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I. TOTAL SYNTHESIS OF (+, -)-LINDERALACTONE, (+, -)-ISOLINDERALACTONE AND (+, -)-NEOLINDERALACTONE II.
SYNTHESIS AND STUDY OF ELECTROPHILIC AND ENE REACTIVITY OF ELECTRON DEFICIENT ALLYLSILANES
I. TOTAL SYNTHESIS OF (+)-LINDERALACTONE, (+)-ISOLINDERALACTONE AND (+)-NEOLINDERALACTONE

II. SYNTHESIS AND STUDY OF ELECTROPHILIC AND ENE REACTIVITY OF ELECTRON DEFICIENT ALLYLSILANES

DISTRIBUTION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Aravamudan S. Gopalan, M.Sc.

* * * * *

The Ohio State University

1980

Reading Committee:
Professor H. Shechter
Professor D. Hart
Professor P. D. Magnus

Approved By
P. D. Magnus
Department of Chemistry
To my great grandfather and parents
whose constant love, encouragement and countless
sacrifices that made all this possible.
ACKNOWLEDGEMENTS

I should like to thank Professor Philip D. Magnus for his patience, constant encouragement and guidance during my degree program. It has been a real pleasure to work with him for the last four years. The members of the Magnus research group are warmly thanked for their help and friendliness. Mr. Dick Weissenberger is thanked for his mass spectral assistance. I should also like to thank Dr. Doskotch, Dr. Shechter and Dr. Hart for their valuable suggestions regarding the writing of the thesis. Dixie is warmly thanked for her patient typing.

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VITA

November 28, 1954........................Born, Mannargudi, Tamil Nadu, India

1973.................................B.Sc., Loyola College, University of Madras

1975 M.Sc., University of Madras

1975-1978 Teaching Associate, Department of Chemistry, The Ohio State University, Columbus, Ohio

1978-1979 Research Associate, Department of Chemistry, The Ohio State University, Columbus, Ohio

PUBLICATIONS


FIELDS OF STUDY

Organic Chemistry. Professor P. D. Magnus.
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### Abbreviations

<table>
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<th>Description</th>
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<tr>
<td>n-BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>s-BuLi</td>
<td>s-Butyllithium</td>
</tr>
<tr>
<td>t-BuLi</td>
<td>t-Butyllithium</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>magnesium sulfate</td>
</tr>
<tr>
<td>BF₃·Et₂O</td>
<td>boron trifluoride etherate complex</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylene diamine</td>
</tr>
<tr>
<td>MCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>mm/Hg</td>
<td>millimeters of mercury</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>mult</td>
<td>multiplet</td>
</tr>
<tr>
<td>-TMS</td>
<td>trimethylsilyl group</td>
</tr>
<tr>
<td>-OCH₃</td>
<td>methoxyl group</td>
</tr>
<tr>
<td>-CH₃</td>
<td>methyl group</td>
</tr>
<tr>
<td>-OH</td>
<td>hydroxyl group</td>
</tr>
<tr>
<td>sec.</td>
<td>seconds</td>
</tr>
<tr>
<td>min.</td>
<td>minutes</td>
</tr>
<tr>
<td>h.</td>
<td>hours</td>
</tr>
<tr>
<td>r.t</td>
<td>room temperature</td>
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Lindera strychnifolia Vill, is an aromatic shrub from central China and Taiwan. The root is used medicinally as a stomachic. Linderalactone (1), isolinderalactone (2), and neolinderalactone (3) along with other furanosesquiterpenes were isolated by Takeda and coworkers from the neutral extract of the root of Lindera strychnifolia Vill. The isolation of (1) and (2) has also been reported from other plant sources.

![Chemical structures](image)

No reports of attempts to synthesize (1), (2) and (3) have been published. It was decided to synthesize (1), (2) and (3) by a common strategy. Success would result in the first total synthesis of these furanosesquiterpenes. The presence of the germacrene ring, the furan,
and the α-methylene-γ-lactone units made the synthesis of these molecules a
challenging task. In the following review, the Cope-rearrangement
chemistry of linaleralactone (1), and related compounds has been discussed.
Also the current methodology available to synthesize the key structural
units present in (1), (2) and (3) has been reviewed.

It was found linaleralactone (1) on heating at 160°C readily undergoes
a reversible Cope rearrangement to isolinaleralactone (2), to give a
mixture of (1) and (2) in a ratio of 2:3. The structures of linal-
eralactone (1), isolinaleralactone (2), and neolinaleralactone (3) were
determined by Takeda on the basis of chemical degradation studies and
spectroscopic properties. The crystal and molecular structure of
linaleralactone was established by three dimensional X-ray analysis.
Takeda also determined the absolute configuration of isolinaleralactone
(2) as antipodal elemane type, by chemical correlation with isofurano-
germacrene (4) of known absolute configuration. The configuration of
linaleralactone (1) was easily deduced from that of isolinaleralactone
(2), its Cope rearranged product.

Isolinaleralactone (2) is the first example of a sesquiterpene
of antipodal elemane type. Ten membered ring sesquiterpenes when subjected
to Cope rearrangement usually give rearrangement products with the
absolute configuration of the elemane type.

Cope rearrangements of linaleralactone (1) and related compounds.

