (Scheme 4.1e). An H $\pi/2(y)$ pulse then rotates the H magnetization back onto the z-axis. A simultaneous I $\pi/2(x)$ pulse aligns I_A and I_B with the +y and -y axes (Scheme 4.1f). I_A and I_B then represent the enhanced I magnetization coupled to H. Acquisition and manipulation of data at this point, gives a doublet with relative intensities +1 and -1, while decoupling gives no net signal.


a
z
H_A I_A H_B
x
y
I_B
90^0 (H, x)
b
I_A
H_B
H_A
I_B
½ D_3
c
I_A
H_B
H_A
I_B
180^0 (H, x)
180^0 (I, x)
d
I_B
H_B
H_A
I_A
½D_3
e
I_B
H_B
H_A
I_A
90^0 (H, y)
90^0 (I, x)
f
H_A
I_A
I_B
H_B
Acquire
or D_2
g
H_A
I_A
I_B
H_B
Decouple
Acquire

Scheme 4.1

In systems of IH_n where n>1, the situation is somewhat more complex. If n=2, for example, the nuclei I_A and I_B receive polarization from the surplus of protons in the $\uparrow\uparrow$ state over those in the $\downarrow\downarrow$ state. That is, the coupling of I_A with the excess of $\uparrow\uparrow$ over $\downarrow\downarrow$ protons, leads to a net -1 signal, while the coupling of I_B with the excess of $\uparrow\uparrow$ over $\downarrow\downarrow$ protons leads to a net +1 signal. There is, however, no net proton magnetization for I nuclei coupled to protons in opposite eigenstates ($\uparrow\downarrow$). Thus, the expected triplet in the coupled INEPT spectrum of an IH_2 system has three lines of relative intensity, +1:0:-1. Such zero intensity centre lines are found in all cases where n is even and allows the easy distinction between even and odd multiline patterns.

When n=3, the coupled INEPT spectrum displays the expected quartet, but with different relative intensities than the corresponding normal H-coupled spectrum. As previously stated, the I nuclei receive polarization from the excess of protons aligned with the magnetic field over those opposed to the field. In this case, two such proton conditions exist, $\uparrow\uparrow\uparrow$ *versus* $\downarrow\downarrow\downarrow$, and $\uparrow\uparrow\downarrow$ *versus* $\downarrow\downarrow\uparrow$. The first pair can be formed by three different combinations of spins while the second pair has only one form. This provides the usual 1:3:3:1 pattern. However, the latter pair has three times as great an energy gap as the first, and therefore, a three-fold greater Boltzman population difference. When these two effects are combined, the result is a 1:1:-1:-1 spectrum. The relative intensities of an IH_n system can therefore be calculated by multiplying the binomial expansion observed for a normal H-coupled spectrum, by n, n-2, n-4.....2,0,-2,.....4-n, 2-n, -n for n=even, and n, n-2, n-4.....3,1,-1,-3,....4-n, 2-n, -n for n=odd. It can be seen that INEPT enhances the weak outer lines ($E=n\gamma H/\gamma I$) by more than the center lines

($E = \gamma H/\gamma I$) and allows observation of more lines in a multiple pattern.

A decoupled spectrum may be obtained by performing the proceeding multi-pulse sequence and then allowing an additional time delay of D_2 (the coupled and decoupled spectra of tetramethylsilane and chlorotrimethylsilane are shown on the following page, Fig. 4.3). In the case of n=1, this allows the two halves of the doublet (Scheme 4.1f) to come into phase (Scheme 4.1g). A refocusing pulse may be applied halfway through this delay period depending on the particular pulse sequence being employed. The values of the optimum delay times for each value of n, can be calculated (Table 4.2). The equation expressing the theoretical enhancement E_d, of the decoupled spectrum, has been derived by Doddrell[338] (Eqn. 4.1, where $D_3=D_{3opt}$).

$$E_d = n(\gamma H/\gamma I)\sin(\pi J(D_2)\cos^{n-1}(\pi J(D_2) \qquad \text{Eqn. 4.1}$$

In addition, Ernst has shown that E_d is dependent on the initial delay period of D_3 (Eqn. 4.2).

$$E_d \propto \sin(2\pi J(1/2D_3)) \qquad \text{Eqn. 4.2}$$

Combining these two equations expressions gives an expression for the theoretical enhancement (Eqn. 4.3).

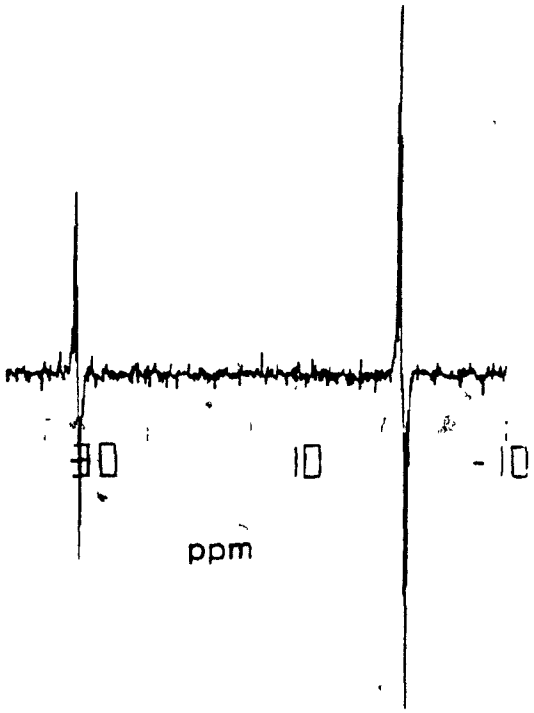
$$E_d = n(\gamma H/\gamma I)\sin(\pi JD_2)\cos^{n-1}(\pi JD_2)\sin(1/2D_3)(2\pi J) \qquad \text{Eqn. 4.3}$$

It can be seen that the enhancement depends on four variables; I, n, $1/2D_3$ and D_2. I is the magnetogyric ratio of the nucleus I and

Figure 4.3

INEPT ^{29}Si-N.M.R. Spectra of Tetramethylsilane and Chlorotrimethylsilane

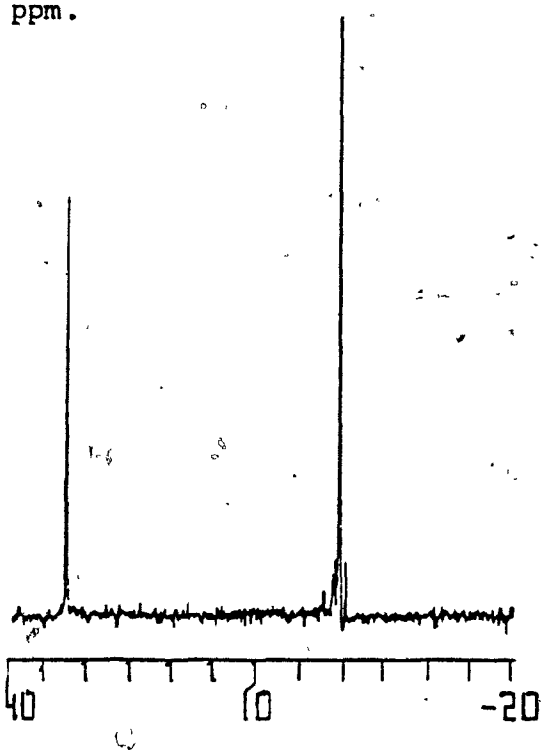
Coupled



$(Me_3)_4Si$, n=12, 13 lines, centre line is null, δ = 0.00 ppm.

$(Me_3)_3SiCl$, n=9, 10 lines, δ = 31.6 ppm.

Decoupled



$(Me_3)_4Si$, n=12, δ = 0.00 ppm.

$(Me_3)_3SiCl$, n=9, δ = 31.6 ppm.

contributes to the enhancement Ed, by the value of the $\gamma H/\gamma I$ ratio. This ratio varies from 4.0 for ^{13}C, to 9.9 for ^{15}N and to 5.0 for ^{29}Si. This factor represents the ratio of the ^{1}H population difference, (which becomes the new I population difference immediately following the INEPT pulse sequence) to the natural I population difference.

Table 4.2:Optimum Values of E_d and D_2 as a Function of Coupled Protons (n)

n	1	2	3	6	9	12	18
E_d *	5.04	5.04	5.82	7.83	9.44	10.82	13.15
$D_{2\ opt}$ **	0.5	0.25	0.196	0.134	0.108	0.093	0.076

* E_d for ^{29}Si, where $\gamma H/\gamma Si = 5.04$.

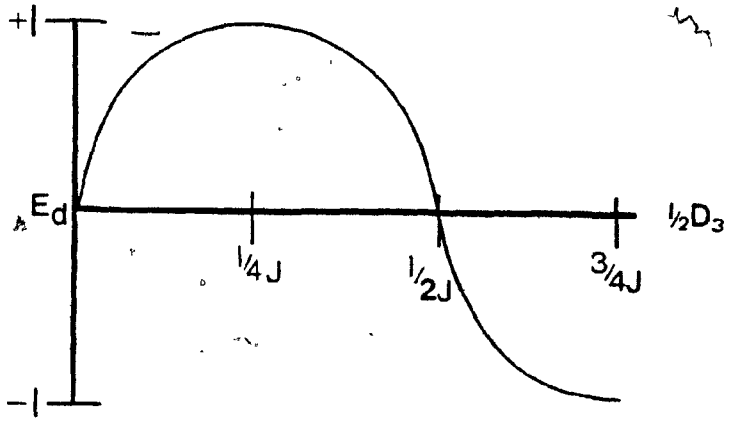
** In units of $J^{-1}.^{338}$

The variable n is the number of protons to which I is coupled. While the enhancement is related directly to the number of protons, the relationship is not additive as can be seen by the presence of the $\cos^{n-1}$ term which reduces E_d in the expression which relates n and E_d (Eqn. 4.4).

$$E_d \propto n^{1/2}(1-1/n)^{(n-1)/2} \qquad \text{Eqn. 4.4}$$

The only two parameters which can be manipulated, therefore, while taking a spectrum are the two delay times, D_2 and D_3. The optimum value of $1/2D_3$, which gives a 90^{o} divergence between H_A and H_B and corresponds to a maximization of the enhancement is $1/2D_3=1/(4J)$. From Eqn. 4.2, the following relationship of E_d to $1/2D_3$ was obtained (Fig. 4.4).

Figure 4.4:Plot Of The Calculated Enhancement (E_d) *versus* The Delay Time ($1/2D_3$)



The sinusoidal relationship makes E_d insensitive to minor variations in D_3, and furthermore, allows all systems with similar coupling constants ($J\pm25\%$) to be enhanced significantly (85% E_d) from a properly chosen D_3. Moreover, if D_3 is chosen judiciously, detailed information about the various IH_n coupling constants in a spectrum can be found. For example, if the value of $1/2D_3=1/(4X)$, the sequence will give full enhancement of a nuclei where $J_{HI}=X$, 71% when $J_{HI}=X/2$, but zero enhancement[345] when $J_{HI}=2X$. This means that is $1/2D_3$ is set for J=10 Hz, it will give a 71% enhancement of a system where J=5 Hz, but if it is set for J=5 Hz, it give a 0% enhancement where J=10 Hz.

The last parameter D_2 is important only in the case of decoupled spectra. Its optimum value (Table 4.2) is dependent both on n and the value of J (Eqn. 4.5).

$$D_{2opt} = (\pi J)^{-1}(\arcsin(n^{-1/2})) \qquad \text{Eqn. 4.5}$$

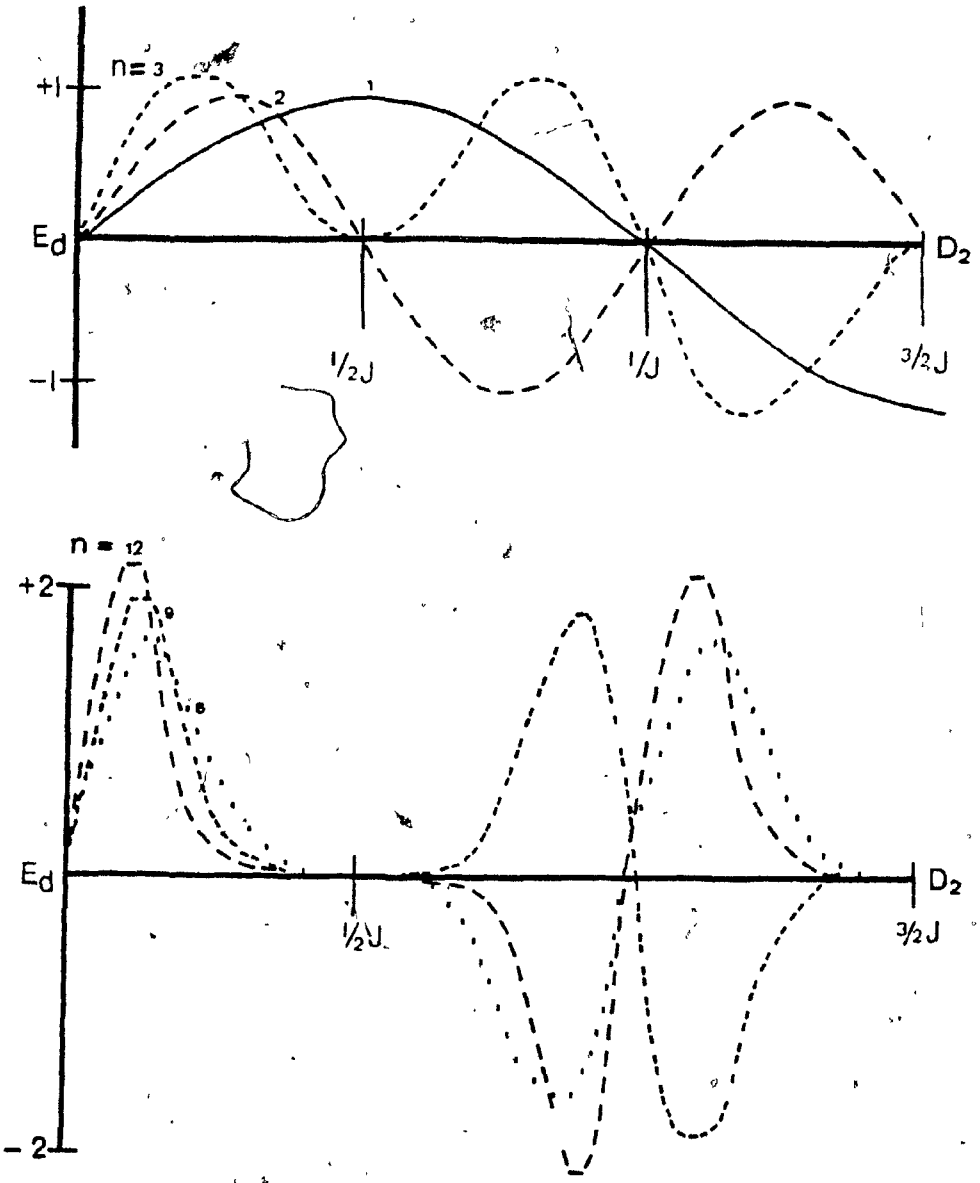
Fig. 4.5 shows the relationship of D_2 to E_d and to n. It can be seen that

as n is increased D_{2opt} becomes smaller and E_d becomes more sensitive to variations in D_2. If a larger value for D_2 is used, the enhancements of nuclei coupled to an even number of protons become negative. This has been used[339,340] to differentiate CH, CH_2, and CH_3 groups in the ^{13}C-N.M.R..

There are some limitations to the use of this method. First, reasonably correct values of D_2 and D_3 must be selected to obtain a good spectrum from a given I-H interaction. Second, the spin-spin relaxation time, T_2, must be long relative to the length of the pulse sequence so that there are still observable signals when acquisition is begun. Third, while I and H can be separated by any number of bonds, the resultant coupling J_{H-I} must be resolvable on the instrument use Problems in any of these areas will cause the observed enhancement to be less than the theoretical value.

Outweighing these disadvantages, however, are the advantages over standard heteronuclear methods. These are; faster pulse repetition rate, decrease in the time required to take a spectrum, signal enhancement, enhancement of outer lines in multi-line patterns, clear distinction between even and odd line patterns, and elimination of signals from solvent or uncoupled I nuclei. Moreover, the detailed knowledge of either the proton or insensitive nuclei spectra is not required. Furthermore, the variable parameters (D_2 and D_3) are easily predicted and are quite insensitive to the differences between systems.

Figure 4.5:A Plot Showing the Relationship of D_2 to E_d for ^{29}Si and the Dependence of That Relationship on n



EXPERIMENTAL SECTION

1. All solvents were distilled after drying by reluxing with the indicated drying agent.
   a) benzene, hexanes, tetrahydrofuran, (sodium-benzophenone ketyl).
   b) methylene chloride, acetonitrile (P_2O_5).
   c) methanol (magnesium).
   d) triethylamine, di-*iso*-propylamine (CaH_2).
2. Infra-red spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer with polystyrene calibration.
3. Proton Magnetic Resonace spectral were recorded on a Varian T60, T60A or XL-200 spectrometer. Tetramethylsilane was used as either an internal or external reference.
4. Carbon-13 Magnetic Resonance spectra were recorded on a Bruker WH-90 spectrometer with deuterochloroform as internal reference.
5. Silicon-29 Magnetic Resonance spectra were recorded on a Varian XL-200 spectrometer with tetramethylsilane as internal reference.
6. Mass spectra were recorded on a Dupont 492B spectrometer using a direct insertion probe with an ionization potential of 70 ev.
7. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Boiling points are also uncorrected.
8. Gas Liquid Chromotographic separations were performed with a Hewlett-Packard 5730A Gas Chromatograph using either flame ionization of thermal conductivity detectors.
9. Column chromatography was performed on silica gel (40-60 microns, flash[79], TLC grade, mesh[80]) obtained from E. Merck.
   Preparative High Pressure Liquid Chromatography was performed on a Waters Prep 500A Liquid Chromatograph using silica gel (40-60 microns, E. Merck see Appendix 2)

ACETALS

1,1-Dimethoxyacetophenone (6)

Freshly distilled phenyl glyoxal (5) (1.12 g, 8.35 mmol) was dissolved in absolute methanol (3.5 mL) containing dry trimethylorthoformate (3.0 mL) and 0.056 g of NH_4Cl, at 0°C under a nitrogen atmosphere. It was left to warm up to room temperature over 4 h and stirred for a further 28 h.

The solution was cooled to 0°C and 25mL of 0.2 N NH_4OH was added. The solution was extracted with ether (2 x 50 mL) and washed with brine (3 x 25 mL). The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and the ether removed under reduced pressure. The residue was pumped at high vacuum for 4 h at 40°C to give 1.03 g of a crude mixture of the title compound, the trimethylorthoformate and the starting material. Further pumping at high vacuum for 4 h at 40°C led to essentially pure title compound (0.722 g) in 48% yield. For spectral data see the following experiment.

Method A

1,1-Dimethoxyacetophenone (6)

To a solution of freshly distilled phenyl glyoxal (5) (8.26 g, 62.0 mmol) in absolute methanol (75 mL.), under a nitrogen atmosphere, was added chlorotrimethylsilane (18.0 mL., 143.0 mmol). The yellow colour of the starting material immediately disappeared. The reaction was stirred overnight at room temperature.

The solvents were removed under reduced pressure and the residue was distilled (b.p. 89°C/0.6 torr, lit.[312] 85-6°C/0.25 torr) to give 8.35 g of the pure title compound. An additional 0.74 g was present in the stillpot (as determined by ^{1}H-N.M.R.) to give a total of 9.09 g in 83% yield.

Under forcing conditions (reflux, excess TMSCl), ^{1}H-N.M.R. analysis indicated the presence of a small amount (<20%) of the ketal-acetal ($C_6H_5C(OCH_3)_2CH(OCH_3)_2$). This product remained elusive and was never

successfully isolated. The spectral data for compound 6 is as follows;

I.R.(neat): ν = 1692, 1601, 1581, 1451 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =3.48 (s, 6H, $HC(O\underline{CH_3})_2$), 5.23 (s, 1H, $\underline{CH}(OCH_3)_2$), 7.2-7.6, 8.0-8.2 ppm (m, $5H_{arom}$).

[Ketal-acetal

^{1}H-N.M.R.($CDCl_3$): δ =3.48 (s, 6H, $HC(O\underline{CH_3})_2$), 3.54 (s, 6H, $C_6H_5C(O\underline{CH_3})_2$), 5.10 (s, 1H, $\underline{CH}(OCH_3)_2$), 7.2-7.7 ppm (m, $5H_{arom}$).]

α, α-Dimethoxy-*p*-methylacetophenone (8)

p-Methylphenylglyoxal (7) (1.21 g, 8.2 mmol) was dissolved in dry methanol (25 mL) under an argon atmosphere. Chlorotrimethylsilane (2.3 mL, 18.1 mmol) was added and the solution stirred overnight.

The solvent was removed under reduced pressure and the residue was purified by flash chromatography (4:1 hexanes-ethyl acetate, v/v) which gave, after evaporation, 1.55 g of the title compound in 98% yield. The spectral data are;

I.R.(neat): ν =1688, 1562, 1445, 1116, 1061 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =2.39 (s, 3H, $\underline{CH_3}C_6H_4$), 3.47 (s, 6H, $HC(O\underline{CH_3})_2$), 5.18 (s, 1H, $\underline{HC}(OCH_3)_2$), 7.65, 8.03 (ABq, $4H_{arom}$, J_{ortho}=8.4 Hz).

M.S.: m/z=180 (2%, M^+-CH_2), 163 (2%, M^+-OCH_3), 135 (8%, $M^+-COOCH_3$) 121 (29%, 135^+-CH_2), 119 (25%, $M^+-CH(OCH_3)_2$), 91 (27%, $M^+-COCH(OCH_3)_2$), 75 (100%, $CH(OCH_3)_2^+$).

Methyl 2,2-dimethoxyphenylacetate (10)

Benzoylformic acid (1.50 g, 10.0 mmol) was dissolved in absolute methanol (50 mmol) under a nitrogen atmosphere. Chlorotrimethylsilane (5.6 mL, 44.2 mmol) was added and the reaction stirred at room temperature overnight.

The solvents were removed *in vacuo* to give 1.80 g of a crude residue. A quantity of 0.149 g of this residue was submitted to flash chromatography (9:1 hexanes-ethyl acetate, v/v, two elutions). The title

compound (0.096 g, 55% yield) and methyl benzoylformate (9) (0.051 g, 37% yield) were isolated. Increasing the reaction temperature, quantity of chlorotrimethylsilane, or reaction time, did not substantially alter the product distribution. Accounting for the recovered methyl benzoylformate, which could be recycled, the yield was 93%.

A mixture of the crude methyl benzoylformate and methyl 2,2-dimethoxyphenylacetate (40:60) was dissolved in dry methanol under an argon atmosphere, and then chlorotrimethylsilane was added. After a work-up as described above, ^{1}H-N.M.R. analysis indicated a 1:5 equilibrium mixture of the two compounds (ester:acetal-ester). Thus, higher isolated yields are possible when starting with the ester rather than the acid. Spectral data for the compound are;

I.R. (CCl_4): ν = 1740, 1451, 1432, 1258, 1238, 1192, 1112, 1078 cm^{-1}.
^{1}H-N.M.R. (CCl_4): δ = 3.08 (s, 6H, $C(OCH_3)_2$), 3.50 (s, 3H, $COOCH_3$), 7.1-7.5 ppm (m, $5H_{arom}$).

$C_{11}H_{14}O_4$	calc.	C	62.84	H	6.71
(210.2)	found		62.95		6.81

Methyl 2,2-dimethoxypropionate (11)

Methyl pyruvate (0.51 g, 5.0 mmol) was dissolved in dry methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred overnight at room temperature.

The reaction was neutralized with a 5% solution of sodium methoxide in methanol to pH 6 (wet alk-acid paper). Most of the methanol was removed *in vacuo* and ether was added to the residue. After filtration through silica gel and the evaporation of solvents, 0.72 g of the crude product was isolated. A quantity of 0.093 g of the residue was submitted to flash chromatography (9:1 hexanes-ethyl acetate, v/v) and gave after evaporation 0.086 g of the title compound in 92% yield.