Takeda has extensively examined the relationship between the
conformation of cyclodeca-1,5-diene type sesquiterpenes and the stereo-
chemistry of their Cope rearrangement products. It is well known that
germacrene type cyclodeca-1,5-diene sesquiterpenes undergo Cope
rearrangement to give elemane type derivatives (eg. (5) and (6)). The mechanism of the Cope-rearrangement has been predicted by Doering, Vogel and Gill as well as by Woodward-Hoffmann. The reaction is now defined as a sigmatropic change of order (3,3) and proceeds through a four-center cyclohexane chair-like transition state. The angular methyl of the produced elemane-type derivatives generally has the _β_-configuration.

On heating linderalactone (1) at 160°C a mixture of (1) and isolinderalactone (2) was obtained in a ratio of 2:3. When isolinderalactone was heated under the same conditions, the same equilibrated mixture was obtained. The absolute configuration of isolinderalactone (2) has been established as antipodal elemane type. On the other hand the diol (7), prepared by reductive cleavage of the lactone in (1) and the ether (8) yield products (9) and (10) respectively on Cope rearrangement, with absolute configuration of the elemane type. Takeda et al., have postulated that the abnormal stereochemistry of the Cope rearranged product (2) is controlled by the conformation of the carbocyclic ten-membered ring in the starting material. This difference in the stereochemistry is doubtless due to the presence of the α,β-unsaturated γ-lactone ring in (1), which imparts additional rigidity to the system.
The conformation, in solution, of a ten-membered ring sesquiterpene can be determined by means of measurements of the nuclear Overhauser effect (NOE)\(^1\) of substituents in the nmr spectra. Takeda has studied the conformational isomerism of linderalactone (1),\(^3\) neolinderalactone (3) and several other germacrene sesquiterpenes using NOE techniques. If a compound contains suitable substituents, the assignments of each nmr signal then becomes reliable, and NOE provides a very effective tool
for ascertaining the more stable conformer in solution.

Molecular models show that four major conformations (A to D) are possible for linderalactone (Fig. 1).

Conformations of Linderalactone (1)

Conformations (A and B) have crossed orientations of the two double bonds, whereas conformations (C and D) have their double bonds parallel. The interactions between the pairs of groups joined by an arrow in Fig. 1 are important. If an NOE between these pairs of protons is observed, then the major conformer should be assignable. NOE was in fact observed between protons at position 2 and 6 and position 2 and 10, and the main conformer of linderalactone was determined to be A as shown in Fig. 1.
Cyclodeca-1,5-diene derivatives in which one double bond is cis usually undergo Cope rearrangement to give cis-1,2-divinyl derivatives. 

However, when neolinderalactone (3) was heated at 300°C for 1-2 min., it gave a mixture of isolinderalactone (ca 3%) and starting material (ca 80%). This indicates that neolinderalactone (3) undergoes an abnormal Cope rearrangement to give the trans-1,2-divinyl derivative, isolinderalactone (2) in ca 5% yield, since the latter (2) is in equilibrium with linderalactone (1) in the ratio 3:2 at temperatures above 160°C. This result is explicable if compound (3) cannot form

\[
(3) \xrightarrow{\Delta, 300^\circ C} (2)
\]

the four-centered transition state favourable for the Cope rearrangement, because of the rigidity of the ten-membered ring caused by the presence of the cis-double bond and the α,β-unsaturated γ-lactone. Takeda et al. have also found that this abnormal Cope rearrangement only occurred with furanoid germacrene type sesquiterpenes, and it is reasonable that this abnormality is caused by the furan ring. NOE studies showed neolinderalactone (3) exists as a 8:2 mixture of the two conformers E and F (Fig. 2). The Cope rearrangement probably occurs via the conformer F in Fig. 2.
In conclusion, the two double bonds in the ten-membered ring have a crossed orientation in conformer A (Fig. 1) of linderalactone (1). This conformer rearranges via the chair-like transition state (11) to give the antipodal elemane derivative, isolinderalactone (2).

(1) $\xrightarrow{\Delta} [\text{structure}] \xrightarrow{\Delta} (2)$

(11) $R=H$
In conclusion, it is the conformation of the ten-membered ring which governs the ease and nature of the Cope rearranged product in the furanogermacrene sesquiterpenes.

Synthetic approaches towards germacrene-sesquiterpenes

Several kinds of sesquiterpenes having a ten-membered ring structure have been recently isolated. This group consists of cyclo-decadienes (or cyclodecatrienes) such as (12) and more highly oxygenated and/or esterified compounds. Linderalactone (1) and neolinderalactone (3) are examples of germacrene type furanosesquiterpenes.

![Germacrene C (12)](image1)

![Hedycaryol (13)](image2)

![Costunolide (14)](image3)

![Linderalactone (1)](image4)

No synthetic approaches to linderalactone (1), isolinderalactone (2) and neolinderalactone (3) have been reported. In fact, germacrene-type furanosesquiterpenes have received no synthetic attention.
Over the years the cyclodecane ring system of germacranolides has received little notice from synthetic chemists. This is primarily due to the primitive state of the conformational analysis of 10-membered rings, and the lack of methods for elaboration of the ten-membered carbocyclic framework. Very few of the germacranolides have been synthesized. Corey's synthesis of dihydrocostunolide (17) provided the first real breakthrough in this area. His synthesis employed a photolytic cleavage of a hexahydronaphthalene derivative (16), derived from santonin (15) in 5 steps for the construction of the cyclodecane ring system. The experimental conditions for the photolysis of the diene (16) and the subsequent hydrogenation are very critical and the yield is only 10%. In spite of this, Corey's work provided the first successful application of the photofission of 1,3-cyclohexadienes to the synthesis of a medium ring system.

\[
\text{Santonin (15)} \xrightarrow{\text{5 steps}} \xrightarrow{\text{hv}} \xrightarrow{\text{not isolated}} \xrightarrow{\text{H}_2/\text{Pd}} \text{Dihydrocostunolide (17)} \sim 10\%
\]
Another synthesis of dihydrocostunolide (17) has appeared which is also based on the Corey use of photolytic cleavage of hexahydronaphthalene derivatives, and once again uses santonin (15) as the starting block.

In 1967, N. H. Fisher and T. J. Mabry reported the first example of the formation of a germacranolide from a \textit{trans}-1,2-divinylcyclohexane derivative. Also, J. E. McCloskey and co-workers demonstrated the reversibility of the Cope rearrangement of dihydrocostunolide (17) and costunolide (14). P. Grieco and M. Nishizawa achieved the first total synthesis of costunolide (14), via synthetic dehydrosaussurea lactone (18) utilising the Cope rearrangement for construction of the ten-membered carbocyclic unit.

\[
\begin{align*}
\text{Deydrosaussurea lactone} & \quad \xleftrightarrow{220^\circ \text{C}} \quad \text{Costunolide} \\
(18) & \quad (14)
\end{align*}
\]
The starting material for Grieco's synthesis was the keto lactone (19), which was prepared from santonin (15) in 2 steps. The synthesis involves an elegant use of the Shapiro reaction to give the olefin (20), which is further degraded by use of selenium chemistry to saussurea lactone (21).

1. **TsNH$_2$, PhH, BF$_3$ Et$_2$O**
   2. **LDA, THF, $-78^\circ$C $\rightarrow$ 0°C, 65%**

Ar Se

1. **O$_3$, CH$_2$Cl$_2$–MeOH, $-78^\circ$C**
   2. **NaBH$_4$, $-78^\circ$C $\rightarrow$ 25°C**
   3. **O$_2$NC$_6$H$_4$SeCN, Bu$_3$P, 81%**

THF–Py (1:1)

50% H$_2$O$_2$, THF (90%)

1. **O$_2$NC$_6$H$_4$SeCN, Bu$_3$P, THF**
   2. **50% H$_2$O$_2$, THF $\sim$ 80%**

1. **LDA, PhSeSePh $-78^\circ$C $\rightarrow$ -20°C**
   2. **30% H$_2$O$_2$, (93%)**

 Saussurea lactone (21)

Dihydrocostunolide (17)

Costunolide (14)
Grieco's work has clearly established trans-1,2-divinylcyclohexane derivatives as good precursors for construction of the germacranolides. All the syntheses of costunolides are in fact indirect total syntheses as they use santonin (15) as the starting point. Using santonin (15), considerably simplifies the synthetic challenge, as a considerable amount of the functionality is already present in the required geometry (for example the lactone ring). No direct synthesis of complicated germacranolides has yet been achieved.

Attempts to simulate biogenetic pathways for the construction of germacranolides have not had much success. Kodomo, Matsuki and Ito synthesized hedycaryol (13), by converting trans,trans-farnesyl phenyl sulfide (22) to the epoxide (23) in 54% yield. Cyclisation of the epoxide (23) was performed using n-BuLi in the presence of 1,4-diazabicyclo[2.2.2]octane. The reaction afforded after chromatographic separations, two isomeric hydroxy thioethers (24) and (25) in 35% and 25% yield respectively. The alcohol (24) was desulfurized with Li/ethylamine at -78°C to give an inseparable mixture of hedycaryol (13) and the alcohol (26).
In conclusion, methodology to construct germacranolides is still lacking. Furanogermacrene sesquiterpenes present a hitherto unexplored, difficult synthetic challenge.

Construction of Substituted 3-Methyl-4,5,6,7-tetrahydrobenzofuran System.

As discussed earlier, isolinderalactone (2) undergoes reversible Cope rearrangement to linderalactone (1). Therefore, isolinderalactone (2) and episolinderalactone (27) are obvious precursors for the total synthesis of linderalactone (1), and neolinderalactone (3), respectively.

The synthesis of iso- and episolinderalactone could involve the construction of a suitably substituted 3-methyl-4,5,6,7-tetrahydrobenzofuran system, which could be developed to the final synthetic targets (1), (2) and (3).
Only a few furanoterpenes, having a substituted 3-methyl-4,5,6,7-benzofuran system have been synthesized. Stetter and Lauterbach reported the first synthesis of evodon (28), a furanoterpene obtained from the essential oil of leaves of *Evodia hortensis*. The condensation of 5-methyl-1,3-cyclohexanedione (29) with ethyl α-chloroacetoacetate gives the furan ester (30) in good yields. The ester (30) was hydrolysed to the acid (31) which was successfully resolved using cinchonidine. The decarboxylation of the levorotatory acid (31) gave the ketone (28) which was identical with natural evodon (28). The d,l-evodon was also easily transformed by a Wolff-Kishner reduction to d,l-menthofuran (32).