Alternatively, pyruvic acid (0.44 g, 5.0 mmol) was dissolved in absolute methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane was added (2.8 mL, 22.0 mmol) and the reaction stirred overnight.

The reaction was neutralized to pH 6 (wet alk-acid paper) with a 5% solution of sodium methoxide in methanol. Most of the methanol was

removed *in vacuo* and ether added. After filtration through silica gel and evaporation of the solvents, 0.67 g of the title compound, pure by G.L.C., was isolated in 90% yield.

The reaction may also be worked up by quenching with a 5% aqueous sodium bicarbonate solution and multiple extractions with ether (8 x 50 mL). The ether was washed with water until the volume remained constant (3 x 10 mL). The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and the ether removed *in vacuo*. The residue was purified as above to give the product in 50% yield. Spectral data for the compound are;

I.R.(neat): ν =1748, 1440, 1371, 1293, 1214, 1193, 1043 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =1.40 (s, 3H, $\underline{CH_3}C(OCH_3)_2$),
3.14 (s, 6H, $C(OCH_3)_2$), 3.65 ppm (s, 3H, $COOCH_3$).
G.C. 5% OV-101 on CHROMOSORB W 100°C

$CH_3COCOOCH_3$	RT=0.70 min.
$CH_3C(OCH_3)_2COOCH_3$	RT=2.27 min.

1,1-Dichloroacetone (12)

This compound was prepared following the method of Wyman[348]. To acetone (29.0 g, 0.50 mol) was added sulfuryl chloride (135.0 g, 1.00 mol) under a nitrogen atmosphere, over 35 min (at a rate which kept the temperature below 35°C). The reaction was cooled in ice for the first 5 min.

Distillation of the crude product led to extensive decomposition due to the presence of excess sulfuryl chloride. Therefore, the sulfuryl chloride was removed at room temperature under high vacuum and the residue was then distilled (45°/53 torr, lit.[152] 117-8°C/760 torr) to give 22.9 g of the pure product in 36% yield. The spectral data for the compound are;

I.R.(neat): ν =3483, 3024, 1748, 1426, 1362, 1209, 1154 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =2.43 (s, 3H, CH_3CO), 5.76 ppm (s, 1H, $CHCl_2$).

1,1-Dichloro-2,2-dimethoxypropane (13)

1,1-Dichloroacetone (12)(0.64 g, 5.0 mmol) was dissolved in dry methanol (25 mL) under a nitrogen atmosphere. Trimethylchlorosilane (1.4 mL, 11.0 mmol) was added and the solution stirred overnight.

The solution was neutralized to pH 6 (wet alk-acid paper) with a 5% solution of sodium methoxide in methanol. Ether was added and the solution filtered. The solvents were removed under reduced pressure. G.L.C. indicated 90% of the final product in the reaction mixture. As some sodium methoxide persisted in the crude residue, ether was again added and the solution filtered through silica gel.

After solvent removal *in vacuo*, 0.38 g of the title compound was recovered in 44% yield, pure by G.L.C. and ^{1}H-N.M.R.. Co-evaporation of dichloroacetone, the title compound, and methanol probably accounts for the reduced yield. The G.L.C. yield was 71%. The spectral characteristics of the compound are;

I.R.(neat) : ν =1381, 1287, 1243, 1174, 1131, 1051, 802, 783 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$) : δ =1.52 (s, 3H, $\underline{CH_3}C(OCH_3)_2$),

3.25 (s, 6H, $CH_3C(O\underline{CH_3})_2$), 5.70 ppm (s, 1H, $CHCl_2$).

M.S.:m/z=161, 159, 157, (0.4%, 1.4%, 2.0%, M^+-CH_3),

145, 143, 141, (5%, 30%, 48%, M^+-OCH_3), 89 (52%, M^+-CHCl_2),

43 (100%, CH_3CO^+).

G.L.C.:6' 5% CARBOWAX 20M on CHROMOSORB W, 100°C:

$CH_3COCHCl_2$	RT=0.67 min.
$CH_3C(OCH_3)_2CHCl_2$	RT=1.57 min.

3,3-Dimethoxy-2-butanone (14)

2,3-Butanedione (4.30 g, 50.0 mmol) was slowly added (15 min) to a solution of chlorotrimethylsilane (6.0 mL, 47 mmol) in absolute methanol (150 mL) under an argon atmosphere. Only a faint yellow colour persisted from the unreacted starting material.

A saturated aqueous solution of $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2 until no volume change was noted (6 x 100 mL). The colour of the combined extracts was a deep yellow. To ensure that the reaction was complete approximately half of this solution was added to a

mixture of absolute methanol (50 mL) and chlorotrimethylsilane (3.0 mL), and stirred for 1 h at room temperature. There was no colour change from the dark yellow and the solution was worked up as above. The CH_2Cl_2 was distilled from the combined extracts through a Widmer column. The residue was distilled (b.p. 58°C/28 torr, lit.[313] 145-6°C/760 torr) to give 6.04 g of the title compound in 91% yield. Spectral characteristics of the compound are;

I.R.(neat): ν =1730, 1433, 1369, 1353, 1192, 1127, 1042, 883 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =1.38 (s, 3H, $\underline{CH_3}C(OCH_3)_2$),
2.21 (s, 3H, CH_3CO), 3.22 ppm (s, 6H, $CH_3C(O\underline{CH_3})_2$).
M.S.:m/z=101 (14%, M^+-OCH_3), 89 (32%, M^+-CH_3CO),
73 (11%, 89^+-CH_4), 43 (100%, CH_3CO^+).
G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 100°C:

$CH_3COCOCH_3$	RT=0.20 min.
$CH_3COC(OCH_3)_2CH_3$	RT=0.45 min.

3,3-Diethoxy-2-butanone (15)

2,3-Butanedione (4.30 g, 50.0 mmol) was dissolved in absolute ethanol (200 mL) under an argon atmosphere. Chlorotrimethylsilane (13.0 mL, 102 mmol) was added and the reaction was stirred for 30 min. At this point, most of the yellow colour of the starting material had disappeared.

It proved impossible to separate the ethanol from the product even by spinning-band distillation. Therefore, the reaction was quenched with an excess of $NaHCO_3$ (5% aqueous solution). The ethanol was removed by extraction with CH_2Cl_2 (7x50 mL) until no volume change in the chlorinated layer was noted. The CH_2Cl_2 was distilled from the combined extracts using a Widmer column and the residue was further distilled (b.p. 70°C/23.5 torr, lit.[313] 163-5°C/760 torr) to give 4.78 g of the title compound in 60% yield. The spectral data for the compound are as follows;

I.R.(neat): ν =1729, 1442, 1418, 1388, 1352, 1126, 1048, 953 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =1.23 (t, 6H, $(OCH_2\underline{CH_3})_2$, J=7.0 Hz),
1.40 (s, 3H, $\underline{CH_3}C(OCH_2CH_3)_2$), 2.24 (s, 3H, CH_3CO),
3.45, 3.51 ppm (qABq, $OCH^aH^bOCH_3^c$, J_{ab}=9.0 Hz, J_{ac}=7.0 Hz).

M.S.:m/z=117 (33%, M^+-CH_3CO), 115 (19%, $M^+-CH_3CH_2O$),
89 (14%, $117^+-CH_2CH_2$), 87 (59%, $115^+-CH_2CH_2$),
61 (100%, 89%$-CH_2CH_2$), 43 (84%, CH_3CO^+).
G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 100°C:

$CH_3COCOCH_3$	RT=0.20 min.
$CH_3COC(OCH_2CH_3)_2CH_3$	RT=0.80 min.

2-Oxononanal (16)

Selenium dioxide (15.6 g, 141 mmol) was heated at 80°C in a solution of water (2.8 g, 156 mmol) and dioxane (85 mL). Nonanal was added (20.0 g, 141 mmol) and the reaction refluxed for 4 h.

The solution was cooled to room temperature and filtered through Celite. After evaporation of the solvents *in vacuo*, the residue was again filtered through Celite and the Celite washed with dioxane. The dioxane was removed under reduced pressure and the yellow residue was distilled to give 2.1 g of starting material and 15.5 g of the title compound (b.p. 76-90°C/1 torr), in 70% yield. Accounting for recovered starting material, the yield was 79%. The spectral data for the compound are;

I.R.(neat): ν=2923, 2856, 1731, 1459, 1378, 1193, 1117, 1071 cm^{-1}(trimer).
^{1}H-N.M.R.($CDCl_3$): δ=1.87 (t, 3H, $\underline{CH_3}(CH_2)_6$, J=4.8 Hz),
1.1-1.9 (m, 10H, $CH_3(\underline{CH_2})_5$), 1.72 (t, 2H, $(CH_2)_5\underline{CH_2}CO$, J=6.8 Hz),
9.23 ppm (s, 1H, CHO).

1,1-Dimethoxy-2-oxononane (17)

2-Oxononanal (16) (9.2 g, 59.0 mmol) was added to absolute methanol (200 mL) under an argon atmosphere. After 20 min, the yellow colour of the starting material had disappeared. Chlorotrimethylsilane (20.0 mL, 158 mmol) was added and the reaction stirred overnight at room temperature.

The green-brown reaction mixture was quenched with a 5% solution of sodium bicarbonate (500 mL). This was extracted with ether (2 x 250 mL), washed with brine (2 x 50 mL), and the combined extracts dried over

anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the residue distilled to give 3.40 g of a mixture of the starting material and the title compound, (b.p. 86-92°C/1 torr) and 6.50 g of the pure compound (17) (b.p. 92-106°C/1 torr). The total yield was 76% (9.56 g, 45.1 mmol). The yield after accounting for recovered starting material was 79% but the isolated yield was only 52%. The spectral data for this compound are as follows;

I.R.(neat):ν =2920, 2861, 1729, 1471, 1403, 1376, 1349, 1338, 1213, 1191, 1068, 991, 953, 909 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$):δ =1.87 (t, 3H, $(CH_2)_5\underline{CH_3}$, J=5.5 Hz), 1.1-1.9 (m, 10H, $OCCH_2(\underline{CH_2})_5CH_3$), 2.55 (t, 2H, $OC\underline{CH_2}(CH_2)_5$, J=6.2 Hz), 3.41 (s, 6H, $HC(O\underline{CH_3})_2$), 4.43 ppm (s, 1H, $\underline{CH}(OCH_3)_2$).

M.S.:m/z=127 (9%, $M^+-CH(OCH_3)_2$), 75 (100%, $CH(OCH_3)_2^+$).

Camphorquinone (18)

(2,3-dioxo-1,7,7-trimethyl-[2,2,1]-bicycloheptane)

Selenium dioxide (11.0 g, 99.1 mmol) and water (2 mL, 111 mmol) were heated to reflux in dioxane (60 mL). Camphor (15.0 g, 98.6 mmol) was added and the reaction refluxed (mechanical stirring) for 30 h. Several colour changes from yellow, red to dark brown ensued. The solution was allowed to cool to room temperature and was filtered through Celite to remove precipitated selenium metal.

The solvents were removed under reduced pressure and redissolved in a minimum of ethyl acetate, refiltered through Celite, and a red precipitate was separated from a yellow solution. The yellow solution was evaporated to dryness and recrystallized from ethanol-water. Unfortunately, a mishap caused about half of the product to be lost permanently and only 4.6 g of a yellow crystalline material was isolated. The crystals were sublimed under low vacuum and mild heating (30 torr, <50°C) to give 4.4 g of the product contaminated with camphor. The residue was purified by flash chromatography (19:1 hexanes-ethyl acetate, v/v) to give 4.1 g of pure camphorquinone in 25% yield as yellow crystals (m.p. 200°C, lit.[346] 199°C). The spectral data for the compound are;

I.R.($CHCl_3$): ν =2959, 1770, 1245 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =0.92 (s, 3H, $\underline{CH_3}^a$-C7-CH_3^b),
1.05 (s, 3H, CH_3^a-C7-$\underline{CH_3}^b$), 1.12 (s, 3H, CH_3^c-Cl),
1.2-2.4 (m, 4H, CH_2CH_2), 2.62 ppm (m, 1H, HC4CO).

M.S.:m/z=166 (38%, M^+), 138 (47%, $M^+-CH_2CH_2$), 123 (43%, 138^+-CH_3),
110, (22%, M^+-COCO), 95 (100%, 110^+-CH_3),
83 (74%, 95^+-CH_3, $123^+-2 \times CH_3$), 69 (91%, 95^+-CH_2), 67 ($95^+-CH_2CH_2$).

3,3-Dimethoxycamphor (19)

Pure camphorquinone (18) (0.040 g, 0.241 mmol) was dissolved in dry methanol (15 mL) under an argon atmosphere. Chlorotrimethylsilane (0.07 mL, 0.55 mmol) was added and the reaction stirred at room temperature overnight. The yellow colour of the starting material disappeared within 10 min.

The colourless solution was extracted with hexanes (3 x 50 mL). A 10% aqueous sodium bicarbonate solution (20 mL) was added to the methanol layer and this was further extracted with hexanes (2 x 50 mL). The latter fractions were dried over anhydrous Na_2SO_4 and filtered. The combined fractions had the solvents removed *in vacuo* to give 0.043 g of the title compound in 84% yield. The product, as shown by ^{1}H-N.M.R. was an inseparable mixture of the 3- and 2-dimethyl ketal in a ratio of 83:17.

If the reaction was simply worked up by extraction with ether or methylene chloride, followed by washing with aqueous bicarbonate solution, only the starting camphorquinone was isolated. Before work-up, T.L.C. analysis of the reaction showed the presence of the camphorquinone ketal in large quantity. Extraction with hexanes eliminated this problem. The spectral characteristics of the compounds are;

I.R.($CHCl_3$): ν =1756, 1451, 1371, 1303, 1210, 1131, 1067, 1029 cm^{-1}.

3-dimethyl ketal (83% relative proportion)

^{1}H-N.M.R.(CCl_4): δ =0.86 (s, 3H, Cl-CH_3^c),
0.94 (s, 3H, $\underline{CH_3}^a$-C7-CH_3^b), 0.95 (s, 3H, CH_3^a-C7-$\underline{CH_3}^b$),
1.5-1.8 (m, 4H, CH_2CH_2), 2.0-2.1 (m, 1H, $\underline{HC4}C(OCH_3)_2$),
3.20 (s, 3H, OCH_3 endo), 3.30 ppm (s, 3H, OCH_3 exo).

2-dimethyl ketal (17% relative proportion)

^{1}H-N.M.R.(CCl_4) : δ =0.86 (s, 3H, Cl-CH_3^c),

1.03 (s, 3H, $\underline{CH_3}^a$-C7-CH_3^b), 1.05 (s, 3H, CH_3^a-C7-$\underline{CH_3}^b$),

1.5-1.8 (m, 4H, CH_2CH_2), 2.66 (t, 1H, $\underline{HC4}C(OCH_3)_2$),

3.25 (s, 3H, OCH_3 endo), 3.40 ppm (s, 3H, OCH_3 exo).

M.S.:m/z=212 (0.6%, M^+), 184 (15%, $M^+-CH_2CH_2$),

181 (13%, M^+-OCH_3), 153 (6%, 184^+-OCH_3), 101 (100%, $C_4H_5O_3^+$).

Methods B, C and D

2-Phenyl-1,3-dioxolane (20)

Benzaldehyde (0.53 g, 5.0 mmol) was dissolved in a solution of ethylene glycol (3 mL) and absolute methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred overnight at room temperature.

The solution was neutralized to pH 6 (wet alk-acid paper) with a 5% solution of sodium methoxide in methanol. Most of the methanol was removed under reduced pressure and the residue was filtered through Celite. The remaining volatile compounds were removed *in vacuo*. The ethylene glycol solution was subjected to preparative H.P.L.C. (4:1 hexanes-ethyl acetate, v/v) to give 0.46 g of the title compound in 64% yield.

Alternatively, benzaldehyde (0.53 g, 5.00 mmol) was dissolved in a solution of dry ethylene glycol (3 mL) and methylene chloride (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (2.8 mL, 22.0 mmol) was added and the reaction stirred at reflux overnight. The reaction was not complete and so a further 1.4 mL of TMSCl was added and the reaction refluxed for 24 h.

The reaction was quenched with a 5% aqueous solution of sodium bicarbonate. The solution was then extracted with ether (2 x 75 mL), washed with brine (3 x 40 mL), and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*, to give 0.60 g of crude residue. A quantity of 0.158 g of the residue was submitted to flash chromatography (10:1 hexanes-ethyl acetate, v/v, two elutions) and gave, after evaporation, 0.153 g of the title compound in

77% yield.

Several other preparations were attempted using similar reaction conditions. These other conditions;

1) C_6H_5CHO, 1 eq.; $HOCH_2CH_2OH$, 10 eq.; $(CH_3)_3SiCl$, 2.2 eq.; solvent, *iso*-propanol.
2) C_6H_5CHO, 1 eq.; $HOCH_2CH_2OH$, 10 eq.; $(CH_3)_3SiCl$, 2.2 eq.; solvent, methylene chloride, reflux.
3) C_6H_5CHO, 1 eq.; $HOCH_2CH_2OH$, 15 eq.; $(CH_3)_3SiCl$, 4.4 eq.; solvent, methylene chloride, reflux.
4) C_6H_5CHO, 1 eq.; $HOCH_2CH_2OH$, 15 eq.; $(CH_3)_3SiCl$, 6.6 eq.; solvent, methylene chloride, reflux.
5) C_6H_5CHO, 1 eq.; $(CH_3)_3SiCl$, 4 eq.; solvent $HOCH_2CH_2OH$, room temperature or 100°.

led to incomplete reactions (never greater than 70% by G.L.C.). The spectral data are as follows;

I.R.(neat): ν =1456, 1393, 1315, 1222, 1093, 1069,1039, 968, 944, 918 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=4.03 (bs, 4H, OCH_2CH_2O), 5.77 (m, 1H, $\underline{CH}(OCH_2CH_2O)$), 7.1-7.6 ppm (m, $5H_{arom}$).

G.L.C.:5% CARBOWAX 20M on CHROMOSORB W, 150°:

C_6H_5CHO	RT=0.77 min.
$C_6H_5CH(OCH_2CH_2O)$	RT=2.27 min.

2-Methyl-2-phenyl-1,3-dioxolane (21)

Acetophenone (0.60 g, 5.0 mmol) was dissolved in ethylene glycol (25 mL) under a nitrogen atmosphere. Trimethylchlorosilane (4.2 mL, 33.0 mmol) was added and the reaction stirred overnight at room temperature.

The reaction was quenched with a 5% aqueous sodium bicarbonate solution and extracted with ether (2 x 75 mL). The combined extracts were dried over anhydrous $MgSO_4$. After filtration through Celite, the ether was removed under reduced pressure. The solution was suspended in methanol and 0.12 g of pure title compound crystallized out. The remainder was filtered through silica gel, with hexanes as solvent, to yield after evaporation, 0.52 g of a crystalline compound pure by G.L.C..

The total yield was 0.64 g (78%).

The mixed melting point of the two crystalline materials was identical with the individual melting points (m.p. 61°C, lit.[156] 61°C)). The spectral characteristics of the compound are;

I.R.(CCl_4): ν =1436, 1367, 1217, 1201, 1190, 1023 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =1.66 (s, 3H, CH_3), 3.6-4.2 (m, 4H, OCH_2CH_2O),
7.1-7.6 ppm (m, $5H_{arom}$).
M.S.:m/z=149 (100%, M^+-CH_3), 105 (91%, $M^+-OCH_2CH_2CH_3$),
87 (34%, $M^+-C_6H_5$), 77 (70%, $C_6H_5^+$).
G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 150°C:
$C_6H_5COCH_3$ RT=0.43 min.
$C_6H_5C(OCH_2CH_2O)CH_3$ RT=0.65 min.

α-Chloroacetophenone (22)

Acetophenone (24.0 g, 0.20 mol) was dissolved in glacial acetic acid (100 mL). Chlorine gas (dried by passing through concentrated H_2SO_4) was bubbled through the solution. The temperature was kept below 30°C by cooling with an ice-bath.

After 1 h, the yellow solution was poured onto 1 kg of ice. A flaky white precipitate was isolated by filtration and was air dried. After recrystallization from hexanes-ethyl acetate, 14.03 g of the crystalline title compound (m.p. 54-55°C, lit.[346] 55-6°C) was isolated in 52% yield. The spectral data are;

I.R.(CCl_4): ν=1692, 1543, 1448, 1280, 1203 cm^{-1}.
^{1}-N.M.R.(CCl_4): δ=4.52 (s, 2H, CH_2Cl),
7.2-7.5, 7.7-8.0 ppm (m, $5H_{arom}$).
M.S.:m/z=156, 154 (1%, 2.5%, M^+), 120 (20%, $C_6H_5OCH_3^+$),
105 (100%, $C_6H_5CO^+$), 77 (77%, $C_6H_5^+$).

2-Chloromethyl-2-phenyl-1,3-dioxolane (23)

α-Chloroacetophenone (22) (0.83 g, 5.4 mmol) was dissolved in dry ethylene glycol (25 mL) under a nitrogen atmosphere. Trimethylchloro-

silane (2.8 mL, 22.1 mmol) was added and the reaction stirred overnight at room temperature.

The reaction was quenched with a 5% aqueous sodium bicarbonate solution and extracted with ether (2 x 75 mL). After drying the combined extracts over anhydrous $MgSO_4$ and filtration through Celite, the ether was removed *in vacuo* to yield 1.08 g of a crude precipitate. The compound was recrystallized from methanol to give 0.29 g of the pure crystalline material (m.p. 90°C) and 0.79 g of a crystalline material shown to be 98% pure by G.L.C.. The yield of the combined crystalline materials was 99%. The spectral characteristics of the compound are;

I.R.(nujol mull): ν =1446, 1375, 1222, 1180, 1171, 1017 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =3.75 (s, 2H, CH_2Cl), 3.6-4.4 (m, 4H, OCH_2CH_2O), 7.2-7.7 ppm (m, $5H_{arom}$).
M.S.m/z=149 (100%, M^+-CH_2Cl), 105 (81%, $C_6H_5CO^+$), 77 (58%, $C_6H_5^+$).
G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 150°:
$C_6H_5C(OCH_2CH_2O)CH_2Cl$ RT=5.22 min.

2-Dichloromethyl-2-phenyl-1,3-dioxolane (25)

To α,α-dichloroacetophenone (24) (0.95 g, 5.0 mmol) dissolved in dry ethylene glycol (25 mL) under a nitrogen atmosphere, was added chlorotrimethylsilane (1.4 mL, 11.0 mmol). The reaction was stirred overnight at room temperature.

The reaction was quenched with a 5% aqueous sodium bicarbonate solution and extracted with ether (2 x 75 mL). The ether extracts were dried over anhydrous $MgSO_4$, and the combined extracts had the ether removed under reduced pressure to give, after filtration, a crystalline product (1.32 g). A quantity of 0.130 g of the crude material was submitted to flash chromatography (9:1 hexanes-ethyl acetate, v/v) to give 0.116 g of the pure dioxolane in essentially quantitative yield (m.p. 58.5-59°C, lit.[158] 59-61°C). The spectral data for the compound are;

I.R.(nujol mull): ν =1301, 1210, 1141, 1021 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =3.9-4.6 (m, 4H, OCH_2CH_2O), 5.8 (s, 1H, $CHCl_2$), 7.2-7.9 ppm (m, $5H_{arom}$).

M.S.:m/z=149 (100%, M^+-CHCl_2), 105 (78%, $C_6H_5CO^+$), 77 (53%, $C_6H_5^+$).
G.L.C.:6' 5% OV-101 on CHROMOSORB W, 150°C:

$C_6H_5COCHCl_2$	RT=1.40 min.
$C_6H_5C(OCH_2CH_2O)CHCl_2$	RT=3.57 min.

Dioxaspiro-(4,5)-decane (26)

Cyclohexanone (0.52 g, 5.3 mmol) was dissolved in a mixture of dry ethylene glycol (3.0 mL, 54.0 mmol) and absolute methanol (20 mL). Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred for 16 h at room temperature.

The mixture was neutralized to pH 6 (wet alk-acid paper) using a 5% solution of sodium methoxide in methanol and the solvent were removed *in vacuo*. The residue was dissolved in ether, filtered through coarse silica gel (5 g), and the silica gel washed with ether (2 x 10 mL). The ether was then removed under reduced pressure. The crude product was submitted to flash chromatography (10:1 hexanes-ethyl acetate, v/v) to give 0.63 g of the title compound as a colourless oil in 83% yield.

Alternatively, cyclohexanone (0.57 g, 5.2 mmol) was dissolved in dry ethylene glycol (25 mL) under a nitrogen atmosphere. Trimethylchlorosilane (1.4 mL, 11.0 mmol) was added and the reaction stirred at room temperature overnight.

The reaction was quenched by the addition of a 10% aqueous sodium carbonate solution. This mixture was extracted with ether (2 x 50 mL) and the combined extracts were dried over anhydrous $MgSO_4$. After filtration, the ether was removed under reduced pressure. Purification by flash chromatography (10:1 hexanes-ethyl acetate, v/v) led to the title compound (0.35) in 48% yield. The G.L.C. yield of the reaction was 95%. The spectral data of the compound are;

I.R.(neat): ν =2943, 2864, 1447, 1366, 1335, 1284, 1164, 1102, 1036 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =1.58 (bs, 10H, $-(CH_2)_5-$), 3.90 ppm (s, 4H, OCH_2CH_2O).
M.S.:m/z=142 (3%, M^+), 113 (6%, $M^+-CH_2CH_3$), 99 (74%, $M^+-C_3H_7$), 86 (23%, $M^+-C_4H_8$), 55 (43%, $C_4H_7^+$), 43 (100%, $C_3H_7^+$).

G.L.C.:6' 5% CARBOWAX 20M on CHROMOSORB W, 150°C:

$-CO(CH_2)_5-$	RT=0.53 min.
$-C(OCH_2CH_2O)(CH_2)_5-$	RT=1.03 min.

2-*n*-Octyl-1,3-dioxolane (27)

Nonanal (0.71 g, 5.0 mmol) was suspended with vigourous stirring in dry methanol (25 mL) and dry ethylene glycol (3 ml) under a nitrogen atmosphere. Trimethylchlorosilane (1.4 mL, 11.0 mmol) was added and the solution stirred overnight.

Neutralization to pH 6.0 (wet alk-acid paper) was accomplished with a 5% solution of sodium methoxide in methanol. The solution showed 3% of the starting material, as determined by G.L.C.. The methanol was removed under reduced pressure and ether added. The solution was filtered through Celite and the ether removed under reduced pressure. The dioxolane, which remained dissolved in ethylene glycol, was purified using preparative H.P.L.C. (10:1 hexanes-ethyl acetate, v/v) to give 0.60 g of the pure dioxolane in 64% yield.

The same reaction conditions using a different work up gave an improved yield. The reaction was neutralized with a 5% solution of sodium methoxide in methanol to pH 6 (wet alk-acid paper). The methanol was removed *in vacuo*. The residue was distilled (b.p. 117-135°C/14 torr, lit.[161] 141-2/40 torr) using a Kugelrohr apparatus to yield a compound 98% pure by G.L.C. analysis. The yield is essentially quantitative giving 0.95 g of the slightly impure product. The spectral data are:

I.R.(neat): ν=2925, 1467, 1408, 1144, 1122 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=0.86 (t, 3H, $\underline{CH_3}(CH_2)_7$, J=5.5 Hz),
1.1-2.0 (m, 14H, $CH_3(\underline{CH_2})_7$), 3.7-4.1 (m, 4H, OCH_2CH_2O),
4.82 ppm (t, 1H, $\underline{HC}(OCH_2CH_2O)CH_2$, J=4.3 Hz).

M.S.:m/z=185 (1%, M^+-H), 141 (1%, $M^+-CH_3CH_2O$),
73 (100%, $CH_3CH_2CH_2CH_2O^+$), 57 (13%, $CH_3CH_2CH_2CH_2^+$),
43 (24%, $CH_3CH_2CH_2^+$).

G.L.C.:6' 5% CARBOWAX 20M on CHROMOSORB W, 150°C:

$CH_3(CH_2)_7CHO$	RT=0.60 min.
$CH_3(CH_2)_7CH(OCH_2CH_2O)$	RT=1.12 min.

2-Methyl-2-(2'methyl-1',3'-dioxolane)-1,3-dioxolane (28)

Diacetyl (0.43 g, 5.0 mmol) was dissolved in a solution of ethylene glycol (0.61 mL, 11.0 mmol) and methylene chloride (25 mL) under a nitrogen atmosphere. Trimethylchlorosilane (2.8 mL, 22.0 mmol) was added and the reaction stirred overnight. The yellow colour of the starting material disappeared within 40 min.

The reaction was quenched with a 5% aqueous bicarbonate solution and extracted with ether (2x75 mL). The combined extracts were dried over anhydrous $MgSO_4$ and the ether removed, after filtration through Celite, under reduced pressure to give 0.83 g of the title compound in 95% yield (m.p. 89°C). A single recrystallization from hexanes improved the m.p. to 90°C (lit.[162] 90°C).

Several attempts were made to isolate the monodioxolane. The reaction was performed under the following conditions.

1) 0.050 mol 2,3-butanedione, 150 mL anhydrous tetrahydrofuran, 0.018 mol ethylene glycol.
2) 0.050 mol 2,3-butanedione, 150 mL anhydrous tetrahydrofuran, 0.044 mol ethylene glycol.
3) Reaction 1 but *iso*-propanol as solvent.
4) Reaction 2 but *iso*-propanol as solvent.

The reactions followed a thermal gradient from -78° to 0°C. At the coldest temperature tested, -78°C, there was no observable reaction. At -60°C, G.L.C. analysis indicated the presence of the *bis*-dioxolane and a new peak of intermediate retention time between the starting material and the *bis*-dioxolane. It is suspected that this is the monodioxolane (2-acetyl-2-methyl-1,3-dioxolane). At -42°C, the intensity of this peak was substantially reduced, and at -25°C it was no longer present. This was true for all of the reaction conditions used. The relative concentration of the starting material was not determined (because at the G.L.C. oven temperature used, the peak for this compound was coincident with the solvent peak), but the relative intensities of the two product peaks are shown below.

Temperature (°C)	monodioxolane (?)	*bis*-dioxolane
-78	0	0
-60	79	21
-42	17	83
-25	0	100

The reaction was quenched with a variety of bases in an attempt to isolate the elusive monodioxolane. Using aqueous Na_2SO_4, methanolic NaOMe, or NaH in reactions 1 and 2, ^{1}H-N.M.R. indicated the possibility of the existence of this product only if the spectrum was taken immediately after quenching. Otherwise it rapidly dissociated into a mixture of the starting materials and the *bis*-dioxolane. As a result, the compound was never isolated nor was its structure ever really determined. Is is interesting to speculate that one of the compounds in the reaction mixture, the 2,3-butanedione, the monodioxolane or the *bis*-dioxolane, is acting as an acidic catalyst. The spectral data are as follows;

I.R. (CCl_4): ν=2965, 2881, 1450, 1372, 1279, 1261, 1195, 1142, 1110, 1092, 902 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=1.42 (s, 6H, $[\underline{CH_3}C(OCH_2CH_2O)_2]_2$), 3.4-4.2 ppm (m, 8H, $[CH_3C(O\underline{CH_2CH_2}O)_2]_2$).

M.S.: m/z=114 (1%, M^+-OCH_2CH_2O), 87 (27%, M^+-$C(OCH_2CH_2O)CH_3$), 73 (36%, $HC(OCH_2CH_2O)^+$), 43 (100%, CH_3CO^+).

G.L.C.: 6' 5% CARBOWAX 20M on CHROMOSORB W, 150°C:

$CH_3COCOCH_3$	RT=0.25 min.
$CH_3COC(OCH_2CH_2O)CH_3$	RT=1.06 min.
$[CH_3C(OCH_2CH_2O)_2]_2$	RT=1.42 min.

Cyclohexenone-ketal

Cyclohexenone (0.48 g, 5.0 mmol) was dissolved in four different solvent systems as listed below. Chlorotrimethylsilane was added (1.4 mL, 11.0 mmol) to each system and the reaction stirred at the listed temperature overnight.

1) solvent, methanol, 25 mL; room temperature.
2) solvent, methanol, 25 mL; reflux.

3) solvent, ethylene glycol, 25 mL; room temperature.

4) solvents, methanol, 25 mL, ethylene glycol, 3 mL; reflux.

Each reaction was quenched with a 5% aqueous sodium bicarbonate solution or with Amberlyst A21 (dimethylamine) resin. G.L.C. analysis of the ensuing residues indicated products which appeared to correlate to the expected products (1,1-dimethoxycyclohex-2-ene or 1,1-ethylenedioxycyclohex-2-ene). That is, peaks were observed which had higher retention times than those of the starting materials.

Complex reaction mixtures were retrieved from conditions 2,3 and 4. However, from reaction 1 the ^{1}H-N.M.R. spectrum of the crude reaction mixture was revealing. No olefinic protons were observed, and in addition, three peaks ascribable to CH_3O were present. It is tempting to suggest 1,1,3-trimethoxycyclohexanone as a possible product. Unfortunately, all attempts to isolate this product by Kugelrohr distillation or chromatography failed to yield any identifiable product. Thus, the experiment was considered a failure.

Reaction 1:

^{1}H-N.M.R. ($CDCl_3$): δ=0.9-2.9 (m, 24.5H, $-(\underline{CH_2})_3C3(OCH_3^c)\underline{CH_2}C-$, plus polymeric products), 3.15 (s, 3H, $\underline{CH_3}^aOC1OCH_3^b$), 3.22 (s, 3H, $CH_3^aOC1\underline{OCH_3}^b$), 3.34 (s, 3H, $HC3\underline{OCH_3}^c$), 3.65 ppm (s, 1H, $\underline{HC}(OCH_3^c)$.

G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 100°C:

$(CH_3)_3SiCl$	RT=0.61 min.
$-(CH_2)_3CH=CHCO-$	RT=0.80 min.
$-(CH_2)_3CH(OCH_3)CH_2C(OCH_3)_2-$ (?)	RT=1.65 min.

Reaction 2:

G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 100°C:

$(CH_3)_3SiCl$	RT=0.54 min.
$-(CH_2)_3CH=CHCO-$	RT=0.75 min.
unknown	RT=3.23 min.

G.L.C.:6' 5% CARBOWAX 20M on CHROMOSORB W, 150°C:

Reaction 3:

$-(CH_2)_3CH=CHCO-$	RT=0.75 min.
$HOCH_2CH_2OH$	RT=1.24 min.

unknown	RT=1.62 min.
unknown	RT=1.90 min.

Reaction 4:

$-(CH_2)_3CH=CHCO-$	RT=0.76 min.
$HOCH_2CH_2OH$	RT=1.03 min.
unknown	RT=1.44 min.
unknown	RT=2.60 min.

2-Methyl-3-(2'-hydroxyethanoxy)-cyclopent-2-enone (30)

2-Methyl-1,3-cyclopentanedione (29) (0.56 g, 5.0 mmol) was dissolved in methylene chloride (30 mL) under an argon atmosphere. Ethylene glycol (3.0 mL, 54.0 mmol) and chlorotrimethylsilane (1.4 mL, 11.0 mmol) were added and the reaction stirred at room temperature for 48 h. By T.L.C., after 23 h, only more polar compounds were detected.

The reaction was quenched with a 5% aqueous solution of Na_2CO_3. The solution was extracted with ether (2 x 50 mL), washed with brine (2x10 mL) and the combined extracts were dried over anhydrous $MgSO_4$ and gave 0.53 g of a crude crystalline material (m.p. 80-2°C) after evaporation.

A quantity of 0.1087 g was submitted to mesh chromatography (2 elutions, 92.5:7.5, hexanes-ethyl acetate, v/v) to give 0.0624 g of the crystalline title compound (m.p. 80-2°C) in 39% yield. In addition, another compound was isolated (0.0067 g) which eluded identification. The spectral characteristics of the compounds are as follows;

Compound 30

I.R. ($CHCl_3$): ν =3691, 3488, 1683, 1625, 1392, 1336 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ =1.63 (s, 3H, $C=CCH_3$), 2.44 (t, 2H, CH_2CH_2CO, J=4.7 Hz),
2.67 (m, 2H, CH_2CH_2CO), 3.18 (bs, 1H, CH_2OH),
3.94 (t, 2H, OCH_2CH_2OH, J=4.4 Hz),
4.30 ppm (t, 2H, OCH_2CH_2OH, J=2.2 Hz).

M.S.:m/z=156 (96%, M^+), 112 (57%, $M^+-CH_2CH_2O$), 83 (70%, $CHCH_2COCCH_3$).

Unknown Compound

I.R. ($CHCl_3$): ν =3361, 1295, 1191, 983 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ =2.63 (s, nH), 2,67 (s, nH).

M.S.:m/z=219 (3%), 203 (1%), 179 (57%), 135 (98%), 99 (60%), 92 (59%).

2,3-Ribofuranose monoacetonide (32)

Ribose (0.299 g, 1.99 mmol) was suspended in acetone (20 mL) and methanol (10 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.1 mL, 8.7 mmol) was added and the reaction was stirred for 10 min.

The solvents were removed *in vacuo* to give 0.585 g of a crude residue. A quantity of 0.075 g was submitted to flash chromatography (1:1 hexanes–ethyl acetate, v/v). After evaporation of the solvents, 0.035 g of pure acetonide was isolated in in 72% yield. The spectral data for this compound are;

I.R.($CHCl_3$): ν =3398, 1454, 1372, 1208, 1157, 1063 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =1.41 (s, 3H, $\underline{CH_3}^a$-C-$CH_3{}^b$),
1.60 (s, 3H, $CH_3{}^a$-C-$\underline{CH_3}^b$), 3.77 (d, 2H, H_2C5, $J_{4,5}$=6.4 Hz),
4.27 (bs, 1H, C5OH), 4.47 (m, 1H, C4H),
4.63 (d, 1H, C3H, $J_{2,3}$=5.8 Hz), 4.84 (d, 1H, C2H, $J_{3,2}$=5.8 Hz),
5.43 (bs, 1H, C1OH), 5.47 ppm (s, 1H, C1H).

^{13}C-N.M.R.($CDCl_3$): =24.17 ($H_3\underline{C}8C6$), 26.29 ($H_3\underline{C}7C6$), 63.46 ($C5H_2OH$),
81.59 (C3O), 86.71 (C2O), 87.63 (C4O), 102.73 (C1OH),
112.12 ppm ($C7H_3\underline{C}6C8H_3$).

1,2-*iso*-Propylidineglucofuranose (33)
(1,2-glucofuranose acetonide)

Glucose (1.8 g, 10.0 mmol) was suspended in acetone (175 mL) and methanol (50 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (5.0 mL, 53.8 mmol) was added and the reaction stirred for 20 h at room temperature.

The solvent was removed under reduced pressure to give a white amorphous solid. Recrystallization from ether gave 0.933 g of pure crystalline (m.p. 159-60°C, lit.[137] 160-1°C) title compound and left 0.962 g of "crude" material which showed only one spot on T.L.C. and was also pure by ^{1}H-N.M.R.. The overall yield was 86%. A mixed melting point of the "crude" and pure materials was identical with the individual melting points. The spectral characteristics of the compound are;

I.R.(nujol mull):ν =3439, 3312, 1222, 1162, 1084, 1063, 1039, 1009, 959 cm^{-1}.

^{1}H-N.M.R.(D_2O:CD_3OD 1:1, v/v):δ =1.36 (s, 3H, $\underline{CH_3}^a$-C-$CH_3{}^b$), 1.52 (s, 3H, $CH_3{}^a$-C-$\underline{CH_3}^b$), 3.6-3.9 (m, 2H, C6H$\underline{2}$), 3.9-4.2 (m, 2H, C4H + C5H), 4.26 (d, 1H, C3H, $J_{3,4}$=2.2 Hz), 4.52 (d, 1H, C2H, $J_{2,1}$=3.8 Hz), 4.79 (bs, 3H, 3 x OH(HOD)), 5.91 ppm (d, 1H, C1H, $J_{1,2}$=3.8 Hz).

2',3'-*iso*-Propylidineuridine (34)

(2',3'-uridine acetonide)

Uridine (0.171 g, 0.70 mmol) was suspended in acetone (15 mL) and methanol (5 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (0.2 mL, 1.6 mmol) was added and the reaction was stirred for 40 min at room temperature.

The solvents were removed under reduced pressure and gave, after pumping at high vacuum, 0.211 g of a white foam. A quantity of 0.047 g of the crude residue was submitted to flash chromatography (3:1 hexanes-ethyl acetate, v/v) to give after evaporation 0.039 of the crystalline title compound (m.p. 163-4°C, lit.[138] 162°C) in 88% yield. The spectral data for the compound are as follows;

I.R.(nujol mull):ν =3304, 3242, 1702, 1664, 1284, 1273, 1244, 1213, 1159, 1119, 1074 cm^{-1}.

^{1}H-N.M.R.(d_6-acetone):δ =1.35 (s, 3H, $\underline{CH_3}^a$-C-$CH_3{}^b$), 1.89 (s, 3H, $CH_3{}^a$-C-$\underline{CH_3}^b$), 3.74 (d, 2H, H_2C5', $J_{4,5}$=3.8 Hz), 3.5-3.8 (m, 2H, NH + OH), 4.0-4.3 (m, 1H, C4'H), 4.7-5.0 (m, 2H, $(CH_3)_2C(O\underline{C2'H})(O\underline{C3'H})$), 5.60 (d, 1H, N-CH=$\underline{CH}$-CO, J=7.8 Hz), 5.82 (d, 1H, C1'H, J=2 Hz), 7.78 ppm (d, 1H, N-$\underline{CH}$=CH-CO, J=7.8 Hz).

1,2,4-Butanetriol-2,4-acetonide (35)

1,2,4-Butanetriol (0.45 g, 4.3 mmol) was suspended at room temperature in acetone (250 mL) under an argon atmosphere. The reaction was cooled to -90°C and chlorotrimethylsilane was added (2.0 mL, 15.8

mmol).

After 2 h, the reaction mixture was brought to pH 8 (wet alk-acid paper) with a 3% solution of sodium methoxide in methanol. The solvents were removed *in vacuo* and the residue was suspended in a minimum of methanol, diluted with ether, and filtered through silica gel, to yield after evaporation 0.742 g of the title compound mixed with 17% of the dioxolane (36), in 91% overall yield. If the reaction was quenched with an aqueous base, very much lower yields were realized. The spectral data of the dioxolane are;

I.R.(neat): ν =3422, 1380, 1271, 1234, 1193, 1162, 1099, 969 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =1.40 (s, 3H, $\underline{CH_3}^a$-C-$CH_3{}^b$),

1.48 (s, 3H, $CH_3{}^a$-C-$\underline{CH_3}^b$), 1.5-1.9 (m, 2H, $ROCH_2\underline{CH_2}$),

2.72 (bs, 1H, OH), 3.4-4.1 ppm (m, 5H, $RO\underline{CH_2}CH_2\underline{CH}(OR)\underline{CH_2}OH$).

1,2,4-Butanetriol-1,2-acetonide (36)

1,2,4-Butanetriol (0.85 g, 8.2 mmol) was dissolved in acetone (250 mL at room temperature under an argon atmosphere. Chlorotrimethylsilane (3.0 mL, 23.7 mmol) was added and the reaction was stirred for 4 h.

The reaction mixture was brought to pH 8 (wet alk-acid paper) with a 5% solution of sodium methoxide in methanol. The solvents were removed *in vacuo* and the residue was suspended in a minimum of methanol, diluted with ether, and filtered through silica gel. After evaporation, 0.676 g of the title compound, mixed with 10% of the dioxane (35) was isolated in an overall yield of 57%. If the reaction was quenched with an aqueous base, very much lower yields were realized.

Alternatively, 1,2,4-butanetriol (0.364 g, 3.5 mmol) was dissolved in acetone (50 mL). *p*-Toluenesulfonic acid (25.0 mg, 0.13 mmol) was added and the reaction stirred at room temperature under an argon atmosphere for 4 h.

The reaction was quenched with a 5% aqueous $NaHCO_3$ solution (50 mL), extracted with ether (2 x 70 mL), washed with brine (2 x 10 mL) and the combined extracts were dried over Na_2SO_4. After removal of the solvents under reduced pressure, 0.200 g of the title compound, contaminated with 10% of the dioxane (35) was isolated in 39% overall yield. The spectral

data of the dioxolane are;

I.R.(neat): ν=3361, 1380, 1235, 1159, 1095 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=1.37 (s, 3H, $\underline{CH_3}^d$-C-CH_3^e),
1.43 (s, 3H, CH_3^d-C-$\underline{CH_3}^e$), 1.83 (q, 2H, $OCH_2\underline{CH_2}CH$, J=6.0 Hz),
3.60 (dd, 1H, $RO\underline{CH}^aH^bCH^c(OR)CH_2$, J_{ab}=7.6 Hz, J_{ac}=7.6 Hz),
3.81 (t, 2H, $HO\underline{CH_2}$, J=5.7 Hz),
4.09 (dd, 1H, $RO\underline{CH}^bH^aCH^c(OR)CH_2$, J_{ab}=7.6 Hz, J_{bc}=6.0 Hz),
4.28 ppm (pent, 1H, $ROCH_2\underline{CH}(OR)CH_2$, J=6.0 Hz).

Preparation of the 3,5-Dinitrobenzoates of the Acetonides of 1,2,4-Butanetriol

To confirm the identity of the acetonides (35) and (36), the 3,5-dinitrobenzoate esters were synthesized. To a solution of 3,5-dinitrobenzoyl chloride (120 mg, 36.2 mmol) and N,N-dimethylaminopyridine (50 mg, 0.40 mmol) in anhydrous triethylamine (30 mL) was added (35)(34.9 mg, 0.24 mmol) at room temperature under an argon atmosphere. The reaction was stirred for 48 h (the reaction turned a dark brown colour within 3 h).

The reaction was quenched with a 5% aqueous solution of $NaHCO_3$, extracted with ether (3 x 50 mL) and washed with brine (2 x 10 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and after filtration, the solvents were removed *in vacuo*. The crude residue was submitted to gradient mesh chromatography (100 mL each of 14:1, 9:1, 4:1, 2:1 and 1:1 hexanes-ethyl acetate, v/v) to give slightly impure the 3,5-dinitrobenzoate ester (89) in 18% yield (16.2 mg). The same procedure was repeated with the dioxolane (36) from the chlorotrimethylsilane procedure (51.3 mg, 0.35 mmol) and the *p*-toluenesulfonic acid procedure (25.0 mg, 0.17 mmol). Both these compounds gave the same dinitrobenzoate ester (90) in 9% (11.2 mg) and 23% (24.9 mg) yield, respectively. The spectral data for the compounds are;

I.R.(both compounds, $CHCl_3$): ν=1735, 1630, 1547, 1343, 1282 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$)

(89)

δ=1.40 (s, 3H, $\underline{CH_3}^a$-C-$CH_3{}^b$), 1.51 (s, 3H, $CH_3{}^a$-C-$\underline{CH_3}^b$),
1.6-1.8 (m, 2H, $ROCH_2\underline{CH_2}CHOR$), 3.9-4.2 (m, 3H, $RO\underline{CH_2}CH_2\underline{CH}OR$),
4.42 (d, 2H, $CH_2CH^c(OR)\underline{CH_2}OCO$, J=5.7 Hz), 9.1-9.3 ppm (m, $3H_{arom}$).