![Chemical structures and reactions](image)

Evodon (28) 79%

Menthofuran (32)
A second synthesis of evodon also used 5-methyl-1,3-cyclohexanedione as the starting block. Yoshikoshi recently reported the preparation of 1-nitro-1-phenylthiopropane (33), and its reactions with 1,3-cyclohexanediones in the presence of KF in hot xylene, leading to 3-methylfurano derivatives. He has applied this reaction to the synthesis of evodon (28).

A suspension of 5-methyl-1,3-cyclohexanedione (29), KF (0.2 mol equiv.) and the nitroolefin (33) (1.2 mol equiv.) in xylene was heated at 110°C for 8 h. to afford a 18:82 mixture of the dihydrofurans (34a and 34b) as the major product (63%) in addition to the α-(phenylthio)furan (35a, 6%). After separation, both isomers (34a and 34b) were converted to evodon (28) by oxidation with NaIO₄ in methanol and subsequent elimination of benzenesulphinic acid in refluxing CCl₄ containing pyridine (74% from 34a and 70% from 34b).
To illustrate the potential of this new 3-methylfuran annulation in more complex systems, Yoshikoshi has recently synthesized ligularone (36), a representative furanoeremophilanoloid sesquiterpene. His synthesis gave a mixture of (+)-ligularone (36) and its thermal isomerisation product, isoligularone (37). The bicyclic dione (39), the key intermediate in this synthesis was stereoselectively synthesized from the known enedione (38) in nine steps. (Scheme 1.)

\[
\begin{align*}
(38) & \rightarrow \text{4 steps} \rightarrow (39) \\
1) \text{OH, } H_2O_2 & \rightarrow (84\%) \\
2) \text{Li, NH}_3 & \rightarrow (93\%) \\
(33) + (38) & \rightarrow (39) \quad \text{Jones oxdn (72\%)} \\
\text{KF, benzene, } & \text{80°C, 7h. (62\%)} \\
1) \text{NaIO}_4, \text{MeOH} & \rightarrow \text{1) NaIO}_4, \text{MeOH} \\
2) \text{benzene, pyridine and active alumina, } & \rightarrow 2) \text{benzene, pyridine and active alumina} \\
\Delta & \Delta
\end{align*}
\]
Both Stetter's and Yoshikoshi's procedures involve the transformation of cyclohexane-1,3-diones to furan products. Unfortunately, the cyclohexane-1,3-diones are not easily accessible synthetic intermediates, and several steps may be required to generate this functionality. Also, with unsymmetrical β-diketones both procedures yield mixtures of furan products and lack regiochemical controls. Yoshikoshi's procedure also has the disadvantage of not giving the furan moiety directly and involves separation of diastereomers as discussed.

Lindestrene (40) is one of the furan sesquiterpenes isolated from the root of *Lindera strychnifolia* Vll. Minato and Nagasaki have reported the synthesis of this molecule. They had earlier found that reduction of α,β-unsaturated-γ-lactones with alkyl aluminum hydrides leads to β-methyl furan derivatives and this formed the basis of their synthetic approach to lindestrene (40). The key intermediate that is transformed to the furan is the trans-decalone (41) and not a cyclohexane-1,3-dione as in the Stetter and Yoshikoshi procedures. The construction of the butenolide (42) is a long and tedious operation. (Scheme 2). In the final step, the butenolide (43) was reduced to give racemic lindestrene (40).
Scheme 2
This synthesis of *lindastrene* (40) clearly shows the need for better methodology for the synthesis of complicated furanosesquiterpenes. The synthesis is contrived and long. The furan ring is formed through a sequence of 5 reactions involving rather harsh conditions. It is important that the rest of the functionality in the molecule be compatible with the final hydride reduction that generates the furan moiety.

The same authors synthesized (+)-*attractylon* (29) by a slightly better route. The intermediate (45) was converted to its enamine and alkylated with ethyl α-bromopropionate to generate the furan precursor (46) in poor yield. (Scheme 3).

![Scheme 3](image-url)

In conclusion, the construction of the 3-methyl-4,5,6,7-tetrahydrobenzofuran system present in several furanosesquiterpenes, still remains a difficult task. Most current methods are long, involve not readily available synthetic intermediates, and have poor regioselectivity.
Construction of α-methylene-γ-lactones

The synthesis of both iso- and episolinderalactone (2 and 2?) must involve the synthesis of a α-methylene-γ-butyrolactone unit. This structural unit characterizes a rapidly expanding group of sesquiterpenes. Recently, there has been a large amount of research devoted to developing synthetic routes to α-methylene-γ-lactones and several reviews have appeared. This has been in large part due to interest in the synthesis of several biologically active natural products, which have the α-methylene lactone moiety as a major structural feature.