(90)

δ=1.37 (s, 3H, $\underline{CH_3}^d$-C-$CH_3{}^e$), 1.44 (s, 3H, $CH_3{}^d$-C-$\underline{CH_3}^e$),
2.09 (q, 2H, $OCOCH_2\underline{CH_2}CH^cOR$, J=6.3 Hz),
3.65 (dd, 1H, $RO\underline{CH}^aH^bCH^c(OR)CH_2$, J_{ab}=8.0 Hz), J_{ac}=6.6 Hz),
4.15 (dd, 1H, $RO\underline{CH}^bH^aCH^c(OR)CH_2$, J_{ab}=8.0 Hz, J_{bc}=6.0Hz),
4.2-4.4 (m, 1H, $ROCH^aH^b\underline{CH}^c(OR)CH_2$),
4.60 (t, 2H, $OCO\underline{CH_2}CH_2CH^c(OR)$, J=6.6 Hz), 9.1-9.3 (m, $3H_{arom}$).

The Attempted Preparation of Orthoesters

Methyl benzoate (0.68 g, 5.0 mmol) was dissolved in methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred at reflux overnight.

The solvents were removed *in vacuo*. ^{1}H-N.M.R., T.L.C. and G.L.C. analyses indicated only the presence of starting material.

Methyl phenylacetate (0.40 g, 2.67 mmol) was dissoved in CH_2Cl_2 (25 mL) under an argon atmosphere. Chlorotrimethylsilane (1.5 mL, 11.8 mmol) and ethylene glycol (0.8 mL, 14.4 mmol) were added and the reaction was stirred for 16 h at room temperature and a further 8 h at reflux.

The reaction was quenched with a 5% aqueous solution of $NaHCO_3$. The solution was extracted with methylene chloride (5 x 25 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered through silica gel to trap the excess ethylene glycol, washed with ether and the solvents were removed under reduced pressure to give only the starting methyl phenylacetate.

ESTERS

Methyl benzoylformate (9)

Benzoylformic acid (0.75 g, 5.0 mmol) was dissolved in dry tetra-

hydrofuran (40 mL) under an argon atmosphere. Chlorotrimethylsilane (1.1 mL, 8.25 mmol) and methanol (0.2 mL) were added. Additional methanol was added at 16 h (0.2 mL) and 26 h (3.0 mL, total 84.0 mmol).

After 64 h, the solvents were removed under reduced pressure to give 1.01 of a crude product. A quantity of 0.24 g was submitted to flash chromatography (3:1 hexanes-ethyl acetate, v/v) to give 0.18 g of the pure compound in 89% yield. If two equivalents of TMSCl and excess methanol were used, as in all of the syntheses of the methyl esters listed below, a mixture of the title compound and 2,2-dimethoxyphenylacetaldehyde (*vide supra*, Acetals) was isolated (relative proportion 37:55 ester:acetal-ester). The spectral characteristics of the title compound are;

I.R.(neat): ν =1742, 1693, 1598, 1582, 1457, 1433, 1324, 1207, 1173, 1003 cm^{-1}.

^{1}H-N.M.R.(CCl_4): δ =3.90 (s, 3H, $COOCH_3$), 7.2-7.6, 7.8-8.1 ppm (m, $5H_{arom}$).

M.S.:m/z=164 (1%, M^+), 105 (100%, $C_6H_5CO^+$), 77(78%, $C_6H_5^+$).

G.L.C.:10' 6% OV-101 on CHROMOSORB W, 150°C:

$C_6H_5COCOOCH_3$	RT=3.78 min.
$C_6H_5C(OCH_3)_2COOCH_3$	RT=5.53 min.

Methyl benzoate (39)

Benzoic acid (0.61 g, 5.0 mmol) was dissolved in absolute methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred overnight. Gas chromatographic analysis showed the presence of a single peak and indicated the absence of benzoic acid.

The solution was neutralized to pH 6.0 (moist alkacid paper) with a 10% solution of sodium methoxide in methanol. The solvent was removed under reduced pressure, ether added, and the suspension filtered through Celite. After evaporation, 0.67 g of methyl benzoate, pure by G.L.C. and ^{1}H-N.M.R., was isolated in 98% yield. The spectral characteristics of the compound are;

I.R.(neat): ν=1730, 1602, 1588, 1496, 1455, 1440, 1320, 1280,

1197, 1180, 1120, 1072, 1029, 969 cm^{-1}.

^1H-N.M.R.($CDCl_3$): δ =3.89 (s, 3H, $COOCH_3$),

7.1-7.9, 7.8-8.2 ppm (m, $5H_{arom}$).

G.L.C.:6' 5% CARBOWAX 20M on CHROMOSORB W, 200°C:

C_6H_5COOH	RT=2.52 min.
$C_6H_5COOCH_3$	RT=0.50 min.

Dimethyl 1,12-dodecandioate (40)

1,12-Dodecandioic acid (1.15 g, 5.0 mmol) was dissolved in a solvent mixture of absolute methanol (25 mL), hexanes (10 mL) and ethyl ether (15 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (2.8 mL, 22.0 mmol) was added and the reaction stirred overnight.

The solution was neutralized to pH 6.0 (wet alk-acid paper) with a 10% solution of sodium methoxide in methanol. The solvent was removed *in vacuo* after filtration through 5.0 g of coarse silica gel to give, after evaporation, 1.04 g of the dimethyl ester in 85% yield (m.p. 30.5-31°C, lit[222] 31°C). The spectral characteristics of this compound are;

I.R.(neat): ν=2940, 2860, 1731, 1439, 1253, 1200, 1172 cm^{-1}.

^1H-N.M.R.($CDCl_3$): δ=1.28(bs, 12H, $H_3CO_2C(CH_2)_2\underline{(CH_2)_6}(CH_2)_2CO_2CH_3$),

1.63 (bs, 4H, $H_3CO_2CCH_2\underline{CH_2}(CH_2)_6\underline{CH_2}CH_2CO_2CH_3$),

2.30 (t, 4H, $H_3CO_2C\underline{CH_2}(CH_2)_8\underline{CH_2}CO_2CH_3$),

3.65 ppm (s, 6H, 2 x $COOCH_3$).

M.S.:m/z=227 (25%, M^+-OCH_3), 185 (30%, $M^+-CH_2COOCH_3$),

153 (24%, $HC(CH_2)_9CO^+$), 98 (95%, $(CH_2)_7^+$)

55 (88%, $C_4H_7^+$), 43 (60%, $C_5H_7^+$), 41 (64%, $C_3H_5^+$).

G.L.C.:6' 5% CARBOWAX 20M on CHROMOSORB W, 200°C:

$H_3COOC(CH_2)_{10}COOCH_3$	RT=3.08 min.

Methyl 12-hydroxydodecanoate (41)

12-Hydroxydodecanoic acid (1.08 g, 5.0 mmol) was suspended in absolute methanol (25 mL), ethyl ether (15 mL) and hexanes (15 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the solution stirred overnight.

Neutralization to pH 6.0 (moist alk-acid paper) with a 10% solution of sodium methoxide in methanol, was followed by evaporation to dryness under reduced pressure and redissolution in a 1% methanol-ether solution. Filtration through coarse silica gel (5 g) was followed by evaporation to give 1.11 g of the methyl ester in 96% yield (m.p. 30.5-31.5°C). The residue was purified by flash chromatography (10:1 hexanes-ethyl acetate, v/v,) to give 1.05 g of the pure compound with the melting point increased to 31-32°C (lit.[222] 33-4°C). The spectral characteristics of the compound are;

I.R.(neat): ν =3400, 2940, 2862, 1746, 1460, 1439, 1365, 1250, 1200, 1175, 1109, 1054 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =1.10 (bs, 19H, $\underline{HO}CH_2(\underline{CH_2})_9$), 1.74 (m, 2H, $\underline{CH_2}COOCH_3$), 2.25 (t, 2H, $\underline{CH_2}OH$, J=6.0 Hz), 3.65 ppm (s 3H, $COOCH_3$).

M.S.m/z=200 (5%, M^+-CH_2), 185 (6%, $M^+-CH_2CH_2OH$), 153 (6%, $M^+-CH_2CH_2COOCH_3$), 139 (3%, $M^+-(CH_2)_3COOCH_3$), 125 (4% ($M^+-(CH_2)_4COOCH_3$), 111 (11%, $M^+-(CH_2)_5COOCH_3$), 98 (28%, $C_7H_{14}^+$); 97 (18%, $C_7H_{13}^+$), 87 (55%, $(CH_2)_2COOCH_3^+$), 83 (25%, $C_6H_{11}^+$), 69 (43%, $C_5H_9^+$), 55 (89%, $C_4H_7^+$).

Methyl glutamate (42)

Glutamic acid (4.42 g, 30.0 mmol) was suspended in absolute methanol (100 mL) under an argon atmosphere. Chlorotrimethylsilane (7.0 mL, 55.2 mmol) was added and the reaction stirred at room temperature.

After 5 min, all the precipitate had dissolved and the solvent was then removed under reduced pressure. The residue was recrystallized from methanol-ether to give 3.98 g of the glutamate contaminated with 21% of the dimethyl ester (by ^{1}H-N.M.R) and 1.84 g of pure crystalline 5-methyl glutamate with a total yield of 85% (m.p. 157-8°C, lit.[228,229] 160-1°C). The spectral characteristics of this compound are;

I.R.(KBr): ν =1725, 1609, 1489, 1437, 1239, 1018 cm^{-1}.

^{1}H-N.M.R.(D_2O:CD_3OD, 1:9, v/v): δ =2.2-3.0 (m, 4H, CH_2CH_2), 3.72 (s, 3H, $COOCH_3$), 4.32 (bs, 5H, Cl $\underline{H_3N}\underline{CH}\underline{COOH}$);

N.B. in pure d_6-acetone the α-proton triplet is distinguishable from the labile NH and OH protons: 4.33 ppm (t, 1H, NCHCOOH, J=5.5 Hz).

[Dimethylester

^{1}H-N.M.R.(CD_3OD): δ =2.2-3.0 (m, 4H, CH_2CH_2), 3.72 (s, 3H, $COOCH_3$), 3.87 (s, 3H, $H_3NCHCOOCH_3$), 4.33 ppm (bs, 4H, ClH_3NCH).

M.S.:m/z=130 (13%, M^+-HCl-CH_3O), 116 (61%, M^+-HCl-COOH) 98 (44%, 116^+-H_2O), 84 (82%, M^+-HCl-CH_3OH-COOH), 73 (31%, $CH_3CH_2COOH^+$).

Methyl hippurate (43)

Hippuric acid (benzoylglycine, 0.36 g, 2.03 mmol) was dissolved in absolute methanol (40 mL). Chlorotrimethylsilane (0.6 mL, 4.7 mmol) was added and the reaction stirred under an argon atmosphere at room temperature.

After 12 h, the methanol was removed under reduced pressure to give 0.35 g of a crude product. A quantity of 0.075 g of the residue was submitted to flash chromatography (1:1, ethyl acetate-hexanes, v/v) to give 0.074 g of methyl hippurate in 85% yield m.p. 80.5-81°C, lit.[222] 85°C). The spectral chacteristics of the compound are;

I.R.(CCl_4): ν =3340, 1744, 1654, 1535, 1262, 1206 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =3.66 (s, 3H, OCH_3), 4.14 (d, 2H, $NHCH_2$, J=5.2 Hz), 6.03 (bs, 1H, NH), 7.1-7.5, 7.6-7.8 (m, $5H_{arom}$).

M.S.:m/z=193 (39%, M^+), 161 (25%, M^+-CH_3OH), 134 (57%, M^+-$COOCH_3$), 105 (100%, $C_6H_5CO^+$), 77 (60%, $C_6H_5^+$).

G.L.C.:6' OV-101 on CHROMOSORB 750, 200°C:

$C_6H_5CONHCH_2COOCH_3$ RT=1.35 min.

Methyl leucinate (44)

Leucine (0.66 g, 5.0 mmol) was dissolved in dry methanol (25 mL) under an argon atmosphere. Chlorotrimethylsilane 1.4 mL, 11.0 mmol) was added and the reaction stirred overnight. More chlorotrimethylsilane (1.4

mL, 11.0 mmol) was added and the reaction stirred a further 48 h at room temperature.

The solvent was removed *in vacuo* and the precipitate dried at the pump yielding 0.83 g of crude methyl leucinate·HCl salt. Although the crude residue was recrystallized from methanol-ether, it was found that the recrystallized material had an identical melting point (m.p. 145-6°C, lit.[222] 146°C) to that of the crude material. The obtained yield was 97%. The spectral characteristics of the compound are;

I.R.(KBr): ν=1745, 1580, 1504, 1435, 1274, 1216 cm^{-1}.

^{1}H-N.M.R.(CD_3OD): δ=1.00 (d. 6H, $CH(\underline{CH_3})_2$, J=5.8 Hz),
1.0-1.1 (m, 1H, $\underline{CH}(CH_3)_2$),
1.6-2.0 (m, 4H, $CH_2\underline{CH_2}$), 3.85 (s, 3H, $COOCH_3$),
4.04 (t, 1H, $\underline{CH}COOCH_3$, J=7.0 Hz), 4.85 ppm (s, 3H, NH_3Cl).

M.S.:m/z=88 (76%, M^+-HCl-$(CH_3)_2CHCH_2$), 86 (83%, M^+-HCl-$COOCH_3$),
57 (22%, $(CH_3)_2CHCH_2^+$), 44 (100%, $(CH_3)_2CH_2^+$).

Methyl 6-amino-penicillanoate(HCl salt) (45).

(Methyl 6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3,2,0] heptane-2-carboxylate·HCl salt)

6-Aminopenicillanic acid (0.1088 g, 0.504 mmol) was dissolved in absolute methanol (25 mL) under an argon atmosphere. Chlorotrimethylsilane (0.14 mL, 1.11 mmol) was added and the reaction was stirred for 5 minutes.

The solvents were removed at 10-15°C under high vacuum and the crystals pumped very dry to give a crude product. This was recrystallized from methanol-ether and gave, after pumping, 0.1128 g of the title compound in 84% yield (m.p. 136-40°C). The spectral characteristics of the compound are;

I.R.(CH_3OH): ν =1790, 1725, 1638, 1206 cm^{-1}.

^{1}H-N.M.R.(CD_3OD): δ=1.36 (s, 3H, $\underline{CH_3}^a$-C-$CH_3{}^b$),
1.67 (s, 3H, $CH_3{}^a$-C-$\underline{CH_3}^b$), 3.87 (s, 3H, $COOCH_3$),
3.94 (s, 1H, $\underline{CH}COOCH_3$), 4.25 (d, 1H, $ClH_3NCH\underline{CH}S$),
4.97 (s, 3H, NH_3Cl), 5.16 ppm (d, 1H, $ClH_3N\underline{CH}CHS$).

Methyl phenylacetate (46)

Phenylacetic acid (2.70 g, 19.9 mmol) was dissolved in methanol (40 mL) under an argon atmosphere. Trimethylchlorosilane (5.50 mL, 43.4 mmol) was added and the reaction stirred overnight at room temperature.

The solvents were removed *in vacuo* and the residue filtered through silica gel which was washed with ether. The filtrate and the ether washings had the solvents removed under reduced pressure to give 2.52 g of the title compound in 84% yield. The spectral data for the compound are;

I.R.(neat): ν =3084, 3063, 3027, 2956, 1738, 1493, 1452, 1432 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =3.48 (s, 3H, OCH_3), 3.55 (s, 2H, $C_6H_5\underline{CH_2}$),
7.17 ppm (s, $5H_{arom}$).

Ethyl p-methylbenzoate (47)

p-Methylbenzoic acid (toluic acid, 0.68 g, 5.0 mmol) was dissolved in absolute etnanol (25 mL) under an argon atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction was stirred overnight at room temperature. After 16 h, very little reaction had occurred, so the reaction was refluxed for a further 18 h.

The reaction mixture was dissolved in ether (2 x 50 mL) and washed with water (2 x 20 mL). After drying the organic layer over anhydrous $MgSO_4$, evaporation of the solvents under reduced pressure gave 0.83 g of crude product. A quantity of 0.13 g was submitted to flash chromatography (6:1 hexanes-ethyl acetate, v/v) to give 0.12 g of the pure product in 96% yield. The spectral data for the compound are;

I.R.(CCl_4): ν=1710, 1605, 1584, 1454, 1367, 1277, 1110, 913 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =1.35 (t, 3H, $CH_2\underline{CH_3}$, J=7.0 Hz),
2.36 (s, 3H, $\underline{CH_3}C_6H_4$), 4.37 (q, 2H, $\underline{CH_2}CH_3$, J=7.0 Hz).
7.08, 7.91 ppm (ABq, $4H_{arom}$, J_{om}=8.4 Hz).

Ethyl *p*-nitrobenzoate (48)

p-Nitrobenzoic acid (0.84 g, 4.8 mmol) was dissolved in dry ethanol (25 mL) under an argon atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred for 1 h at room temperature and then refluxed for 36 h. As a result of technical problems, the reaction boiled dry. Therefore, more chlorotrimethylsilane (1.4 mL, 11.0 mmol) and dry ethanol (25 mL) were added and the reaction was refluxed a further 12 h.

Removal of the solvent under reduced pressure gave 0.83 g of a crude crystalline product (m.p. 55.5-57°C, lit.[222] 56°C). A quantity of 0.112 g was purified by flash chromatography (6:1, hexanes-ethyl acetate, v/v) to give 0.102 g of pure title compound in 78% yield. When accounting for recovered starting material the isolated yield was 81%. The spectral characteristics of the compound are;

I.R.(neat): ν=1726, 1528, 1276, 908 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=1.40 (t, 3H, $CH_2\underline{CH_3}$, J=7.0 Hz),
4.38 (q, 2H, $\underline{CH_2}CH_3$, J=7.0 Hz), 8.17 ppm (s, $4H_{arom}$).

M.S. m/z=195 (15%, M^+), 178 (44%, M^+-OH), 167 (73%, $M^+-CH_2CH_3$),
150 (100%), $M^+-OCH_2CH_3$), 104 (62%, 150^+-NO_2), 76 (52%, 104^+-CO).

Ethyl hippurate (49)

Hippuric acid (0.36 g, 2.0 mmol) was dissolved in absolute ethanol (22 mL) under an argon atmosphere. Chlorotrimethylsilane (0.6 mL, 2.0 mmol) was added and the reaction stirred at room temperature for 40 h.

The solvent was removed *in vacuo* and the residue crystallized from ethanol-ether to give 0.41 g of crude product. A quantity of 0.109 g of the crude product was submitted to flash chromatography (4:1 hexanes-ethyl acetate, v/v) to give, after evaporation, 0.107 g of pure product in 97% yield. The melting points of the crude and chromatographed material were identical (m.p. 61.5°C, lit.[222] 67.5°C). The spectral characteristics of the compound are;

I.R.(CCl_4): ν=3252, 1739, 1654, 1531, 1209, 913 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=1.25 (t, 3H, $CH_2\underline{CH_3}$, J=7.5 Hz),
4.06 (d, 2H, CH_2N, J=5.0 Hz), 4.13 (q, 2H, $\underline{CH_2}CH_3$, J=7.5 Hz),
7.0-7.5, 7.6-7.9 ppm (m, 6H, C_6H_5CONH).
M.S.:m/z=207 (67%, M^+), 161 (49%, $M^+-CH_3CH_2OH$),
134 (94%, $M^+-COOCH_2CH_3$), 105 (56%, $C_6H_5CO^+$),
77 (93%, $C_6H_5^+$).

Ethyl glutamate (50)

Glutamic acid (4.42 g, 30.0 mmol) was suspended in absolute ethanol (150 mL) under a nitrogen atmophere. Chlorotrimethylsilane (4.5 mL, 48.5 mmol) was added and the reaction was stirred at room temperature for 0.5 h (no precipitate remained). HCl gas was partially removed by bubbling with nitrogen under vacuum for 0.5 h.

The ethanol was removed *in vacuo*, and the crude glutamate was recrystallized from ethanol-ether. Three crops of crystals were isolated; one crop of pure 5-ethyl glutamate·HCl (2.39 g, m.p. 166.5-167.5°C. lit.[222] 170-170.5°C), one crop of starting material (1.25 g) and the final crop which consisted of approximately 63% 5-ethyl glutamate·HCl (2.80 g, by T.L.C. and ^{1}H-N.M.R.). The yield (67%) was calculated by the addition of the proportion of the product in the crystalline mixture (1.86 g) and the pure product. After accounting for recovered starting material, the yield was 92%. The isolated yield of pure compound was 38%; after accounting for the recovered starting material, the isolated yield was 52%. The spectral characteristics of the compound are;

I.R.(KBr): ν=2952, 1725, 1603, 1426, 1212 cm^{-1}.
^{1}H-N.M.R.(CD_3OD:D_2O, 2:1, v/v): δ=1.28 (t, 3H, $CH_2\underline{CH_3}$, J=7.0 Hz),
2.0-2.8 (m, 4H, CH_2CH_2), 3.98 (t, 1H, $CH_2(NH_3)\underline{CH}COO$, J=6.0 Hz),
4.20 (q, 2H, $\underline{CH_2}CH_3$, J=7.0 Hz), 4.77 ppm (s, 3H, NH_3Cl).
M.S.:m/z=157 (4%, $M^+-HCl-H_2O$), 130 (57%, $M^+-HCl-COOH$),
84 (94%, $CHCOOCH_2CH_3^+$).

Benzyl 12-hydroxydodecanoate (51)

To 12-hydroxydodecanoic acid (0.555 g, 2.57 mmol), dissolved in dry

tetrahydrofuran (12 mL), was added chlorotrimethylsilane (0.7 mL, 5.5 mmol) and benzyl alcohol (1.0 mL, 9.7 mmol). The reaction was stirred for 48 h under an argon atmosphere at room temperature.

The solvent was removed under reduced pressure to give 0.822 g of crude product. A quantity of 0.142 g of the crude mixture was submitted to flash chromatography (7:1 hexanes-ethyl acetate, v/v), to give 0.102 g of a mixture of the benzyl ester and the benzyl ether (81:19). These were inseparable by normal phase chromatography; flash, T.L.C., preparative H.P.L.C.. The yields of the two products were determined by ^{1}H-N.M.R. to be 61% for the benzyl ester and 14% for the benzyl ether.

I.R.(neat): ν=3360, 2920, 2843, 1725, 1453, 1368, 1174, 1018 cm^{-1}.

Benzyl ester:

^{1}H-N.M.R. ($CDCl_3$): δ =1.0-1.9 (m, 18H, $HOCH_2(\underline{CH_2})_9$),
2.1-2.4 (m, 3H, $\underline{CH_2}CO_2$ + $\underline{OH}$), 3.57 (t, 2H, $HO\underline{CH_2}$, J=6.0 Hz),
4.63 (s, 2H, $C_6H_5\underline{CH_2}O$), 7.30 ppm (s, $5H_{arom}$).

Benzyl ether:

^{1}H-N.M.R. ($CDCl_3$): δ =1.0-1.9 (m, 18H, $HO_2CCH_2(\underline{CH_2})_9$),
2.1-2.4 (m, 2H, $HO_2C\underline{CH_2}$), 4.10 (t, 2H, $C_6H_5CH_2O\underline{CH_2}$, J=7.2 Hz),
5.07 (s, 2H, $C_6H_5\underline{CH_2}O$) 7.30 ppm (s, $5H_{arom}$).

M.S.:m/z=120 (2%, $C_6H_5CH_2OCH^+$), 108 (85%, $C_6H_5CH_2OH^+$),
107 (77%, $C_6H_5CH_2O^+$), 91 (28%, $C_6H_5CH_2^+$), 79 (86%, $C_6H_7^+$),
77 (64%, $C_6H_5^+$), 65 (12%, $C_5H_5^+$), 51 (33%, $C_4H_3^+$).

Cyclohexyl Hippurate (52)

Hippuric acid (0.90 g, 5.0 mmol) was dissolved in cyclohexanol (15 mL) under an argon atmosphere. Chlorotrimethylsilane was added (1.4 mL, 11.0 mmol) and the reaction was stirred for 24 h at room temperature.

Most of the cyclohexanol was removed at 80°C using a high vacuum (1 torr). The product spontaneously crystallized out. Hexanes were added to the residue and more crystals precipitated out. The solid was filtered from the hexanes-cyclohexanol solution, rinsed with hexanes and the solid was recrystallized (m.p. 101°C, lit.[330] 105°C) from hexanes-ethyl acetate to give 1.31 g of the title compound in 84% yield.

I.R.($CHCl_3$)): ν =3436, 3000, 2939, 1728, 1658, 1576, 1519, 1481, 1446, 1380, 1358, 1222 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=1.1-2.1 (m, 10H, $-CH(\underline{CH_2})_5-$), 4.19 (d, 2H, $NH\underline{CH_2}$, J=5 Hz), 4.86 (m, 1H, $-\underline{CH}(CH_2)_5$), 6.81 (bs, 1H, $\underline{NH}CH_2$), 7.3-7.6, 7.7-7.9 ppm (m, $5H_{arom}$).

M.S.:m/z=261 (1%, M^+), 180 (26%, $M^+-C_6H_9$), 162 (15%, $M^+-OC_6H_{11}$), 134 (68%, $M^+-CO_2C_6H_{11}$), 122 (17%, $M^+-C_5H_5CONH_2$), 119 (26%, $C_6H_5CON^+$), 105 (100%, $C_6H_5CO^+$), 83 (55%, $C_6H_{11}^+$), 77 (50%, $C_6H_5^+$).

Benzyl hippurate (53)

Hippuric acid (benzoyl glycine, 0.45 g, 2.5 mmol) was dissolved in dry tetrahydrofuran (40 mL) under an argon atmosphere. Benzyl alcohol (0.8 mL, 7.7 mmol) and chlorotrimethylsilane (0.7 mL, 5.5 mmol) were added and the reaction stirred at room temperature for 18 h. A further 0.7 mL of chlorotrimethylsilane was added and the reaction was refluxed for 24 h.

The solvents were removed *in vacuo* to give 1.03 g of the crude product. A quantity of 0.162 g of the crude residue was submitted to flash chromatography (3:1, hexanes-ethyl acetate, v/v) to give 0.071 g of the pure product in 65% yield. The spectral characteristics of the compound are;

I.R.(neat):ν =3308, 2926, 2846, 1758, 1644, 1537, 1453, 1403, 1376, 1203 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=4.17 (d, 2H, $NH\underline{CH_2}$, J=5.0 Hz), 5.14 (s, 2H, $C_6H_5\underline{CH_2}$), 6.78 (bs, 1H, NH), 7.28 (s, 5H, $\underline{C_6H_5}CH_2$), 7.2-7.4, 7.6-7.8 ppm (m, 5H, C_6H_5CO).

M.S.:m/z=269 (5%, M^+), 162 (13%, $M^+-OCH_2C_6H_5$), 149 (24%, $M^+-C_6H_5CONH$) 135 (44%, $C_6H_5CH_2OCO^+$), 134 (40%, $C_6H_5CONHCH_2^+$), 105 (100%, $C_6H_5CO^+$), 91 (69%, $C_6H_5CH_2^+$), 77 (66%, $C_6H_5^+$).

β-Trimethylsilylethyl 12-hydroxydodecanoate (54)

12-Hydroxydodecanoic acid (0.54 g, 2.5 mmol) was dissolved in dry tetrahydrofuran (12 mL) under an argon atmosphere. Chlorotrimethylsilane

(0.7 mL, 5.5 mmol) and 2-trimethylsilylethanol (1.0 mL, 8.5 mmol) were added and the reaction was stirred at reflux overnight. More chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred for a further 48 h at reflux.

All low boiling materials were removed under reduced pressure to give 0.77 g of a crude product. A quantity of 0.14 g of the residue was submitted to flash chromatography (3:1 hexanes-ethyl acetate, v/v) to give 0.11 g of the pure title compound. The total yield was 73%. However, when recovered starting material was accounted for, the yield was 79%. The spectral data for the compound are;

I.R.(neat): ν =2928, 2854, 1731, 1452, 1249, 1170 cm^{-1}.

^{1}H-N.M.R.(CCl_4): δ =0.10 (s, 9H, $Si(CH_3)_3$),
0.97 (t, 2H, $OCH_2\underline{CH_2}Si$, J=8.0 Hz), 1.35 (bs, 18H, $(CH_2)_9$),
2.21 (t, 2H, CH_2CO, J=5.0 Hz), 2.25 (s, 1H, OH),
3.52 (t, 2H, $\underline{CH_2}OH$, J=5.0 Hz), 4.10 ppm (t, 2H, $O\underline{CH_2}CH_2Si$, J=8.0 Hz).

$C_{17}H_{36}O_3Si$	calc.	C	64.50	H	11.46
(316.6)	found		64.46		11.43

β-Trimethylsilylethyl Hippurate (55)

Hippuric acid (benzoyl glycine, 0.37 g, 2.1 mmol) was dissolved in dry tetrahydrofuran (40 mL) under an argon atmosphere. 2-Trimethylsilylethanol (0.6 mL, 5.1 mmol) and chlorotrimethylsilane (0.7 mL, 5.5 mmol) were added and the reaction stirred at room temperature for 18 h. Additional chlorotrimethylsilane (0.7 mL, 5.5 mmol) was added and the reaction stirred a further 24 h.

The solvents were evaporated under reduced pressure to give 0.98 g of crude product. A quantity of 0.13 g was submitted to flash chromatography (2:1 hexanes-ethyl acetate, v/v) to give 0.07 g of pure title compound in 98% yield. The spectral data for the compound are;

I.R.(CCl_4): ν=3348, 2956, 1743, 1650, 1538, 1251, 1183 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =0.05 (s, 9H, $Si(CH_3)_3$),
1.00 (t, 2H, $OCH_2\underline{CH_2}Si$, J=8.0 Hz),
4.04 (t, 2H, $NH\underline{CH_2}$, J=4.8 Hz), 4.20 (t, 2H, $O\underline{CH_2}CH_2Si$, J=8.0 Hz).

7.1-7.4, 7.6-7.8 ppm (m, $5H_{arom}$),

M.S.: m/z=193 ($M^+-(CH_3)_3SiH$), 162 (8%, $M^+-CH_2CH_2Si(CH_3)_3$), 134 (14%, $M^+-COOCH_2CH_2Si(CH_3)_3$), 105 (88%, $C_6H_5CO^+$), 77 (57%, $C_6H_6^+$), 73 (100%, $Si(CH_3)_3^+$).

$C_{14}H_{21}NO_3Si$	calc.	C 60.18	H 7.58	N 5.01
(279.41)	found	60,06	7.67	5.07

Esterification with 2,2,2-trichloroethanol

12-Hydroxydodecanoic acid (0.540 g, 2.50 mmol) was dissolved in a solution of 2,2,2-trichloroethanol (1.0 mL, 10.4 mmol) and anhydrous tetrahydrofuran (11.0 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (0.7 mL, 5.5 mmol) was added and the reaction refluxed overnight. More chlorotrimethylsilane was added at 12 h (0.6 mL, 4.7) and at 36 h (2.1 mL, 16.6 mmol).

The solvents were removed *in vacuo* to give 0.792 g of a residue. T.L.C. analysis showed in excess of 16 compounds. The residue was submitted to flash chromatography (3:1 hexanes-ethyl acetate, v/v) but it proved impossible to isolate any pure compounds.

p-Nitrobenzoic acid (0.835 g, 5.00 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) and 2,2,2-trichloroethanol (1.0 mL, 10.4 mmol) were added and the reaction stirred at room temperature for 24h.

The solvents were removed under reduced pressure. The residue was extracted with ether (2 x 50 mL) and washed with a 5% aqueous sodium bicarbonate solution (2 x 20 mL) and the combined extracts dried over anhydrous $MgSO_4$. After evaporation, 0.726 g of starting material was isolated.

Benzoic acid (0.61 g, 5.0 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) under an argon atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) and 2,2,2-trichloroethanol (1.0 mL, 10.4 mmol) were added and the reaction refluxed overnight.

The solution was diluted with ether (2 x 75 mL) and extracted with a 5% aqueous sodium bicarbonate solution (2 x 25 mL). The combined extracts

were dried over anhydrous $MgSO_4$. After evaporation of the solvents, only benzoic acid was isolated.

The Formation of *t*-Butyl Esters

The following sets of reaction conditions were tried in the hope of making *t*-butyl esters from *t*-butanol and a carboxylic acid. The conditions for the reactions are listed below;

(a) $C_6H_5CO_2H$ (1 eq), Me_3SiCl (2.2 eq), t-butanol (solvent ~100 eq), room temperature, 48 h.

(b) same as (a) except 100°C, 48 h.

(c) $C_6H_5CONHCH_2CO_2H$ (1 eq), Me_3SiCl (2.2 eq), t-butanol (solvent ~100 eq), room temperature, 24 h, 100°C, 48 h.

In none of the three cases did T.L.C. analysis indicate any product during the course of the reaction or after quenching with a 5% aqueous bicarbonate solution. The *t*-butyl group cannot, apparently, be introduced using *t*-butanol in the presence of chlorotrimethylsilane.

Transesterification

Ethyl glutamate

Methyl glutamate·HCl (0.16 g, 0.81 mmol) was dissolved in absolute ethanol (30 mL) under an argon atmosphere. Chlorotrimethylsilane was added (0.3 mL, 2.73 mmol) and the reaction was stirred at room temperature overnight.

The solvents were removed *in vacuo* to give 0.178 g of crystalline material. ^{1}H-N.M.R. analysis showed the presence of starting material (47%), 5-methyl glutamate (42%), and the 1,5-diethyl ester (11%). For spectral characteristics of the former two, see the experimental section of esters. The ^{1}H-N.M.R. spectral data for the 1,5-diethyl glutamate·HCl are;

^{1}H-N.M.R. (CD_3OD): δ = 1.19 (t, 3H, $H_3NCCOOCH_2\underline{CH_3}$, J=6.8 Hz), 1.26 (t, 3H, $\underline{CH_3}CH_2O_2CCH_2CH_2$, J=7.0 Hz), 2.1-2.9 (m, 4H, CH_2CH_2), 4.1-4.5 (m, 5H, $CH_3\underline{CH_2}O_2CCH_2CH_2\underline{HC}(NH_3)CO_2\underline{CH_2}CH_3$), 5.30 ppm (s, 3H, NH_3).

Methyl glutamate

Ethyl glutamate·HCl (0.125 g, 0.59 mmol) was dissolved in absolute methanol (50 mL) under an argon atmosphere. Chlorotrimethylsilane was added (0.3 mL, 2.37 mmol) and the reaction was stirred overnight at room temperature.

The solvents were removed *in vacuo* to give 0.129 g of crude material. ^{1}H-N.M.R. analysis indicated the 5-methyl (90%) and the 1,5-dimethyl glutamates (10%). Spectral characteristics are given in the experimental section of Esters (*vide supra*).

iso -Butyl acetoacetate

Methyl acetoacetate (0.58 g, 5.00 mmol) was dissolved in anhydrous *iso* -butanol under an argon atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction was stirred for 2 days at room temperature.

The solution was extracted with ether (150 mL) and washed with water (20 x 200 mL). The ether solution was dried over anhydrous $MgSO_4$. The ether was removed under reduced pressure and the residue was submitted to flash chromatography (9:1 hexanes-ethyl acetate, v/v) to give 0.412 g of the *iso*-butyl acetoacetate ester in 56% yield.

I.R.(neat): ν =2963, 1740, 1718, 1643, 1466, 1408, 1357, 1314, 1147 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =0.94 (d, 6H, $HC(\underline{CH_3})_2$, J=6.5 Hz), 1.96 (m, 1H, $H_2C\underline{CH}(CH_3)_2$), 2.28 (s, 3H, CH_3CO), 3.46 (s, 2H, $CH_3CO\underline{CH_2}CO$), 3.93 ppm (d, 2H, $\underline{CH_2}CH(CH_3)_2$), J=6.5 Hz).

M.S.:m/z=158 (1%, M^+), 115 (5%, M^+-CH_3CO), 103 (35%, $M^+-CH_3COCH_2$), 85 (66%, $M^+-OCH_2CH(CH3)_2$), 73 (7%, $OCH2CH(CH_3)_2^+$).

The Attempted Transesterification of Methyl 12-Hydroxydodecanoate, Methyl Benzoate and Methyl Phenylacetate

Methyl 12-hydroxydodecanoate (41)() (1.08 g, 5.00 mmol) was dissolved

in a solution of *p*-nitrophenol and tetrahydrofuran under an argon atmosphere. Chlorotrimethylsilane (1.4 mL, 11.0 mmol) was added and the reaction stirred at room temperature for 12 h.

The reaction by T.L.C., ^{1}H-N.M.R. and G.L.C., showed only the presence of starting materials and the reaction was therefore judged a failure.

G.L.C.:10' 5% OV-101 on CHROMOSORB W, 150°C:

$C_6H_5CO_2CH_3$	RT=1.64,
p-$NO_2C_6H_5OH$	RT=8.50,
Reaction mix	RT=1.67, 8.51.

Methyl benzoate (39) (25 mL, 2.02 mmol) was added to a solution of benzyl alcohol (0.5 mL) and anhydrous tetrahydrofuran (15 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (0.5 mL, 3.9 mmol) was added and the reaction was stirred for 3 h at room temperature.

The solvents were removed *in vacuo* and the residue submitted to flash chromatography (3:1 hexanes-ethyl acetate, v/v) to give 0.21 g of recovered methyl benzoate and 0.13 g of benzyloxytrimethylsilane. The spectral data for the latter compound are;

^{1}H-N.M.R. ($CDCl_3$): δ =1.03 (s, 9H, $(CH_3)_3Si$), 4.70 (s, 2H, CH_2), 7.30 ppm (s, $5H_{arom}$).

G.L.C.:10' 5% OV-101 on CHROMOSORB W, 150°C:

$C_6H_5CH_2OH$	RT=1.36 min,
$C_6H_5CO_2CH_3$	RT=1.67 min,
$C_6H_5CH_2OSi(CH_3)_3$	RT=2.04 min.

Methyl phenylacetate (46) (0.325 g, 2.43 mmol) was dissolved in dry benzyl alcohol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane was added (0.75 mL, 5.92 mmol) and the reaction stirred overnight at room temperature.

Three spots were observed with T.L.C. corresponding to the starting materials and a new spot. Isolation of the new compound was achieved using preparative H.P.L.C. (33:1, hexanes-ethyl acetate, v/v) to give 0.384 g of dibenzyl ether in 65% yield based on the amount of trimethyl-

chlorosilane used.

I.R.(neat): ν =3085, 3062, 3030, 2859, 1494, 1451, 1358, 1264, 1208, 1091, 1069, 1023 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =4.48 (s, 4H, 2x($\underline{CH_2}C_6H_5$)), 7.30 ppm (s, 10H, 2x($CH_2\underline{C_6H_5}$)).

M.S.:m/z=107 (42%, $OCH_2C_6H_5^+$), 91 (100%, $CH_2C_6H_5^+$).

Rate Study in Ester Formation

Benzoic acid (0.244 g, 2.0 mmol) was added (t=0) to a solution of chlorotrimethylsilane (0.5 mL, 3.9 mmol) and methanol (10 mL) under an argon atmosphere. The reaction was followed with G.L.C. over a 48h period by injecting 1 μL.

The same esterification was carried out with catalysis by methanolic HCl. A quantity of methanol (10 g) was saturated with anhydrous hydrogen chloride. The weight of the solution increased to 12.7 g. This acidic solution (0.68 g, 0.4 mL, 4.0 mmol HCl) was added to anhydrous $MgSO_4$ (0.25 g, 2.0 mmol) in methanol (9.6 mL). Benzoic acid (0.244 g, 2.0 mmol) was added and the reaction was followed by G.L.C. for 48 h.

To normalize the errors in injection, a mean of the integrations of the solvent peaks from the individual spectra (at time t) was calculated. The integrals of the other peaks in the G.L.C. spectra were then normalized by multiplying the absolute value of the integration (at time t) by the ratio [absolute solvent integral (at time t)/mean of solvent integrals].

Listed below (Tables 5.1 and 5.2) are the time of injection (sec), absolute integral, corrected integral, value of [final integral - integral (t)] and the log [final integral - integral (t)], where integrals refer to the calculated area of the peak corresponding to methyl benzoate. The points were fitted using a least-squares fit to give the pseudo-first order rate constants of 1.47×10^{-5} and 9.25×10^{-6} for the reaction promoted by chlorotrimethylsilane and hydrogen chloride (Figure 5.1), respectively.

Table 4.3:Reaction Promoted by Chlorotrimethylsilane

Time (sec)	Integral	Corrected Integral	Solvent Integral	log(conc$_f$ - conc$_t$)	Trimethylsilyl benzoate integral
245	0	0	484220	4.662549	433
775	1725	1645.464	449610	4.646756	8772
1345	3329	3376.469	422850	4.629496	12645
1925	5364	5364	NA *	4.608797	13471
3185	8176	8176	NA	4.577712	10131
3485	9669	9669	NA	4.560256	12189
3960	8468	8468	NA	4.574351	6915
4415	8218	8218	NA	4.57723	4245
4905	19923	19923	NA	4.416578	16044
11005	21420	21586.27	425576	4.388033	0
14315	23151	24616.25	403351	4.330664	0
16540	27741	27025.38	440236	4.278934	0
16930	27676	28312.55	419237	4.248543	0
17800	29498	29746.69	425294	4.211971	0
20265	29150	29924.17	417784	4.207223	0
22500	30246	31745.14	408626	4.155252	0
85695	38428	41224.1	399790	3.684447	0
85915	43618	44716.36	418345	3.129995	0
177410	49465	46067.06	460514	9999	0

* not calculated

Average Solvent Integral 428879.5
Total Solvent Integrals 5575433
Number of data points 13

Table 4.4:Reaction Catalyzed by HCl

Time (sec)	Integral	Corrected Integral	Solvent Integral	log(conc$_f$ - conc$_t$)
1405	1754	1821.827	392926	4.531537
2300	3985	3338.952	487087	4.550451
40130	4608	4608	NA	4.515054
41720	4328	4867.909	362855	4.511598
44140	5370	5943.566	368736	4.496999

45500	6836	7123.862	391629	4.480399
46700	8196	8852.881	377838	4.454872
56300	12396	10363.62	488156	4.431268
62415	13766	13293.26	422634	4.38148
65100	8657	15886.31	222399	4.332084
66670	15021	16319.34	375651	4.323257
72915	12831	17055.81	307027	4.307822
75350	24422	21158.46	471070	4.210066
76310	25370	22693.58	456253	4.166974
78675	26034	22894.38	464088	4.161008
80330	20716	22060.91	383240	4.185255
123525	32261	30291.51	434925	3.851534
123900	46282	35470.81	532512	3.286442
170775	35095	37407.38	382892	9999

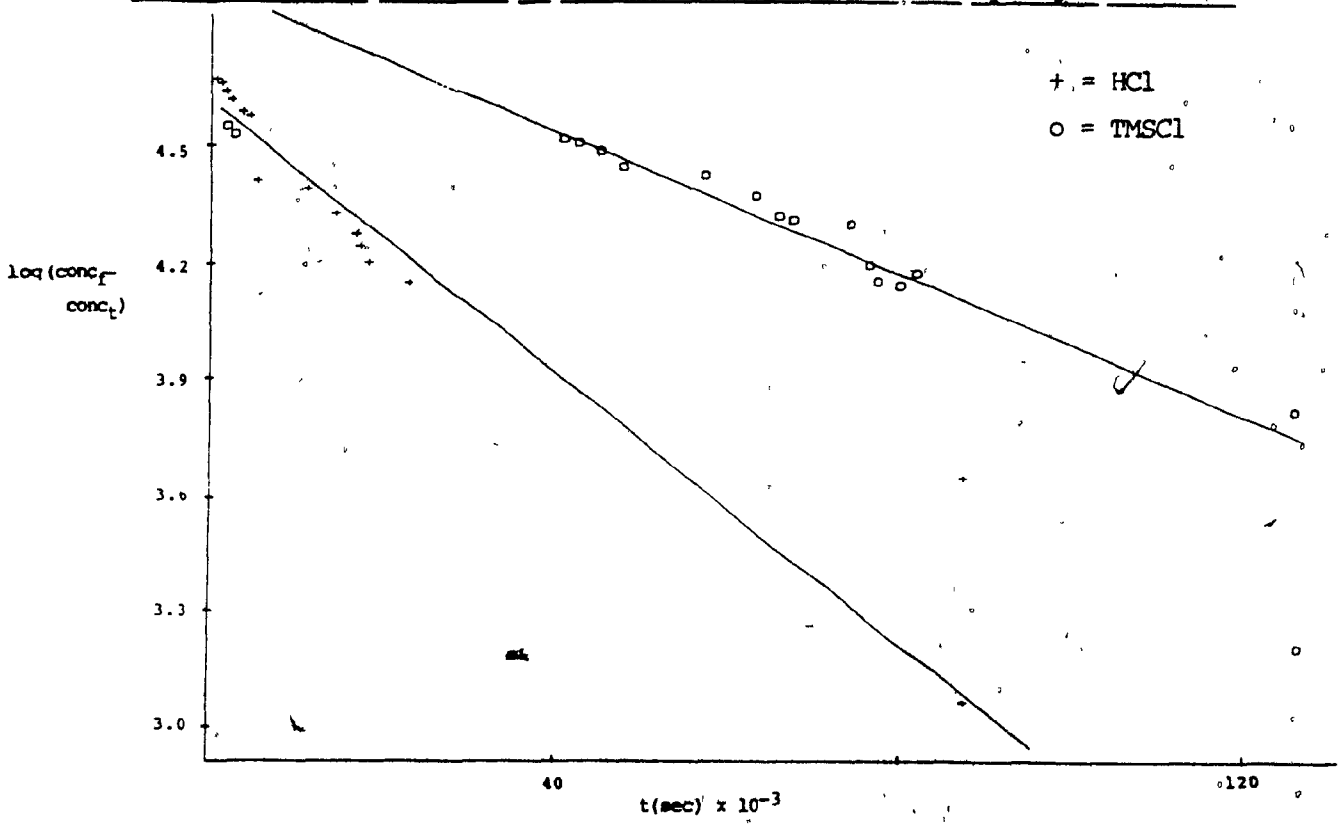
Average Solvent Integral	408120.4
Total Solvent Integrals	7754288
Number of data points	19

The other point of interest is the discovery of a peak of longer retention time which appeared in the spectra taken between t=0 and t=3 h, of the reaction promoted by TMSCl, but not that catalyzed by HCl. A list of the injection time and integration of this peak are listed above. It is anticipated that this peak corresponds to trimethylsilylbenzoate.

G.L.C.:6' 10% OV-101 Chromosorb 750:160°C

Methyl benzoate	RT=1.41
Trimethylsilylbenzoate	RT=2.17

Figure 4.6:A Plot of $\log(conc_f - conc_t)$ *versus* Time (sec) for the Esterifications Promoted by Chlorotrimethylsilane and Hydrogen Chloride



Mechanistic Study of Esterification in the Presence of Chlorotrimethylsilane

Benzoic acid (0.3780 g, 3.098 mmol) was dissolved in a mixture of tetrahydrofuran (5 mL) and d_6-acetone (1 mL) under a nitrogen atmosphere. Chlorotrimethylsilane was added (0.89 mL, 7.02 mmol) and the reaction stirred for 1h. The ^{29}Si-N.M.R. spectrum was observed using the INEPT pulse sequence. Methanol (0.13 mL, 3.21 mmol) was added and the silicon spectrum again observed. ^{1}H-N.M.R. analysis of the final reaction mixture showed the presence of methylbenzoate.

Sodium benzoate (2.00 g, 13.88 mmol) was suspended in tetrahydrofuran (23 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (3.45 mL, 26.23 mmol) was added and the reaction stirred overnight. A 5 mL aliquot was diluted with d_6-acetone (1 mL) and the ^{29}Si-N.M.R. spectrum taken using the INEPT pulse sequence. Methanol (0.14 mL, 3.45 mmol) was added

and the spectrum was again taken. ^{1}H-N.M.R. showed the presence of methyl benzoate.