![Chemical structures]

alantolactone     vernolepin

The various methods of synthesis of α-methylene lactones can be divided into two parts, depending upon whether or not the methylene group is constructed on a preformed lactone ring. Precursors, other than preformed lactones, have mostly proved unsatisfactory because of lack of stereochemical controls or low yields. Several methods now exist for the methylenation of preformed lactones, making it one of the more extensively investigated transformations.
Much attention has recently been focused on the synthesis of the α-methylene lactone unit from lactone enolates. This has resulted in the development of several novel and efficient sequences.

Ouirsson has described a synthetic sequence which permits construction of the cis-fused α-methyl-γ-butyrolactone moiety from the corresponding α-methyl lactone (Scheme 4). Ouirsson has used this apparently general technique for the synthesis of (−)-Frullanolide.

\[
\begin{align*}
&\text{1) (C}_6\text{H}_5\text{Cl/DMF/TMEDA} \\
&\text{2) BrCH}_2\text{CH}_2\text{Br} \\
\end{align*}
\]

60% overall yield.  

Scheme 4

When treated with strong bases (e.g. LDA), lactones can be converted to their corresponding enolates and efficiently alkylated, providing a convenient route to α-methyl lactones from preformed lactone rings. Grieco and Hiroi have demonstrated that lactone enolates of 5 and 6-membered rings undergo high yield α-hydroxymethylation. Lactone enolates generated with LDA in THF at −78°C, reacted at −20°C with formaldehyde (generated by heating paraformaldehyde in a stream of nitrogen). The α-hydroxymethylactone (47) was obtained in a 95% yield. Conversion of (47) into its corresponding mesylate and thence into the trans α-methylene-γ-butyrolactone (48) was achieved in ~80% overall yield.
Lactone enolates undergo efficient $\alpha$-carboxylation. Subsequent treatment with aqueous formaldehyde and diethylamine, followed by sodium acetate in acetic acid, gives typical overall yields of 70-80% of $\alpha$-methylene lactones (Scheme 5).
Johnson had earlier demonstrated that methylmethoxymagnesium carbonate (Stile's reagent) carboxylates butyrolactone in very high yields, thus providing a route to α-methylene-γ-lactones. He has applied this method to the synthesis of d,l-avenaciolide (49).

\[
\text{Stile's reagent} \quad 75\%
\]

Grieco has also developed a method, which uses the low temperature syn-elimination of alkyl phenyl selenoxides to give the exocyclic methylene group exclusively. The selenides are prepared by the selenation of the corresponding α-methyl lactones (Scheme 6).
The above procedure works in excellent yields and the reaction conditions are very mild.

A recent communication by Danishefsky and coworkers describes a useful procedure for the methylenation of lactones in fair overall yield, without protection of free hydroxyl groups present in the same molecule. Thus, bis-norvernolepin and bis-norvernomenin were converted to vernolepin (50) and vernomenin respectively without protection of their free hydroxy functions. The procedure is illustrated for vernolepin (Scheme 7).
The Mannich reagent, dimethyl(methylene)ammonium iodide was first used by Eschenmoser and is now known as Eschenmoser's Salt. The lactone enolate derived from (51) readily reacts with Eschenmoser's Salt to give the adduct (51a). Quaternization with methyl iodide, followed by elimination using diazabicycloundecene (DBU) leads to a fair yield of vernolepin (50).

It is clear that sufficient methodology exists for the formation of the \(-\text{methylene-}-\text{\(\gamma\)-lactone unit. Hence, it was anticipated that methylenation of a preformed lactone intermediate in the final stage of our projected synthesis of isolinderalactone (2) would not be a problem.}

Syntheses of Vernolepin

Vernolepin (50) and its congener vernomenin (52) were isolated by Kupchan from Vernonia hymenolepis and shown to have significant in vitro cytotoxicity (KB) and in vivo tumor inhibitory activity against Walker intramuscular carcinosarcoma in rats. Multifaced synthetic attack towards this complex natural product has led to the total synthesis of (50) by Grieco, Danishefsky, Isobe and a formal total synthesis by Schlessinger, and many other valuable synthetic approaches.
Most of the synthetic approaches involved elaboration of the cis-fused δ-valerolactone system by scission of the C₂-C₃ bond of an angularly functionalised trans-bicyclo(4.4.0)decane. Schlessinger's approach to the total synthesis of vernolepin (50) is different from most of the others. Instead of using a rigid bicyclic ring to control the stereochemistry of the decalin system, he builds the key bicyclic intermediate (56) using an intramolecular enolate alkylation. Only his approach, which closely paralleled our own efforts in this area, is discussed in this brief review.

Schlessinger's synthesis, which results in the exclusive formation of vernolepin (50), begins with the preparation of compound (54). The enone (54) is elaborated to the cis-2-oxydecalin (56). The presence of a remote chiral centre, not present in the natural product, imparts sufficient conformational rigidity to (57) to permit its stereospecific conversion into the epoxide (58). Regiospecific ring opening of the
epoxide (58), followed by successive establishment of the C and A lactone rings, yields the molecule prevernolepin (59). (Scheme 8)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad 1) \text{LDA, HMPA} \quad \text{EtO}_2\text{C} \\
& \quad 2) \text{BrCH}_2\text{CO}_2\text{Et}
\end{align*}
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CH}_2\text{CO}_2\text{Et} \\
& \quad \text{Hg}^{++}, \text{H}_2\text{O} \\
& \quad \text{KOTBu/tBuOH}
\end{align*}
\]

75% from (53)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{OMe} \\
& \quad 1) \text{LDA} \quad \text{EtO}_2\text{C} \\
& \quad 2) \text{LAH}
\end{align*}
\]

(54)
NaI, CH₃-CH₃, reflux

[(54)]

LiN(SiMe₃)₂, -40°C

[(55) → (56) 1:1]

1) LAH
2) I₂, THF

DiBAL

[(57)]

+ isomeric-β alcohol (separation).

MCPBA, -20°C

[(58)]

→ Vernolepin

Prevernolepin (59)
The key step in this synthesis was the cyclization to give (56). It was anticipated that the kinetic enolate derived from (55) would cyclise to (56), since this enolate must be a mixture of isomers with respect to the carbon atom bearing the methoxy and iodomethyl groups. The orientation of these groups as depicted in (60) results in serious interaction of the methoxyl group with the hydrogen atom carried by the enolate carbon, whereas this interaction is not present in (61), leading to the conclusion that (61) would cyclise in preference to (60) to give exclusively compound (56). This surmise proved to be true,

\[
\begin{align*}
\text{(60)} & \quad X=H; \quad Y=\text{OCH}_3 \\
\text{(61)} & \quad X=\text{OCH}_3; \quad Y=H
\end{align*}
\]
Total Synthesis of Linderalactone, isolinderalactone and neoinderalactone - Part A

The reversible Cope rearrangement of linderalactone (1) to isolinderalactone (2) has been well established. On heating either (1) or (2) at 160°C for 15 min, a mixture of (1) and (2) in a ratio of 2:3 is obtained. Also neoinderalactone (3), which exists as a mixture of conformers (3) and (3a) undergoes an abnormal Cope rearrangement to
isolinderalactone (2), albeit in poor yields. This rearrangement should proceed from conformer (3a) rather than (3). It was thought that the hitherto unknown epiisolinderalactone (4) should on heating undergo irreversible rearrangement to neolinderalactone (3). _Cis-_1,2-divinyl cyclohexane derivatives in general, are known to give _cis-_trans-cyclo-deca-1,5-diene derivatives on Cope rearrangement (Scheme 1).

Isolinderalactone (2) and its unknown epimer, epiisolinderalactone (4) were the obvious precursors for the total synthesis of (1) and (3) and these became the target molecules. This choice solved the difficult task of constructing the complicated germacrene ring in these molecules as it could be generated in the final step by the Cope rearrangement of the appropriate 1,2-divinyl derivatives (2) and (4). Now one was left with a problem of sufficient synthetic complexity.

The synthetic task could be broken down into 3 parts:

a) Construction of the quarternary carbon-1 carrying the requisite vinyl and methyl groups of (2) and (4).

b) The synthesis of a suitably substituted 3-methyl-4,5,6,7-tetrahydrobenzofuran system.

c) Construction of the _cis-_α-methylene lactone unit.

The retrosynthetic analysis of the problem is shown in Scheme 2. The preformed _cis_-lactones (5a and 5b) should be good precursors to the final methylenated products (2) and (4). The _cis_-lactones (5a and 5b) were obtainable from a hydride reduction of ketoester (6) which can be made by the alkylation of (7) under kinetic conditions. The condensation of the 5,5-disubstituted cyclohexane-1,3-dione (8) with ethyl _α_-chloroacetoacetate using Stetter's procedure should lead to the key
furan intermediate (7). The plan involved the introduction of the furan unit in the middle of the synthesis and not at the very end, as in most other reported furanesesquiterpene syntheses. The cyclohexane-1,3-dione (8) could be derived from 3,5-dimethoxybenzoic acid, which has a latent 1,3-diketone functionality. The first problem faced was the construction of the appropriately substituted quaternary carbon of the \( \beta \)-diketone (8), which would correspond to C-1 of the final target molecules (2) and (4).

3,5-Dimethoxybenzoic acid (9) was reduced with Li in liquid ammonia using the procedure of Bosch et al. The resultant dianion (10) was alkylated with methyl iodide to give the crystalline product (11) in excellent yields. The disappearance of aromatic protons in the NMR spectrum combined with the appearance of vinylic absorptions at \( \delta 4.73 \) (2 H, bs)
and the quarternary –CH₃ group at δ 1.40 (3 H, s) clearly supported the assigned structure of (11).

Care has to be exercised in the work-up of these reactions to avoid hydrolysis of the sensitive enol-ether functionality. The aqueous solution of the residue was first acidified to pH 7 with conc. HCl and then to pH 5.5 with a saturated solution of sodium dihydrogen phosphate, followed by extraction with dichloromethane. The crude product (11) of this reaction was > 95% pure by NMR and could be directly used in the next step.

The acid (11) was easily reduced to the known alcohol (12) with LAH. Once again, care was taken to prevent any hydrolysis of the enol ether functionality during the work-up. The excess LAH was quenched by addition of 4 equivalents of water and on extraction with ether, the alcohol (12) was obtained pure and crystalline. The appearance of a strong hydroxyl band in the IR spectrum and a singlet at δ 3.30 (2 H, CH₂OH) in the NMR spectrum verified the success of the reduction of (11) to (12).
It was felt that the conversion of the hydroxymethyl group of (12) to a vinyl group by standard methods, followed by acid hydrolysis, would give the desired cyclohexane-1,3-dione (8); one of the partners in the key furan cyclisation (Scheme 3).