4-Hydroxybutyric acid (84)

δ-Butyrolactone (85) (1.60 g, 18.6 mmol) was added to a solution of potassium hydroxide (2.1 g, 36.9 mmol) in methanol:water (1:1, 100 mL). The reaction was stirred overnight at room temperature. G.L.C. analysis showed the absence of any starting material.

The solution was extracted with ether (2 x 100 mL) and washed with a 5% aqueous sodium bicarbonate to remove the methanol. The ether extracts were discarded. The aqueous layer was acidified to pH 6 (wet alk-acid paper) with 1 N aqueous hydrochloric acid. The aqueous solution was then extracted with ether (2 x 150 mL), washed with water (2 x 50 mL) and brine (2 x 25 mL), and the combined extracts were dried over anhydrous $MgSO_4$. The ether was removed *in vacuo* to give 0.29 g of the title compound in 15% yield. The spectral data of the compound are;

I.R.(neat): ν=3360, 1710, 1395, 1254, 1054 cm^{-1}.
G.L.C.:5% OV-101 on CHROMOSORB 750, 150°C:

$-CH_2COO(CH_2)_2-$	RT=1.64 min.
$HO(CH_2)_3COOH$	RT=1.89 min.

δ-Butyrolactone (85)

4-Hydroxybutyric acid (84) (0.1986 g, 1.910 mmol) was dissolved in dry tetrahydrofuran (25 mL) under an argon atmosphere. Chlorotrimethylsilane was added (0.7 mL, 5.5 mmol) and the reaction stirred at room temperature for 1 h.

The brown solution was filtered through coarse silica gel. The silica was washed with carbon tetrachloride (2 x 5 mL) and the combined filtrates were evaporated under reduced pressure to give 0.951 g of the title compound in 50% yield. The spectral characteristics of the compound are;

I.R.(CCl_4): ν =1773, 1461, 1422, 1162, 1034, 990 cm^{-1}.

^{1}H-N.M.R.(CCl_4): δ=2.1-2.5 (m, 4H, $OCCH_2CH_2$),
4.1-4.4 ppm (m, 2H, OCH_2).

G.L.C.:5% OV-101 on CHROMOSORB 750, 150°C:

$HO(CH_2)_3COOH$ RT=1.89 min.

$-CH_2COO(CH_2)_2-$ RT=1.64 min.

Isolation of a Silyl Ester From the Reaction of a Carboxylic Acid With Chlorotrimethylsilane (86)

12-Hydroxydodecanoic acid (1.08 g, 5.00 mmol) was suspended in tetrahydrofuran (40 mL) under an argon atmosphere. Chlorotrimethylsilane (2.8 mL, 22.0 mmol) was added and the reaction was refluxed for 18 h.

The solvents were removed *in vacuo* and the residue was suspended in anhydrous ether, filtered through silica gel, and the solvents were removed under reduced pressure to give 0.62 g of the trimethylsilyl ester contaminated with the starting acid. The spectral data for the ester are as follows;

I.R.(neat): ν=3442, 2930, 2869, 1719, 1248, 1092 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=0.21 (s, 9H, $Si(CH_3)_3$), 1.2 (bs, 21H, $\underline{HO}CH_2(\underline{CH_2})_{10}$), 2.21 (t, 2H, $CH_2\underline{COO}$, J=6.5 Hz), 3.46 (t, 2H, $\underline{CH_2}OH$, J=6.0 Hz).

Oxidation of Cyclododecanone (87)

Cyclododecanone (0.4603 g, 2.525 mmol) was dissolved in methylene chloride (25 mL) under an argon atmosphere. *m*-Chloroperbenzoic acid (0.7161 g, 4.149 mmol) was added and the reaction was refluxed overnight.

The reaction was quenched with a 5% aqueous bicarbonate solution, extracted with ether (2 x 70 mL), washed with brine (2 x 10 mL) and the combined extracts dried over anhydrous $MgSO_4$. The solvents were removed and the residue submitted to flash chromatography (10:1 hexanes-ethyl acetate, v/v) to give, after evaporation, 0.270 g of the 13 membered macrolide (87) in 54% yield. The spectral data for this compound are described in the following experimental procedure.

1,12-Dodecanolide (87)

12-Hydroxydodecanoic acid (0.217 g, 1.00 mmol) was dissolved in a solution of toluene (40 mL) and *p*-toluenesulfonic acid monohydrate (3.073 g, 0.38 mmol). After 4 h at a bath temperature which just allowed reflux conditions to a Dien-Stark trap, no starting material remained as judged by T.L.C..

The toluene was removed under reduced pressure and of the 0.319 g of crude residue, 0.140 g was submitted to flash chromatography (3:1, hexanes-ethyl acetate, v/v) to give two compounds of widely different polarity. The less polar material (0.064 g, 70% yield) was determined by mass spectral analysis to be the dodecanolide (87), and the more polar material (0.31 g, 18% yield), the diolide (88). The spectral data for the compounds are;

Monolide

I.R.(CCl_4): ν =2928, 2856, 1734, 1455 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =1.0-2.0 (m, 18H, $(CH_2)_9$),
2.32 (t, 2H, CH_2CO, J=6.0 Hz), 4.09 ppm (t, 2H, CH_2O, J=5.0 Hz).

M.S.m/z=153 (6%, $C_{10}H_{17}O^+$), 151 (12%, $C_{10}H_{15}O^+$),
139 (12%, $C_9H_{15}O^+$), 137 (13%, $C_9H_{13}O^+$), 125 (28%, $C_8H_{13}O^+$),
123 (27%, $C_8H_{11}O^+$), 111 (38%, $C_7H_{11}O^+$), 109 (48%, $C_7H_9O^+$),
97 (70%, $C_6H_9O^+$), 95 (50%, $C_6H_7O^+$), 85 (62%, $C_5H_9O^+$),
83 (71%, $C_5H_7O^+$), 81 (59%, $C_5H_5O^+$), 71 (100%, $C_4H_7O^+$),
69 (87%, $C_4H_5O^+$), 67 (41%, $C_4H_3O^+$), 57 (90%, $C_4H_9^+$),
55 (85%, $C_4H_7^+$), 43 (100%, CH_3CO^+).

Diolide

I.R.($CHCl_3$): ν =2930, 2856, 1742, 1462 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =1.04-1.80 (m, 36H, $(\underline{CH_2})_9OCOCH_2(\underline{CH_2})_9$),
2.29 (t, 2H, 2 x $\underline{CH_2}COOCH_2$, J=6.0 Hz),
4.04 ppm (t, 2H, 2 x $CH_2COO\underline{CH_2}$, J=6.0 Hz).

M.S.m/z=396 (2%, M^+), 378 (18%, M^+-H_2O), 241 (17%, $M^+-OCO(CH_2)_7CH$),
199 (28%, $M^+-OCO(CH_2)_{10}CH$), 181 (22%, 199^+-H_2O),
97 (61%, $C_6H_9O^+$), 83 (58%, $C_5H_7O^+$), 69 (50%, $C_4H_5O^+$).

Attempts Towards the Synthesis of Oxoesters From Thioester 12-Hydroxydodecanoic Acid

12-Hydroxydodecanoic acid (0.504 g, 2.33 mmol) was dissolved in a solution of tetrahydrofuran (15 mL) and thiophenol (0.8 mL, 7.8 mmol) under an argon atmosphere. Chlorotrimethylsilane was added (0.7 mL, 5.52 mmol) and the reaction stirred at reflux overnight.

There was a decreased solvent volume (to ~10 mL). The solvents were removed under reduced pressure, dissolved in ether and filtered through Celite. After removal of the solvents *in vacuo*, 0.816 g of a crude residue was obtained. T.L.C. analysis indicated a multi-component mixture. A quantity of 0.204 g of this residue was submitted to gradient flash chromatography (100 mL each of 9:1, 3:1 and 1:1 hexanes-ethyl acetate, v/v). Three components were isolated consisting of the monomer (87) (0.017 g, 8% yield) the dimer (88) (0.016 g, 9% yield) and a more polar group of compounds (0.016 g). Rinsing the column with methylene chloride yielded a further (0.035 g) of polar, lactonic material. Each of the two less polar compounds was contaminated with some of the more polar compounds. The low yield clearly results from incomplete reaction. ^{1}H-N.M.R. analysis indicated the presence of a large amount of unreacted starting material which was subsequently trapped on the silica column. For the spectral characteristics of the monomer and dimer see 1,12-dodecanolide (*vide supra*).

Phenylacetic acid (1.40 g, 10.3 mmol) was dissolved in a solution of thiophenol (4.6 mL, 44.8 mmol) and anhydrous tetrahydrofuran (250 mL). Chlorotrimethylsilane (5.7 mL, 55.0 mmol) and 2,2,2-trichloroethanol were added and the reaction was stirred at reflux for 48 h.

The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL), extracted with ether (2 x 100 mL) and washed with brine (2 x 50 mL). The combined extracts were dried over anhydrous $MgSO_4$ and after filtration the solvents were removed *in vacuo*. The residue was dissolved in hexanes and filtered through silica gel to give thiophenol and 2,2,2-trichloroethanol. Phenylacetic acid was washed off the silica gel with methanol. No other materials were detected.

Thioesters

Benzoic acid (0.606 g, 4.97 mmol) was dissolved in a solution of tetrahydrofuran (15 mL) and thiophenol (2.0 mL, 19.5 mmol). Chlorotrimethylsilane was added (1.4 mL, 11.0 mmol) and the reaction stirred at reflux for 24h.

The solvents were removed *in vacuo* to give only the starting material.

Benzoic acid (0.612 g, 5.02 mmol) was dissolved in a solution of tetrahydrofuran (35 mL) and benzylthiol (2.0 mL, 17.0 mmol). Chlorotrimethylsilane was added (1.4 mL, 11.0 mmol) and the reaction stirred at reflux for 24h.

The solvents were removed *in vacuo* to give only the starting material.

12-Hydroxydodecanoic acid (1.059 g, 4.903 mmol) was dissolved in a solution of tetrahydrofuran (20 mL) and benzylthiol (0.65 mL, 5.54 mmol) under an argon atmosphere. Chlorotrimethylsilane was added (0.7 mL, 5.52 mmol) and the reaction was refluxed for 24h.

The solvents were removed *in vacuo* and submitted to gradient flash chromatography (100 mL each of 3:1, 1:1, 1:3 hexanes-ethyl acetate, v/v and 100 mL each of ethyl acetate, and methanol). The only isolated products were benzylthiol and 12-hydroxydodecanoic acid.

Sebacic acid (1,10-decanedioic acid, 1.005 g, 4.967 mmol) was dissolved in a solution of anhydrous tetrahydrofuran and benzylthiol (2.0 mL, 17.0 mmol) under an argon atmosphere. Chlorotrimethylsilane (2.8 mL, 22,0 mmol) was added and the reaction stirred overnight at room temperature.

The solvents were removed *in vacuo* to give 1.150 g of a crude residue which by ^{1}H-N.M.R. was determined to be the starting carboxylic acid contaminated with benzyl thiol.

Alternatively, sebacic acid (1.014 g, 5.012 mmol) was dissolved in a solution of anhydrous tetrahydrofuran (25 mL) and thiophenol (2.0 mL, mmol) under an argon atmosphere. Chlorotrimethylsilane (2.8 mL, 22.0

mmol) was added and the reaction stirred overnight at room temperature.

The solvents were removed *in vacuo* to give 1.121 g of a residue which was determined by ^{1}H-N.M.R. and T.L.C. to be the starting carboxylic acid contaminated with thiophenol.

Reaction of Carboxylic Acids with Alcohols

(in the Presence of Silicon Tetrachloride)

Ethyl Phenylacetate (56)

Phenylacetic acid (1.36 g, 10.0 mmol) was dissolved in absolute ethanol (20 mL) under a nitrogen atmosphere. Silicon tetrachloride (0.65 mL, 5.7 mmol) was added and the reaction stirred for 1.5 h at room temperature.

The solvents were removed *in vacuo* and the residue was purified by mesh chromatography (hexanes) to give 1.00 g of the title compound in 61% yield. The spectral characteristics of the compound are;

I.R. (neat): ν =2900, 1733, 1494, 1364, 1248, 1152 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ =1.13 (t, 3H, $OCH_2\underline{CH_3}$, J=7.5 Hz),
3.45 (s, 2H, $\underline{CH_2}C_6H_5$), 4.00 (q, 2H, $O\underline{CH_2}CH_3$, J=7.5 Hz),
7.10 ppm (s, $5H_{arom}$).

M.S.: m/z=164 (54%, M^+), 119 (14%, $M^+-OCH_2CH_3$), 91 (100%, $CH_2C_6H_5^+$).

Phenylacetic acid (0.67 g, 4.93 mmol) was dissolved in a solution of benzylthiol (1.0 mL, 8.5 mmol) and methylene chloride (25 mL) under an argon atmosphere. Silicon tetrachloride (0.6 mL, 5.24 mmol) was added and the reaction was stirred at room temperature overnight.

The solvents were removed *in vacuo* and the residue was extracted with ether (2 x 75 mL). The cloudy solution was washed with a 5% aqueous solution of KOH (3 x 30 mL, generating a flocculent white precipitate), washed with brine and the combined extracts were dried over anhydrous $MgSO_4$. After the removal of solvents under reduced pressure, only benzyl thiol was isolated.

Phosphorous Esters

Phenylphosphonic acid (0.782 g, 4.95 mmol) was dissolved in methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (2.8 mL, 22.0 mmol) was added and the reaction stirred at room temperature.

After 8h, an aliquot of 5 mL was removed and the solvents removed *in vacuo* to give the starting material (^{1}H-N.M.R.). Similar results were obtained with aliquots removed at 12 h, 24 h, and 48 h.

Diphenylphosphate (0.362 g, 1.45 mmol) was dissolved in methanol (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane was added (1.4 mL, 11.0 mmol) and the reaction stirred at room temperature.

After 14 h, the solvents were removed *in vacuo* from a 5 mL aliquot. ^{1}H-N.M.R. indicated only the presence of starting material. Starting material was also identified after 24 h at reflux, and after the addition of more chlorotrimethylsilane (4.2 mL, 33.0 mmol) and a further 24h at reflux.

Diethylphosphate (0.105 g, 0.68 mmol) was dissolved in a mixture of methanol (15 mL) and tetrahydrofuran (25 mL) under a nitrogen atmosphere. Chlorotrimethylsilane (0.25 mL, 2.0 mmol) was added and the reaction stirred overnight.

The dark brown reaction mixture was evaporated to dryness. T.L.C. analysis indicated a very complex reaction mixture. ^{1}H-N.M.R. spectroscopy did not permit the identification of any component in the mixture.

SILYL ENOL ETHER CONDENSATIONS

STARTING NUCEOPHILES AND ELECTROPHILES

Methyl 3-trimethylsiloxybut-2-enoate (105)

Anhydrous $ZnCl_2$ (2.0 g, 14.7 mmol) was suspended in dry triethylamine (105 mL) with vigourous stirring for 1.5 h under a nitrogen atmosphere. The solution was cooled to 0°C and methyl acetoacetate (39.8 g, 0.343 mol) in dry benzene (135 mL) was added. To this solution was added chlorotrimethylsilane (74.5 g, 0.657 mol) over a 5 min period. The

reaction was stirred overnight at 40-50°C.

The brown solution was added to cold anhydrous hexanes (1L) and the precipitated salts filtered off. The filtrate had the hexanes removed *in vacuo*, and the residue distilled (54-55°C/4 torr, lit.[300] 67-68°C/7 torr) to yield 57.2 g of the title compound in 89% yield. The spectral data for the compound are;

I.R.(neat): ν=1720, 1630, 1432, 1383, 1338, 1137, 1034 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=0.22 (s, 9H, $Si(CH_3)_3$),
1.86 (s, 0.63H, $\underline{H_3C}C(OSi(CH_3)_3)=CHCO_2CH_3$ (Z)),
2.23 (s, 2.37H, $\underline{H_2C}C(OSi(CH_3)_3)=CHCO_2CH_3$ (E)),
3.63 (s, 3H, CO_2CH_3), 5.17 ppm (s, 1H, $(H_3C)_3SiOC=\underline{CH}$).

^{29}Si-N.M.R.(decoupled INEPT pulse sequence): δ=20.09 (85%, (E) isomer), 19.93 (15%, (Z) isomer).

1,3-bis-(Trimethylsiloxy)-1-methoxybuta-1,3-diene (100)

To a solution of di-iso-propylamine (1.0 mL, 7.1 mmol) in dry THF (25 mL) under argon, was added *n*-butyllithium (1.5 M solution in hexanes, 5.0 mL, 7.5 mmol) after cooling to 0°C. The reaction mixture was further cooled to -78°C. Methyl 3-trimethylsiloxybut-2-enoate (105) (1.10 g, 5.9 mmol) was added and the solution stirred for 2 min.

The reaction was quenched with trimethylchlorosilane (1.2 mL, 9.5 mmol). The solvent was removed under reduced pressure after a further 10 min and the residue washed and filtered with cold dry hexanes (distilled from sodium). The solvents were removed from the filtrate *in vacuo* to give 1.42 g of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene in 93% yield. The spectral characteristics of the compound are;

I.R.(neat): ν=1651, 1443, 1382, 1252 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=0.15 (s, 9H, $(CH_3)_3Si$), 0.19 (s, 9H, $(CH_3)_3Si$),
3.50 (s, 3H, $COOCH_3$), 3.90 (d, 1H, HC=, J=1.5 Hz),
4.10 (d, 1H, HC=, J=1.5 Hz), 4.42 ppm (s, 1H, HC=).

^{29}Si-N.M.R.($CDCl_3$, decoupled INEPT pulse sequence):
δ =16.16 (9H, $=C(OCH_3)O\underline{Si(CH_3)_3}$),
21.81 ppm (9H, $H_2C=C(CH=COCH_3[OSi(CH_3)_3])O\underline{Si(CH_3)_3}$).

M.S. m/z=260 (9%, M^+), 245 (64%, M^+-CH_3), 229 (15%, M^+-OCH_3), 156 (30%, $M^+-(CH_3)_3SiH$), 147 (51%), 73 (100%, $(CH_3)_3Si^+$).

1,1-Dichloroacetophenone (24)

In 120 mL of glacial acetic acid was placed acetophenone (48.0 g, 400 mmol). The solution was cooled in an ice bath, and with stirring, dry chlorine gas (dried by bubbling through concentrated H_2SO_4) was introduced for 3 h at a rate which maintained the solution temperature below 30°C.

The bright yellow solution was poured onto 1 kg of ice. A yellow oil separated out from the acetic acid solution which was distilled (89-90°C/1.4 torr, lit.[312] 132-4°C) to yield 70.5 g of colourless oil in 93% yield. The spectral data are;

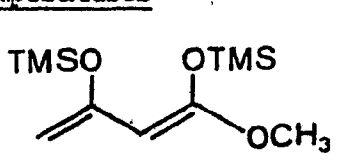
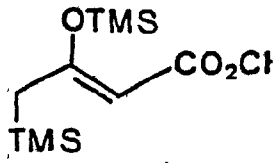
I.R. (neat): ν=1709, 1699, 1682, 1451, 1284, 1223 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=6.77 (s, 1H, $CHCl_2$), 7.4-7.7, 7.9-8.2 ppm (m, $5H_{arom}$).

Thermal Properties of 1,3-*bis*-Trimethylsiloxy-1-methoxy-1,3-butadiene

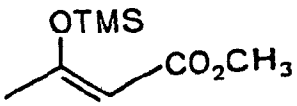
Essentially, the above experimental procedure for 100 was followed. The lithium di-*iso*-propylamide was prepared at 0°C. From that point, the solution was silylated at the temperature to be tested, and the procedure for quenching the reaction and isolating the silylated products was followed as described above. The resulting solutions were analysed by ^{1}H-N.M.R. spectroscopy. The yields in all cases were over 75% based on the ^{1}H-N.M.R. spectra. The following Table gives the results of these experiments.

Table 5.3: Relative Proportion of Silylated Compounds Formed from Methyl 3-Trimethylsiloxycrotonate at Various Temperatures#

Temperature	Conditions	TMSOTMS		
25	No temperature control, compounds rapidly mixed.	x	—	100-x *
25	Temperature controlled using H_2O bath, compounds mixed slowly.**	3	57	21
0	Rapidly mixed.	15	85	—
0	Slowly mixed.	6.5	80	9
-23	CCl_4/CO_2	15	85	—
-42	CH_3CN/CO_2	11	89	—
-78	CH_3COCH_3/CO_2	10	90	—
-78	CH_3COCH_3/CO_2 + TMEDA.	10	90	—
-110	ether/CO_2	13	87	—

The % of the enolic compounds is based on the integration of the vinylic hydrogens. The non-enolic components were evaluated using the integration of the TMS peaks.

* Since TMSOTMS peak is under the C-TMS peak, the relative % is difficult to determine. The major portion (>90%) is the C silylated compound.

** The solution contained 9% of 

Although TMSOTMS is present in all spectra, this compound can be easily removed by pumping at high vacuum. For example, with the second entry at 0°C, after 2 h pumping at 1 torr, the relative % of TMSOTMS dropped from 6.5% to 1.5%.

2.2-Dimethoxyphenylacetaldehyde(109)

Sodium (2.00 g, 87.0 mmol) was reacted with absolute methanol (150 mL) at 0°C under nitrogen atmosphere. α,α -Dichloroacetophenone (24) (7.50 g, 39.7 mmol) was added and the resulting solution stirred for 1 h.

To the cloudy orange suspension was added brine (100 mL) and the methanol removed under reduced pressure. The aqueous residue was extracted with ether (3 x 100 mL) and washed with brine (3 x 50 mL) until no yellow colour was imparted to the aqueous layer. The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was distilled (72-6°C/0.7 torr, lit.[313] 123-30°C/25 torr) to give 5.82 g of a colourless oil in 81% yield.

I.R.(neat): ν =1745, 1451, 1242, 1069 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =3.32 s, 6H, $C(OCH_3)_2$), 7.5-7.7 (m, $5H_{arom}$), 9.38 ppm (s, 1H, CHO).

M.S.:m/z=180 (0.5%, M^+), 151 (28%, M^+-CHO), 149 (4%, M^+-OCH_3), 136 (45%, 151^+-CH_3), 121 (39%, $C_6H_5CO_2^+$), 105 (100%, $C_6H_5CO^+$), 77 (57%, $C_6H_5^+$).

Phenylglyoxal (5)

To 2,2-dimethoxyphenylacetaldehyde (109) (1.90 g, 10.6 mmol) was added acetone (15 mL) and concentrated hydrochloric acid (~0.08 mL). The reaction was stirred for 18 h at room temperature.

The reaction was dissolved in ether (100 mL), washed with a 5% aqueous solution of $NaHCO_3$ (2 x 25 mL), with brine (2 x 20 mL), and the ether extract was dried over anhydrous $MgSO_4$. After filtration, removal of the solvents *in vacuo* led to a brown oil. This was distilled using a Kugelrohr apparatus (80-136°C/23 torr, lit.[314] 95-7°C/25 torr) to give 0.68 g of the glyoxal in 48% yield. Since this yield was judged to be inadequate, an alternate method was chosen.

Seleneous acid (H_2SeO_3, 32.50 g, 252 mmol) was dissolved in dioxane (200 mL). A mechanical stirrer was required, and the temperature was maintained at 50°C until dissolution was complete. Acetophenone (107) (30.0 g, 200 mmol) was added. The solution underwent a series of

colour changes: starting from colourless, proceeding to yellow, then green, and finally to black. After refluxing for 5.5 h, the solution was decanted from precipitated selenium metal. The dioxane-water was distilled from the solution leaving an orange gum. This residue was filtered twice through a small sinter to remove more selenium metal and distilled (52°C, 0.45 torr, lit.[314] 95-7°C/25 torr) to yield 28.24 g of the title compound in 84% yield. The spectral data for the compound are;

I.R.(neat): ν=1697, 1598, 1582, 1459, 1278, 1262, 1120, 963 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ=7.4-8.4 (m, $5H_{arom}$), 9.67 ppm (s, 1H, CHO).

p-Methylacetophenone (108)

Toluene (30.30 g, 0.33 mol) was dissolved in carbon disulfide (150 mL) under a nitrogen atomosphere. Aluminum trichloride (97.5 g, 0.73 mol) was added and the solutions was heated to reflux. Acetic anhydride (28.72 g, 0.28 mol) was added over 40 min and the reaction was left to reflux for 1 h.