However, attempts to oxidize the alcohol (12) to the aldehyde (13) were unsuccessful. Fragmentation occurred under the oxidizing conditions (PCC/CH₂Cl₂) to give aromatic by-products. (Scheme 4).
It was decided to convert the $-\text{CH}_2\text{OH}$ group to the vinyl group at a later point in the sequence, after the construction of the furan unit.

The acid hydrolysis of (12) to (14) also presented unexpected experimental difficulties. When the enol ether (12) was stirred with 2N HCl in aqueous THF for 16 h., TLC showed clean conversion to a strongly UV active, very polar product. However, extraction of the $\beta$-diketone (14) from the aqueous layer, in which it is considerably soluble, proved to be difficult, affording the product (14) after purification by crystallisation in poor yields. It was possible to cyclise $\beta$-diketone (14), by Stetter's procedure, to the furan ester.
Unfortunately, the cyclisation reaction proved to be an unreliable and sensitive reaction. The product was difficult to purify, and the yields were low. The free hydroxyl group of (14) could conceivably interfere with the sensitive furan cyclisation by reacting with the highly activated ethyl α-chloroacetate leading to undesired by-products. Possibly this problem could be readily solved by protecting the hydroxyl group prior to the acid hydrolysis and the furan cyclisation. The protected β-diketone should have reduced solubility, and there would be no free –OH group to interfere in the critical cyclisation reaction which was the backbone of the synthesis.

A protecting group was needed that would be both stable to the acidic conditions of hydrolysis to the β-diketone and to the basic conditions of the furan cyclisation. The benzyl and the methyl groups were considered, both of which met the requirements, but due to the high degree of success with the O-methylation of the alcohol (12), it was decided to use the methyl ether (16) for the purpose of the synthesis. The deprotection of the methyl ether can be achieved by use of certain reagents e.g. Me₃SiI, BBr₃, although fairly harsh conditions are necessary.

The sodium salt of the alcohol (12) was heated under reflux with excess methyl iodide in THF for 3 days to give methyl ether (16). TLC showed clean conversion to a fast running product. Disappearance of the –OH absorption in the IR spectrum and the appearance of a new –OME signal in the NMR spectrum (δ 3.33, 3 H, s) easily identified compound (16). The pure methyl ether (16) was obtained in greater than
95% yield, and immediately hydrolysed to the β-diketone (17). Not surprisingly, the methyl ether (16) fragmented readily under mass spectral conditions and no parent ion (M+) peak was seen.

The hydrolysis of (16) to (17) proved to be simple. The methyl ether (16) on stirring with 2N HCl in aqueous THF for 6 h., was readily hydrolysed to the β-diketone (17), which was isolated as a white crystalline solid. After trituration with a small quantity of ether, the β-diketone (17) was obtained pure in 75% yield. The loss of the methyl groups of the bis-enol ether in the NMR spectrum and the presence of a strong characteristic carbonyl band in the IR spectrum at 1705 cm⁻¹, indicated the success of the hydrolysis. Mass measurement of the molecular ion and elemental analysis further confirmed the structure of (17).
Using conditions identical to those developed by Stetter, a solution of the symmetrical cyclohexane-1,3-dione (17) in aqueous methanolic potassium hydroxide was treated with ethyl α-chloroacetacetate over 3 days. TLC showed the formation of a fast running UV active, major product and the presence of some polar residue. The polar by-products were acidic in nature, and after thoroughly washing with a saturated solution of sodium bicarbonate, the furan ester (18) was obtained in 57% yield, sufficiently pure to be used directly in the next step. The IR spectrum of the product showed two carbonyl absorptions at 1075 cm⁻¹ and 1680 cm⁻¹, corresponding to the aromatic ester and enone groups respectively. The NMR spectrum confirmed the presence of the ethyl ester, and a new absorption at δ 2.40 (3 H, s), corresponding to the methyl group on the furan ring was present. A mass measured molecular ion peak further supported the assigned structure for (18). Because of the symmetry of (17) regiochemical considerations were unnecessary in the formation of (18).

One characteristic behavior of most furan compounds on TLC is worth mentioning. The furan ester (18) produces an intense purple color on TLC, after development with dilute sulphuric acid and heating.
This observation easily identifies most furan compounds and can be an aid in monitoring their reactions. It proved very useful throughout the synthesis.

Attempts to further increase the yield of the furan ester (18) in this reaction have not been successful, as the cyclisation is a sensitive reaction. It is important to use pure starting materials and the correct ratio of the reactants. Excess base considerably decreases the yield of the furan ester (18).