The carbon disulfide was distilled from the solution and the warm residue was added to concentrated hydrochloric acid (50 mL) and ice (500 g). The solution was extracted with ether (2 x 500 mL), washed with water (200 mL), 15% aqueous KOH (50 mL), water (100 mL) and brine (100 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and, after filtration, the ether was removed *in vacuo*. The residue was distilled (97-99°C/14 torr, lit.[346] 226°C/760 torr) to give 31.70 g of *p*-methylacetophenone in 73% yield. The spectral characteristics of this compound are;

I.R.(neat): ν=1688, 1604, 1583, 1357, 1280, 1182 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ=2.42 (s, 3H, $\underline{CH_3}C_6H_5$), 2.58 (s, 3H, CH_3CO),
7.23, 7.87 ppm (ABq, $4H_{arom}$, J_{om}=10 Hz).

α,α-Dichloro-*p*-methylacetophenone (111)

p-Methylacetophenone (108) (27.0 g, 0.20 mol) was dissolved in glacial acetic acid (150 mL). Dry chlorine gas (bubbled through

concentrated H_2SO_4) was introduced to the solution at a rate which allowed the temperature to remain below 20°C. The solution was cooled by an ice-water bath. Care was taken to keep the solution from excessively low temperatures to prevent precipitation of either the starting material or product. After 1 h, the solution was bright yellow and the flow of chlorine was stopped.

The solution was poured into ice-water (500 g) and allowed to warm to room temperature. The colour was discharged and a waxy-flaky white precipitate (m.p. 54-5°C, lit.[349] 54°C) was collected by filtration, and after air drying, gave 36.8 g of the title compound in 91% yield. The spectral characteristics of the compound are;

I.R.(CCl_4): ν=1711, 1691, 1608, 1585, 1276, 1217, 1179, 843 cm^{-1}.
^{1}H-N.M.R.($CDCl_3$): δ =2.43 (s, 3H, $C_6H_4\underline{CH_3}$), 6.50 (s, 1H, $CHCl_2$),
7.10,7.81 ppm (ABq, $4H_{arom}$, J=7.5 Hz).
M.S.:m/z=206, 204, 202 (0.4%, 1.1%, 1.5%, M^+),
170, 168 (0.5%, 1.5%, M^+-Cl), 119 (100%, M^+-$CHCl_2$),
103 (8%, M^+-$OCHCl_2$), 91 (47%, $CH_3C_6H_4^+$), 77 (12%, $C_6H_5^+$).

2,2-Dimethoxy-2(4'-methylphenyl)acetaldehyde (110)

α,α -Dichloro-p-methylacetophenone (111) (5.0 g, 24.6 mmol) was added to a solution of sodium (1.3 g, 56.5 mmol) in absolute methanol (200 mL). The solution was stirred overnight under an argon atmosphere.

The orange reaction mixture was diluted with water (150 mL) and extracted with ether (5 x 100 mL) until the ether extracts were colourless. The combined ether extracts were washed with brine (2 x 25 mL), dried over anhydrous $MgSO_4$, and the ether removed *in vacuo*. The orange residue was submitted to H.P.L.C. (19:1 hexanes-ethyl acetate, v/v) to give 3.40 g of the title compound in 71% yield. The spectral data are;

I.R.(CCl_4): ν=2942, 1742, 1612, 1509, 1444, 1406, 1362, 1242,
1208, 1183, 1113, 1060 cm^{-1}.
^{1}H-N.M.R.(CCl_4): δ=2.31 (s, 3H, $\underline{CH_3}C_6H_5$), 3.23 (s, 6H, $C(OCH_3)_2$),
7.14, 7.35 (ABq, $4H_{arom}$, J_{om}=9.0 Hz),

8.9 ppm (s, 1H, CHO).

M.S.:m/z=165 (100%, M^+-CHO), 163 (17%, M^+-OCH_3), 150 (24%, 165^+-CH_3), 135 (29%, M^+-CO_2CH_3), 119 (67%, $CH_3C_6H_4CO^+$), 105 (27%, $C_6H_5CO^+$), 91 (49%, $CH_3C_6H_4^+$).

p-Methylphenylglyoxal (7)

Selenious acid (H_2SeO_3, 19.35 g, 0.15 mol) was heated until dissolution at 55°C in dioxane (90 mL). *p*-Methylacetophenone (108) (19.8 g, 0.15 mol) was added and the solution refluxed for 4 h. The solution was decanted from the precipitated selenium and the dioxane distilled off. After filtration through Celite, the residue was distilled (81-82°C/2.75 torr) to yield 14.8 g of *p*-methylphenylglyoxal in 67% yield. The spectral data for the compound are;

I.R.(neat): ν=1691, 1594, 1582, 1457, cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=2.48 (s, 3H, $CH_3C_6H_5$), 7.37, 8.17 (ABq, $4H_{arom}$, J_{om}=9.0 Hz), 9.69 ppm (s, 1H, CHO).

CONDENSATIONS

Methyl 5-hydroxy-3-oxo-5-phenylpentanoate (112)

1,3-*bis*-Trimethylsiloxy-1-methoxy-1,3-butadiene (0.2590 g, 0.996 mmol) was dissolved in $CDCl_3$ (2 mL) under an argon atmosphere at -78°C. Benzaldehyde (0.101 g, 0.95 mmol) and then $TiCl_4$ (2.0 M solution in $CDCl_3$, 0.5 mL, 1.0 mmol) were added and after 1 h, the solution was allowed to warm to 0°C over 1 h.

The reaction was poured into a 5% aqueous $NaHCO_3$ solution (25 mL), extracted with ether (100 mL), washed with brine (2 x 10 mL) and the ether extract was dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*, 0.152 g of the title compound was isolated in 72% yield. The spectral characteristics for this compound are;

I.R.(neat): ν=3441, 1744, 1722, 1451, 1437, 1325 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=2.7-3.3 (m, 2H, $CH_2COCH_2COOCH_3$),

3.32 (s, 2H, $\underline{CH_2}COOCH_3$), 3.58 (s, 4H, OH + $COOCH_3$),
5.24 (dd, 1H, $C_6H_5\underline{CH}OH$, J_{bc}=6.3 Hz, J_{ac}=8.0 Hz),
7.19 ppm (s, $5H_{arom}$).

Methyl 6,6-dichloro-5-hydroxy-3-oxo-5-phenylhexanoate (115)

α,α -Dichloroacetophenone (24) (1.32 g, 7.0 mmol) was dissolved in CH_2Cl_2 (30 mL) under an argon atmosphere. After cooling to -78°C, $TiCl_4$ (1.0 M solution in CH_2Cl_2, 8.0 mL, 8.0 mmol) was added. 1,3-bis-Trimethylsiloxy-1-methoxy-1,3-butadiene (2.00 g, 7.7 mmol) was added over 10 min.

After 30 min, the solution was quenched with a 5% aqueous $NaHCO_3$ solution (100 mL), extracted with ether (2 x 50 mL), and washed with brine (3 x 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and the solvents were removed under reduced pressure. A quantity of 0.153 g of the crude residue (total 2.19 g) was submitted to flash chromatography (4:1 hexanes-ethyl acetate, v/v) to give 0.013 g of the starting acetophenone and 0.107 g of the crystalline title compound (m.p. 73-74.5°C) in 71% isolated yield. Based on the recovered starting material, the yield is 85%.

When this reaction was repeated using two equivalents of $TiCl_4$ under otherwise identical condition, the same compound was formed in 74 % yield based on ^{1}H-N.M.R. analysis. The spectral data for this compound are;

I.R. ($CHCl_3$): ν =3483, 1744, 1717, 1642 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ =3.38, 3.44 (ABq, 1H, $CO\underline{CH^a}\underline{H^b}COOCH_3$, J_{ab}=8.1 Hz),
3.43, 3.68 (ABq, 1H, $CO\underline{CH^d}\underline{H^c}COCH^aH^b$, J_{cd}=17.0 Hz),
3.69 (s, 3H, $COOCH_3$), 4.50 (s, 1H, OH), 5.92 (s, 1H, $CHCl_2$),
7.3-7.3, 7.5-7.6 ppm (m, $5H_{arom}$).
M.S.:m/z=271, 269 (37%, 21%, M^+-Cl), 253, 251 (14%, 9%, 269^+-H_2O),
189 (53%, $C_6H_5C(OH)CHCl_2^+$), 117 (31%, $CH_2COCH_2COOCH_3^+$),
105 (31, $C_6H_5CO^+$).

$C_{13}H_{14}Cl_2O_4$	calc	C 51.17	H 4.62	Cl 23.24	
(305.2)	found	51.17	4.78	23.38	

Methyl 6,6-dichloro-5-hydroxy-5-(4-methylphenyl)-3-oxo-hexanoate (116)

α , α-Dichloro- *p*-methylacetophenone (111) (0.274 g, 1.35 mmol) was dissolved in a solution of $TiCl_4$ (1.5 M solution in CH_2Cl_2, 1.0 mL, 1.5 mmol) in CH_2Cl_2 (25 mL) at -78°C under an argon stmosphere. A yellow precipitate formed. 1,3- bis -Trimethylsiloxy-1-methoxy-1,3-butadiene (0.340 g, 1.31 mmol) was added and the reaction stirred for 2 h at -78°C and 30 min at 0°C.

The reaction was quenched with a 5% aqueous $NaHCO_3$ solution (3 mL), $NaHCO_3$ (~5 g) and $MgSO_4$ (~2 g). After filtration, 0.409 g of the product was isolated. When this residue was submitted to mesh chromatography (8:1 hexanes-ethyl acetate, v/v), none of the desired product was isolated, only starting materials were recovered. Therefore, a quantity of 0.153 g of the residue was submitted to flash chromatography (16.5:2.5:1 hexanes-ethyl acetate-methanol, v/v/v) to give 0.068 g of the title compound in 44% yield and 0.054 g of the starting acetophenone. Accounting for recovered starting material, the yield was 88%. The spectral data for the compound are;

I.R. (CCl_4): ν=3490, 1742, 1710, 1238 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ=2.33 (s, 3H, $\underline{CH_3}C_6H_4$), 3.33 (s, 2H, $\underline{CH_2}COOCH_3$), 3.4-3.6 (m, 2H, (HO)HC$\underline{CH_2}$CO), 3.68 (s, 3H, $COOCH_3$), 4.3 (bs, 1H, OH), 5.68 (s, 1H, $CHCl_2$), 7.08, 7.36 ppm (ABq, $4H_{arom}$, J_{om}=9.0 Hz).

M.S. m/z=235 (20%, M^+-CHCl_2), 203 (28%, 235^+-CH_3OH), 119 (100%, $CH_3C_6H_5CO^+$), 91 (54%, $CH_3C_6H_4^+$).

Methyl 6,6-dimethoxy-5-hydroxy-3-oxo-5-phenylhexanoate (113)

α,α -Dimethoxyacetophenone (6) (0.390 g, 2.11 mmol) was dissolved in methylene chloride (25 mL) at -78°C under a nitrogen atmosphere. $TiCl_4$ (1.0 M solution in CH_2Cl_2, 1.5 mL, 1.5 mmol) and then 1,3- bis-trimethylsiloxy-1-methoxy-1,3-butadiene (0.6112 g, 2.35 mmol) were added (the solution turned a deep yellow colour).

After 20 min, the reaction was quenched with a 5% aqueous solution of $NaHCO_3$, extracted with ether (2 x 100 mL), washed with brine (2 x 25 mL) and the combined ether extracts were dried over anhydrous $MgSO_4$. The

solvents were removed *in vacuo*, after filtration, to give 0.577 g of a crude residue. A quantity of 0.1870 g of this residue was submitted to flash chromatography (1:2 ethyl acetate-hexanes, v/v) to give 0.0957 g of the title compound in 47% yield, and 0.059 g of recovered starting material. In consideration of the recovered starting material, the yield was 56% (the yield based on the ^{1}H-N.M.R. of the crude material was 74%). When the same reaction was undertaken using two equivalents of $TiCl_4$ under otherwise identical conditions, only the monoadduct and starting material were recovered in a 2:1 mixture, based on ^{1}H-N.M.R. analysis. The spectral data for the compound are;

I.R.(neat): ν =1745, 1705, 1443, 1432, 1072 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =3.16, 3.30 (ABq, 2H, $\underline{CH}^a\underline{H}^bCOOCH_3$, J_{ab}=8.0 Hz),
3.26 (s, 3H, $HC(O\underline{CH_3}^e)OCH_3{}^f$),
3.44, 3.54 (ABq, 2H, $\underline{CH}^c\underline{H}^dCOCH^aH^b$, J_{cd}=8.0 Hz),
3.47 (s, 3H, $HC(O\underline{CH_3}^f)OCH_3{}^e$), 3.70 (s, 3H, $COOCH_3$), 4.02 (s, 1H, OH),
4.16 (s, 1H, $\underline{CH}(OCH_3)_2$), 7.3-7.4, 7.5-7.6 ppm (m, $5H_{arom}$).

Methyl 6,6-dimethoxy-5-hydroxy-3-oxo-6-phenylhexanoate (114)

1,3- bis-Trimethylsiloxy-1-methoxy-1,3-butadiene (0.751 g, 2.88 mmol) and 2,2-dimethoxyphenylacetaldehyde (109) (0.532 g, 2.96 mmol) were dissolved in CH_2Cl_2 (10 mL) at -78°C under an argon atmosphere. $TiCl_4$ (1.0 M solution in CH_2Cl_2, 2.9 mL, 2.9 mmol) was added and the reaction was stirred for 3 h.

The reaction was quenched with a 5% aqueous solution of $NaHCO_3$ (100 mL), extracted with ether (2 x 100 mL), washed with brine (2 x 25 mL) and the combined ether extracts were dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to give 0.94 g of a crude residue. A quantity of 0.205 g of the residue was submitted to flash chromatography (9:1 hexanes-ethyl acetate, v/v) to give 0.046 g of the slightly impure title compound in ~24% yield. The remaining material was an intractable tar. The spectral characteristics of the compounds are;

I.R.(neat): ν=3460, 1742, 1712, 1433 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=3.1-3.6 (m, 4H, $HC(OH)\underline{CH_2}CO\underline{CH_2}COOCH_3$),

3.47 (s, 6H, $C(OCH_3)_2$), 3.75 (s, 3H, $COOCH_3$), 3.80 (s, 1H, OH), 5.4-5.5 (m, 1H, HC(OH)), 7.2-7.6 ppm (m, $5H_{arom}$).

Methyl 3,6-dioxo-5-hydroxy-6-phenylhexanoate (118)

1,3-*bis*-Trimethylsiloxy-1-methoxy-1,3-butadiene (1.50 g, 5.78 mmol) and 2,2-dimethoxyphenylacetaldehyde (6)(1.04 g, 5.78 mmol) were dissolved in CH_2Cl_2 (10 mL) at -78°C under an argon atmosphere. $TiCl_4$ (1.0 M solution in CH_2Cl_2, 12.0 mL, 12.0 mmol) was added and the reaction was stirred for 3 h.

The reaction was quenched with a 5% aqueous solution of $NaHCO_3$ (100 mL), extracted with ether (2 x 100 mL), washed with brine (2 x 25 mL) and the combined ether extracts were dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to give 1.18 g of a crude residue. A quantity of 0.107 g of this residue was submitted to flash chromatography (9:1 hexanes-ethyl acetate, v/v) to give 0.80 g of slightly impure product in 61% yield. The spectral data are as follows;

I.R.(neat): ν =3450, 1739, 1719, 1690, 1599, 1582, 1448, 1436 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=2.9-3.3 (m, 2H, $CH^aH^bCOCH_2COOCH_3$), 3.02 (s, 1H, OH), 3.55 (s, 2H, CH_2COOCH_3), 3.72 (s, 3H, $COOCH_3$), 5.46 (dd, 1H, $CH^c(OH)$, J_{ac}=4.2 Hz, J_{bc}=7.5 Hz), 7.3-7.6, 7.8-8.1 ppm (m, $5H_{arom}$).

2-Carbomethoxy-4-hydroxy-3-phenylcyclopenten-2-one (119)

2,2-Dimethoxyphenylacetaldehyde (109)(0.264 g, 1.46 mmol) was dissolved in CH_2Cl_2 at -78°C under an argon atmosphere. 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene (0.400 g, 1.53 mmol) and then $TiCl_4$ (1.0 M solution in CH_2Cl_2, 5.0 mL, 5.0 mmol) were added. The reaction was allowed to stir for 1 h at -78°C and then warmed to 0°C over 15 min.

The reaction was quenched with a 5% aqueous solution of $NaHCO_3$ (75 mL), extracted with ether (2 x 75 mL), and washed with brine (2 x 25 mL). The combined etner extracts were dried over anhydrous $MgSO_4$ and the solvents were removed *in vacuo* to give 0.340 g of a crude residue. A quantity of 0.087 g of the residue was submitted to flash chromatography

(16:2:1 hexanes-ethyl acetate-methanol, v/v/v) to give 0.0405 g of the title compound in 49% yield. The yield based on the crude ^{1}H-N.M.R. was ~80%. The spectral data for the compound are as follows;

I.R.(neat): ν=3442, 1736, 1702, 1618, 1433, 1343, 1232 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=2.59 (dd, 1H, OCC$\underline{H}^a$H^{b}CH^{c}OH, J_{ac}=2.3 Hz, J_{ab}=18.6 Hz),
3.04 (dd, 1H, OCC$\underline{H}^b$H^{a}CH^{c}OH, J_{ba}=18.6 Hz, J_{bc}=5.9 Hz),
3.64 (s, 1H, OH), 3.79 (s, 3H, $COOCH_3$),
5.45 (dd, 1H, OCCH^{a}H^{b}C$\underline{H}^c$OH, J_{cb}=5.9 Hz, J_{ca}=2.3 Hz),
7.7-7.8 ppm (m, 5H$_{arom}$).

M.S.:m/z=232 (42%, M^+), 216 (22%), 201 (31%, M^+-OCH_3),
173 (20%, $M^+-COOCH_3$), 137 (76%, $M^+-H_2O-C_6H_5$), 121 (84%),
105 (82%, $C_6H_5CO^+$), 91 (72%, $C_7H_7^+$), 77 (69%, $C_6H_5^+$).

2-Carbomethoxy-4-hydroxy-3-phenylcyclopenten-2-one (119)

Phenyl glyoxal (5)(0.40 g, 2.98 mmol) was added to a solution of 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene (100)(0.75 g, 2.88 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere. After cooling to -78°C, $TiCl_4$ (1.0 M solution in CH_2Cl_2, 10.0 mL, 10.0 mmol) was added. The reaction was stirred for 4.5 h and then allowed to warm to 0°C over 30 min.

The reaction was quenched with an aqueous 5% solution of $NaHCO_3$ (150 mL), extracted with ether (2 x 100 mL), washed with brine (4 x 25 mL) and the combined ether extracts were dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to give 0.621 g of a crude residue. The yield based on the ^{1}H-N.M.R. spectrum was 78%. A quantity of 0.173 g of the residue was submitted to flash chromatography (20:2:1.5 hexanes-ethyl acetate-methanol, v/v/v) to give 0.080 g of the title compound in 43% yield. See the immediately preceeding experimental for spectral data.

2-Carbomethoxy-4-hydroxy-3(4'-methylphenyl)-cyclopenten-2-one (120)

2,2-Dimethoxy-2(4'-methylphenyl)-acetaldehyde (110)(0.2930 g, 1.51 mmol) and 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene (0.3830 g, 1.47 mmol) in CH_2Cl_2 were cooled to -78°C under an argon atmosphere. $TiCl_4$ (1.0 M solution in CH_2Cl_2, 5.0 mL, 5.0 mmol) was added and the reaction was stirred for 1 h. The solution was allowed to warm to 0°C over 15 min.

The reaction was quenched with a 5% aqueous $NaHCO_3$ solution (75 mL), extracted with ether (2 x 50 mL), washed with brine (2 x 10 mL) and the combined ether extracts were dried over anhydrous $MgSO_4$. After removal of the solvents *in vacuo*, 0.4046 g of a crude residue was isolated. Based on ^{1}H-N.M.R. analysis, the crude material consisted of about 75% of the desired cyclopentenone. A quantity of 0.1009 g was submitted to gradient flash chromatography (100 mL each of 3:1, 2:1 and 1:1 hexanes-ethyl acetate, v/v) to give 0.0344 g of the title compound in 38% yield. The spectral data for this compound are;

I.R.(nujol): ν =3484, 1743, 1682, 1604, 1584, 1451, 1350 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =2.41 (s, 3H, $\underline{CH_3}C_6H_4$),

2.47 (dd, 1H, $CO\underline{CH}^aH^bCH^cOH$, J_{ab}=18 Hz, J_{ac}=3.0 Hz),

2.98 (dd, 1H, $CO\underline{CH}^bH^aCH^cOH$, J_{ab}=18.0 Hz, J_{bc}=5.5 Hz),

3.20 (s, 1H, OH), 3.79 (s, 3H, $COOCH_3$),

5.41 (dd, 1H, $COCH^bH^a\underline{CH}^cOH$, J_{ac}=3.0 Hz, J_{bc}=5.5 Hz),

7.28, 7.51 ppm (ABq, $4H_{arom}$, J_{om}=8.5 Hz).

M.S.:m/z=246 (12%, M^+), 214 (16%, M^+-CH_3OH), 182 (95%), 149 (82%),

127 (45%, $M^+-CH_3C_6H_4CO$), 119 (95%, $CH_3C_6H_4CO^+$), 91 (58%, $CH_3C_6H_4^+$).

$C_{14}H_{14}O_4$	calc.	C 68.28	H 5.73
(246.3)	found	68.14	5.87

Attempted *In-situ* Deacetalization

α,α-Dimethoxyacetophenone (109) (0.370 g, 2.06 mmol) and 1,3-bis-trimethylsiloxy-1-methoxy-1,3-butadiene (0.520 g, 2.01 mmol) were mixed in CH_2Cl_2 (10 mL) at -78°C under an argon atmosphere. $TiCl_4$ (1.0 M solution in CH_2Cl_2, 3.2 mL, 3.2 mmol) was added and the reaction stirred for 30 min. T.L.C. analysis indicated mainly the presence of the monoalkylated material. Iodotrimethylsilane (0.44 mL, 3.08 mmol) was added; the solution became purple black. After 15 min, $TiCl_4$ (1.0 M solution, 6.6 mL, 6.6 mmol) was added and the reaction stirred for 30 min at -78°C and 15 min at 0°C.

The reaction was quenched with a 5% aqueous $NaHCO_3$ solution, extracted with ether (2 x 50 mL), washed with a 5% aqueous $Na_2S_2O_3$ solution (2 x 25 mL), washed with brine (2 x 20 mL) and the combined ether

extracts were dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo*. T.L.C. and ^{1}H-N.M.R. analyses of the crude residue indicated the material was a complex mixture of products. Hence, this does not appear to provide a useful approach to the synthesis of 5-membered rings.

ALTERNATE ELECTROPHILES

α-Bromoacetophenone (123)

To a solution of anhydrous ether (80 mL) and dioxane (1.7 mL, 20.0 mmol) was added acetophenone (107)(24.0 g, 0.20 mol). Bromine (0.5 mL, 9.8 mmol) was added and the reaction stirred for 20 min until the red colour had completely dissipated. The solution was cooled to approximately 0°C with an ice-salt bath and bromine (10.0 mL, 195.0 mmol) was dripped in over 1.3 h.

The reaction was quenched with a saturated aqueous sodium carbonate solution (2x100 mL). The ether layer was dried over anhydrous $MgSO_4$, filtered, and the ether removed *in vacuo*, to give 25.9 g of the title compound contaminated with acetophenone (15% by ^{1}H-N.M.R.) and giving a total estimated yield of 55%. A small quantity was recrytallized from petroleum ether (m.p. 48.5-49°C, lit.[346] 50-51°C). The spectral data are;

I.R. (CCl_4): ν =1687, 1596, 1447, 1276 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ=4.33 (s, 2H, CH_2Br),
7.0-7.5, 7.7-8.1 ppm (m, $5H_{arom}$).
M.S.:m/z=200, 198 (2.3%, 2.1%, M^+), 105 (100%, $C_6H_5CO^+$),
77 (88%, $C_6H_5^+$).
G.L.C.:6' 5% OV-101 on CHROMOSORB 750, 150°C:

$C_6H_5COCH_3$	RT=0.43 min.
$C_6H_5COCH_2Br$	RT=3.23 min.

α-Phenylthioacetophenone (124)

Crude α-bromoacetophenone (123)(10.0 g, 42.7 mmol (calc.)) contaminated with acetophenone, was suspended in hexanes (400 mL, the use of methylene chloride as the solvent led to none of the desired product). The solution was cooled to 0°C under a nitrogen atmosphere and then,

thiophenol (5.5 mL, 53.6 mmol) and triethylamine (7.0 mL, 50.2 mmol) were added sequentially. There was immediate formation of a flocculent white precipitate.

After 1 h, the reaction mixture was filtered through Celite, and the solvents removed under reduced pressure* to give a crystalline material smelling strongly of thiophenol. This residue was recrystallized from hexanes to give two crops of crystals, 8.1 g and 2.6 g (total. 10.9 g) contaminated with ~10% thiophenol to give the product in essentially quantitative yield. The melting point of a further recrystallized sample was 53°C (petroleum ether, lit.[347] 51-2°C).

I.R. (CCl_4) : ν=1684, 1600, 1581, 1481, 1449, 1440, 1275 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$) : δ=4.23 (s, 2H, $\underline{CH_2}SC_6H_5$),
7.0-7.6, 7.8-8.0 ppm (m, $10H_{arom}$).
M.S. m/z=228 (34%, M^+), 123 (21%, $M^+-C_6H_5S$), 110 (27%, $C_6H_5SH^+$),
109 (22%, C_6H_5S), 105 (100%, $C_6H_5CO^+$), 77 (33%, $C_6H_5^+$).

α-Chloro-α-phenylthioacetophenone (125)

To a solution of crude α-phenylthioacetophenone (124) (5.24 g, 21.9 mmol (calc.)) in dry methylene chloride under a nitrogen atmosphere at 0°C was dripped in sulfuryl chloride (1.8 mL, 21.8 mmol) over 3 min. The solution turned a bright yellow colour.

The solution was allowed to warm up to room temperature (1.5 h) and was then quenched with a saturated aqueous Na_2CO_3 solution (100 mL). The yellow colour disappeared. The solution was extracted with ether (3 x 100 mL) and washed with brine (2 x 50 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo* to give 5.8 g of a light yellow oil. This essentially pure product (as judged by ^{1}H-N.M.R. and T.L.C.) was used without further purification in the following reactions. The yield was essentially quantitative. The spectral data for the compound are;

I.R. (neat) : ν=1688, 1595, 1589, 1458, 1451, 1276, 1205 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$) : δ=6.35 (s, 1H, $\underline{CH}SC_6H_5$),
7.2-7.6, 7.9-8.2 ppm (m, $10H_{arom}$).

M.S.:m/z=262 (2%, M^+), 228 (24%, M^+-H_2S), 186 (22%, $M^+-C_6H_4^+$), 185 (11%, $M^+-C_6H_5^+$), 184 (11%, $M^+-C_6H_5$), 110 (31%, $C_6H_5SH^+$), 109 (22%, $C_6H_5S^+$), 105 (100%, $C_6H_5CO^+$), 77 (49%, $C_6H_5^+$).

α-Methoxy-α-phenylthioacetophenone (126)

α-Chloro-α-phenylthioacetophenone (125) (1.00 g, 3.8 mmol) was dissolved in absolute methanol (60 mL) under a nitrogen atmosphere and the reaction stirred overnight at room temperature.

A 10% aqueous Na_2CO_3 solution (30 mL) was added and the methanol removed *in vacuo*. The residue was extracted with methylene chloride (100 mL), washed with brine (40 mL) and the organic phase dried over $MgSO_4$. The methylene chloride was removed under reduced pressure to give 1.0 g of a bright yellow oil smelling strongly of benzene thiol and showing two spots on T.L.C.. The residue was crystallized from hexanes and the crystals were filtered and washed with cold hexanes to give 0.71 g of a crystalline material in 72% yield.

Alternatively, α-chloro-α-phenylthioacetophenone (125) was dissolved in absolute methanol (100 mL) which contained Amberlyst A21 resin (0.81g, 3.89 meq) under an argon atmosphere. The reaction was stirred overnight at room temperature.

The solution was filtered through Celite and the solvent was removed *in vacuo* to give 0.96 g of an mixed oil/crystalline material. This residue was recrystallized from hexanes-ethyl acetate to give 0.78 g of pure crystalline (m.p. 56-7°C) and 0.18 g of an oil containing 40%, by ^{1}H-N.M.R., of the desired product. The total yield was 87% although the isolated yield was 80%. The spectral data are;

I.R.(CCl_4): ν =1684, 1597, 1579, 1476, 1445, 1437, 1272, 1185, 1099 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ =3.63 (s, 3H, OCH_3), 5.80 (s, 1H, $\underline{CH}SC_6H_5$), 7.1-7.7, 7.8-8.1 ppm (m, $10H_{arom}$).

M.S.:m/z=258 (2%, M^+), 153 (100%, $M^+-C_6H_5CO$), 121 (29%, 153^+-CH_3OH), 110 ($C_6H_5SH^+$), 109 (27%, $C_6H_5S^+$), 105 (41%, $C_6H_5CO^+$), 77 (33%, $C_6H_5^+$).

1-Methoxy-1-phenylthio-1-phenylacetaldehyde (127)

α -Chloro- α-phenylthioacetophenone (125) (1.0 g, 3.8 mmol) was dissolved in an anhydrous solution of sodium (0.090 g, 3.93 mmol) in absolute methanol (25 mL) at 0°C under a nitrogen atmosphere.

After 1 h, the reaction was quenched with water (15 mL). The solution was extracted with ether (3 x 150 mL) and washed with brine (2 x 30 mL). The combined ether extracts were dried over anhydrous $MgSO_4$ and the ether removed under reduced pressure to give 0.90 g of a crude residue. This was submitted to preparative H.P.L.C. (19:1 hexanes-ethyl acetate, v/v) to give after evaporation, 0.75 g of pure title compound in 77% yield. The spectral characteristics of the compound are;

^{1}H-N.M.R.($CDCl_3$): δ=3.42 (s, 3H, OCH_3), 7.0-7.6 (m, $10H_{arom}$), 9.2 ppm (s, 1H, CHO).

M.S.m/z=258 (1%, M^+), 229 (21%, M^+-CHO), 186 (52%, $C_6H_5SC_6H_5^+$), 149 (48%, $M^+-C_6H_5S$), 121 (100%, $M^+-C_6H_5S-CO$), 110 (68%, $C_6H_5SH^+$), 109 (46%, $C_6H_5S^+$), 105 (41%, $C_6H_5CO^+$), 91 (51%, $C_6H_5CH_2^+$), 77 (66%, $C_6H_5^+$).

α-Bromophenylacetaldehyde

To a solution of phenylacetaldehyde (24.0 g, 200 mmol), in dioxane (0.3 mL, 3.5 mmol) and anhydrous diethyl ether (80 mL), was added bromine (0.2 mL, 3.9 mmol). The reaction was stirred at room temperature until the colour was discharged (10 min). The reaction was cooled with an ice-salt bath to approximately -5°C. Bromine (3.8 mL, 74.2 mmol) was added over 1.5 h. At the completion of this addition, the red-orange colour was not discharged even though an insufficient amount of bromine had been added to allow the complete conversion to the desired brominated material. The solution was warmed to 25°C, but the colour remained. G.L.C. analysis showed three major components; starting material 77%, and two unknowns with a longer retention times, 4% and 17%.

The solution was washed with an aqueous saturated solution of sodium bicarbonate (3x100 mL). The ether extracts was dried over anhydrous $MgSO_4$, and the ether removed *in vacuo*. The residue was distilled to give a large quantity of an intractable black tar and 0.14 g of a mixed

product containing mostly starting material . The ^{1}H-N.M.R. gave no useful information as to the contents of the distillate.

This method was abandoned in favour of the synthesis of the regioisomeric α-bromoacetophenone.

G.L.C.:6' OV-101 on CHROMOSORB 750, 150°C;

Crude mixture before distillation,

$C_6H_5CH_2CHO$	RT=0.87 min,	77%.
unknown	RT=1.35 min,	4%.
unknown	RT=2.02 min,	17%.

CONDENSATIONS

Methyl 5-hydroxy-6-methoxy-3-oxo-5-phenyl-6-phenylthiohexanoate (128)

α-Methoxy-α-phenylthioacetophenone (126) (0.133 g, 0.52 mmol) was dissolved in CH_2Cl_2 (20 mL) at -78°C under an argon atmosphere. $TiCl_4$ (1.0 M solution in CH_2Cl_2, 0.45 mL, 0.45 mmol) and 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene (0.107 g, 0.41 mmol) were added and the reaction stirred. More $TiCl_4$ was added at 20 and 65 min (0.4 mL each time, 0.4 mmol).

After a further 1.5 h, the reaction mixture (10 of 21 mL) was quenched with a saturated aqueous $NaHCO_3$ solution (0.5 mL), $NaHCO_3$ (0.5 g) and $MgSO_4$ (0.5 g). The solution was filtered through Celite, which was then rinsed with ethyl acetate. The solvents were removed *in vacuo* to give 0.172 g of a crude residue. A quantity of 0.104 of this residue was submitted to gradient flash chromatography (300 mL of 19:1 and 100 mL of 1:1 hexanes-ethyl acetate, v/v) to give 0.033 g of the monoalkylated product in 35% yield and 0.032 g of recovered starting material. The spectral data for the monoalkylated title compound are;

I.R.(CCl_4): ν=3482, 1745, 1708, 1445, 1434, 1236 cm^{-1}.

^{1}H-N.M.R.(CCl_4): δ=2.9-3.3 (m, 4H, $\underline{CH_2}CO\underline{CH_2}COOCH_3$), 3.29 (s, 3H, $HCO\underline{CH_3}$), 3.61 (s, 3H, $COOCH_3$), 4.08, (s, 1H, OH), 4.61 (s, 1H, $\underline{H}COCH_3$), 6.9-7.5 ppm (m, $10H_{arom}$).

Modification of the Titanium Catalyst

Dicyclopentadienyltitanium Dichloride

$(C_5H_5)_2TiCl_2$ (0.250 g, 1.0 mmol) was suspended in tetrahydrofuran (40 mL) under an argon atmosphere. Benzaldehyde (0.114 g, 1.08 mmol) and methyl 3-trimethylsiloxybut-2-enoate (0.329 g, 1.75 mmol) were added and the reaction was stirred for 3 h. ^{1}H-N.M.R. analysis indicated only the presence of starting materials. Therefore, the reaction was refluxed overnight. Again, the ^{1}H-N.M.R. spectrum indicated only starting materials.

The tetrahydrofuran was removed *in vacuo* and toluene was added. The reaction was refluxed for 2 days. As no products were detected by ^{1}H-N.M.R. analysis, the catalyst was judged insufficiently activating to be of any use for the desired condensation reactions.

4-Carbomethoxy-5-methyl-2-phenyl-3-phenylthiofuran, 4-Carbomethoxy-5-methyl-3-phenyl-2-phenylthiofuran, and methyl 2-(1-benzoyl-1-phenylthiomethyl)-acetoacetate

Zinc bromide (0.032 g, 0.14 mmol) was suspended in methylene chloride (15 mL) under an argon atmosphere at room temperature. α-Chloro-α benzoyl phenylsulfide (125) (0.023 g, 0.773 mmol) and 1,3-*bis*-trimethylsiloxy-1-methoxy-1,3-butadiene (100) (0.210 g, 0.807 mmol) were added and the reaction was stirred for 4 days.

The reaction was neutralized to pH 7 (wet alk-acid paper) with a slurry of $NaHCO_3$ in methanol. The solution was extracted with ether (2 x 20 mL) and washed with brine (2 x 20 mL). The combined ether extracts were dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure to give 0.260 g of a crude mixture. A quantity of 0.130 g was submitted to flash chromatography (19:1 hexanes-ethyl acetate) to give four compounds; two isomeric furans (129) (0.042 g, 34% yield) and (131) (0.016 g, 13% yield), and a pair of α-alkylation diastereomers (130) (0.033 g, 25% yield). It is not possible, at the time of writing, to differentiate (129) and (131) (future work will attempt the cyclization of (130) to determine the relative yields of the two furans). It is clear that only α-alkylation has occurred and that regardless of

the yields of (129) and (131), α-chloro phenyl sulfides are more reactive electrophiles than ketones.

130 a

I.R.(CCl_4): ν=1750, 1723, 1680, 1282 cm^{-1}.

M.S.:m/z=324(1.5%, M^+-H_2O), 216 (19%, $324^+-C_6H_4S$), 182 (26%), 154 (37%), 110 (22%, $C_6H_5SH^+$), 105 (61%, $C_6H_5CO^+$), 77 (41%, $C_6H_5^+$).

^{1}H-N.M.R.($CDCl_3$) 130a

δ=2.27 (s, 2H, CH_3), 3.91 (s, 2H, $COOCH_3$),
4.33, 5.13 (ABq, 1.33 H, $OCCHCHSC_6H_5$, J=11.5 Hz),
7.2-7.6, 7.8-8.0 ppm (m, $10H_{arom}$).

130b

δ=2.52 (s, 1H, CH_3), 3.64 (s, 1H, $COOCH_3$),
4.40, 5.14 (ABq, 0.66 H, $OCCHCHSC_6H_5$, J=11.4 Hz),
7.2-7.6, 7.8-8.0 ppm (m, $10H_{arom}$).

129 m.p. 98-98.5°C

I.R.(CCl_4): ν=1711, 1433 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=2.68 (s, 3H, CH_3), 3.67 (s, 3H, $COOCH_3$),
7.1-7.5 ppm (m, $10H_{arom}$).

M.S.:m/z=324(70%, M^+), 292 (62%, M^+-CH_3OH), 250 (23%, $M^+-C_6H_4$),
216(75%, $M^+-C_6H_4S$), 201 (93%, 216^+-CH_3), 185 (46%, $C_6H_4SC_6H_5^+$(?)),
156 (32%), 110 (72%, $C_6H_5SH^+$), 109 (57%, $C_6H_5S^+$), 105 (89%, $C_6H_5CO^+$),
77 (100%, $C_6H_5^+$).

131

I.R.(CCL_4): ν=1722, 1439, 1250, 1231 cm^{-1}.

^{1}H-N.M.R.($CDCl_3$): δ=2.65 (s, 3H, CH_3), 3.85 (s, 3H, $COOCH_3$),
7.2-7.6 ppm (m, $10H_{arom}$).

M.S.:m/z=250 (18%, $M^+-C_6H_4$), 235 (16%, 250^+-CH_3), 216 (82%, $M^+-C_6H_5SH$),
201 (64%, 216^+-CH_3), 185 (46%, $C_6H_4SC_6H_5^+$), 110 (18%, $C_6H_5SH^+$),
109 (17%, $C_6H_5S^+$), 105 (100%, $C_6H_5CO^+$), 77 (51%, $C_6H_5^+$).

Determination of the Mechanism

1,3-*bis*-Trimethylsiloxy-1-methoxy-1,3-butadiene (0.250 g, 0.962 mmol) was dissolved in a mixture of 2,2-dimethoxyphenylacetaldehyde (0.162 g, 0.961 mmol) and $CDCl_3$ (2.0 mL). The solution was cooled to -50°C under an argon atmosphere and $TiCl_4$ (2.0 M solution in $CDCl_3$, 0.23 mL, 0.45

mmol) was added and 3 spectra were taken at ~10 min intervals using the INEPT pulse sequence in the ^{29}Si-N.M.R.. Each spectra required accumulations of ~7 min (the time indicated on the following spectra is the time at the half-way point of the aquisition). More $TiCl_4$ (2.0 M solution, 1.25 mL, 2.50 mmol) was added and a further 3 spectra were taken. There was no change in the spectrum following the acquisition of the third spectra.

The reaction was worked-up in a similar fashion to that of compound 119 (*vide supra*) and ^1H-N.M.R. analysis confirmed the presence of the hydroxycyclopentenone system. Four peaks were observed which correspond to the silyl enol ester (a) and silyl enol ether (b) of the starting material, the chelated silyl group of the intermediate (117) (c) and chlorotrimethylsilane (d), the product of the reaction. As the spectra were obtained using a decoupling pulse sequence, all of the observed peaks were singlets.

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

1,3-*bis*-Trimethylsiloxy-1-methoxy-1,3-butadiene

t = 0

δ =21.81 (1.0 Si, a), 16.2 (1.0 Si, b).

t = 6 (after the addition of 0.5 eq of $TiCl_4$)

δ =31.6 (0.2 Si, c), 21.81 (1.0 Si, a), 16.2 (0.8 Si, b).

t = 20

δ =31.6 (0.2 Si, c), 26.1 (0.06 Si, d), 21.81 (1.0 Si, a), 16.2 (0.74 Si, b).

t = 31

δ =31.6 (0.23 Si, c), 26.1 (0.15 Si, d), 21.81 (1.0 Si, a), 16.2 (0.62 Si, b).

t = 40 (a further addition of 2.5 eq of $TiCl_4$ takes place at 37 min).

δ =31.6 (0.34 Si, c), 26.1 (1.46 Si, d), 21.81 (0.2 Si, a).

t = 54

δ =31.6 (1.64 Si, c), 26.1 (0.36 Si, d).

t = 65

δ =31.6 (2.0 Si, c).

Claims to Original Work

1) A new method has been developed for the formation of acetals. This method makes use of inexpensive and readily available trimethylchlorosilane. The reaction displays chemoselectivity; methyl acetals are only formed from electron deficient carbonyl groups, such as those with carbonyl groups at the α-position. Most other carbonyl groups are readily converted into the corresponding dioxolanes under mild conditions.

2) A new method for the formation of carboxylic esters has been developed. This method also makes use of chlorotrimethylsilane. The reaction proceeds under very mild conditions (the methyl ester of 6-aminopenicillanic acid was formed in 84% yield without concomitant scission of the delicate β-lactam bond). Those esters which are usually required in synthesis, that is, the methyl, ethyl, benzyl and 2-trimethylsilylethyl esters are readily accessible by this method. The reaction has been shown to proceed via the silyl ester (based on ^{29}Si-N.M.R. studies).

3) The reactivity of a series of electrophiles towards 1,3-bis-trimethylsiloxy-1-methoxy-1,3-butadiene has been evaluated. The reaction sequences for the syntheses of a variety of dielectrophiles in a 1,2 relationship have been developed and modified from literature procedures. The relative order of reactivity has been shown to be;

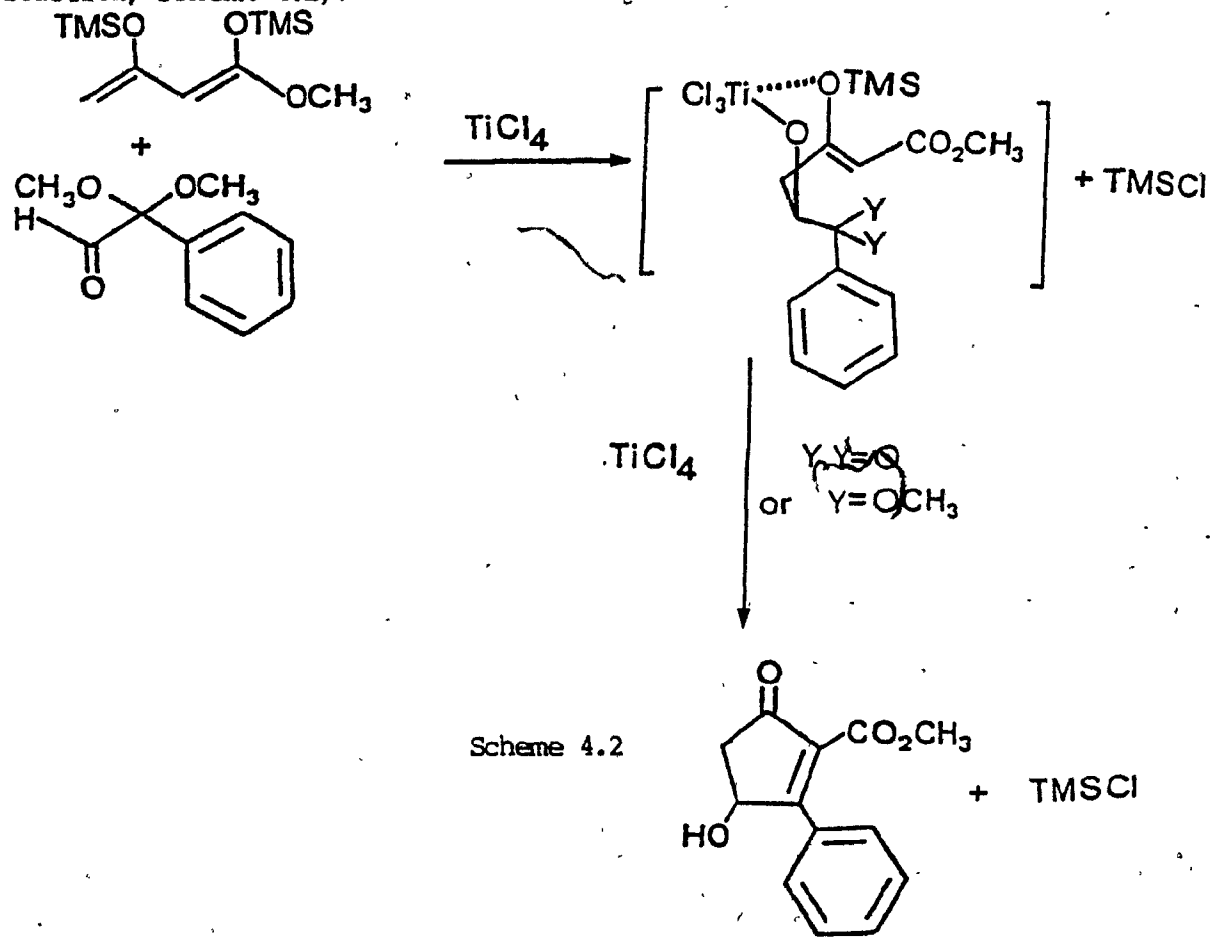
$$RC(Cl)SC_6H_5 > ArCOCHO > ArCOCHO > RC(OCH_3)_2, RC(OCH_3)SC_6H_5 > RCHCl_2$$

The nucleophilic enol ether reacts exclusively at the γ-position with the

exception of the α-chloro phenylsulfide electrophile.

4) The dialkylation of 1,2-electrophiles has led to a novel route to hydroxycyclopentenones (2-carbomethoxy-4-hydroxy-3-phenylcyclopent-2-enone) which have the same substitution pattern as the prostaglandins skeleton, suggesting a possible route to these synthetically interesting compounds.

5) The mechanism of these dialkylations has been shown to proceed in a sequential manner (based on ^{29}Si-N.M.R. studies). The enol ester reacts first at the γ-position to generate an intermediate which is chelated to the $TiCl_4$ catalyst. The thus formed enol ether then reacts to give the 5-membered ring (a deketalization occurs at some intermediate stage in the reaction, Scheme 4.2).



Scheme 4.2

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