The furan ester (18) was readily hydrolyzed to the acid (19) with potassium hydroxide in refluxing aqueous methanol. The NMR spectrum showed the loss of the ester functionality with the rest of the molecule remaining intact. The IR spectrum showed characteristic acid absorptions. The white, crystalline acid (19) was completely characterised by accurate mass measurement and elemental analysis.

\[
\begin{align*}
(18) & \xrightarrow{1) KOH, MeOH, H_2O} (19) \\
& \xrightarrow{2) H^+} (19) \quad 85\%
\end{align*}
\]

The decarboxylation of acid (19) using Stetter's procedure was also a clean high yielding reaction. This reaction was easily followed by TLC, as the polar acid slowly forms the far less polar furan (20). The methylfuran (20), after work up and subsequent bulb to bulb distillation, was obtained \textit{analytically pure} and in 85%
yield, as a colorless oil. The appearance of a broad singlet at $\delta$ 7.11 (1H) corresponding to the hydrogen on the furan ring in the NMR spectrum and loss of the $-\text{COOH}$ absorptions in the IR spectrum clearly indicated the success of the decarboxylation. Also the 8-methyl group of the furan ring at $\delta$ 2.23 showed a small splitting ($J$=1.5 Hz), due to the newly introduced hydrogen on the furan ring.

Having made the key furan intermediate (20) there was a choice of proceeding by the two routes shown in Scheme 5.
The two routes differ only in the sequence by which the vinyl group and the cis-lactone unit are introduced in the molecule. It was decided to investigate both the routes simultaneously. It had to be shown that the 6-methoxymethyl group of (20) could be converted to a vinyl group.

Several reports in the literature indicate that boron tribromide is the reagent of choice for the demethylation of methyl ethers. When the methyl ether (20) was added to a solution of BBr₃ in dichloromethane at -78°C under nitrogen, allowed to warm up to room temperature and stirred for a few hours, demethylation occurred to give the alcohol (21) in an excellent yield.

This reaction was best followed by TLC. The starting material was slowly converted to the more polar product (21). The alcohol (21) was isolated as a pale yellow gum, homogeneous by TLC. The -OH absorption in the IR spectrum and the disappearance of the -OCH₃ protons in the NMR spectrum indicated that demethylation had occurred to give (21). The NMR spectrum also showed that the rest of the molecule was intact. Accurate mass measurement further confirmed the molecular formula of (21). Thus, a reaction which was expected to present some difficulties, due to the presence of the furan ring and general stability of methyl ethers,
turned out to be one of the cleanest and high yielding reactions in the synthetic sequence.

The alcohol (21) was readily oxidized with pyridinium chlorochromate (PCC) to the aldehyde (22). Corey has reported the use of PCC as a mild and effective oxidising agent for acid sensitive molecules and other groups have also used PCC successfully.

\[
\text{OH} \quad \xrightarrow{\text{PCC, CH}_2\text{Cl}_2} \quad \text{CHO}
\]

(21) \hspace{1cm} (22)

One of the advantages of the use of PCC is the ease of the work-up procedure. Dilution of the reaction mixture with ether, followed by filtration through silica gel gave the pale yellow crystalline aldehyde (22) in 74% yield after evaporation of the solvent. IR (1738 (s) cm\(^{-1}\)) and NMR (δ 9.45, 1 H, s) spectra confirmed the success of the oxidation. The aldehyde (22) was of sufficient purity to be used directly in the next step, and although it appears to be fairly stable, was used immediately in the next step.

It was felt that the Wittig reaction of the aldehyde (22) would be quite selective. Although the molecule (22) has an enone functionality, since it is a vinylogous ester, the Wittig reagent should prefer to attack the much more reactive aldehyde group to give the vinylfuran (7).
When the aldehyde in THF was added rapidly to a solution of triphenylphosphonium methyldide in THF at 0°C, rapid reaction occurred to give the vinylfuran (7). The complete removal of triphenylphosphine oxide from the product was tedious, but after filtration through silica gel and bulb to bulb distillation the vinylfuran (7) was obtained pure in 68% yield. The appearance of the typical vinyl pattern in the NMR spectrum combined with the loss of the aldehyde absorption in the IR spectrum and the presence of the intact enone band clearly supported the structure of (7). The compound (7) was further characterized by accurate mass measurement and elemental analysis. Now it was established that the methoxymethyl group could be converted to a vinyl group in three steps and also the key furan intermediate (7) had been synthesized. The last major problem was the construction of the cis-lactone unit.

Appending the fused γ-lactone ring to (7) or (20) poses no stereochemical problems. It does not matter if alkylation of (7) and (20) produces a mixture of epimers. Indeed, it is desirable, as this should lead finally to a mixture of isolinderalactone (2) and episolinderalactone (4).
Following the procedure of Heathcock the kinetic enolate of (20) was made using lithium diisopropylamide in THF at -70°C and subsequent warming to -20°C. One expected the alkylation of the enolate (23) to be fairly difficult due to the steric hindrance caused by the adjacent quaternary carbon center. Also, examination of molecular models did not show a clear preference of alkylation from any particular face of the enolate (23). The enolate was quenched with excess ethyl bromoacetate at -20°C and warmed to room temperature. Work-up gave (24) as a mixture of epimers (ca 2:1 by NMR) at C-6 with some starting material (~25%).

The excess alkylation agent ethyl bromoacetate was removed under high vacuum. The IR spectrum of the product showed the presence of the newly introduced ester group (1730 (s) cm⁻¹). The NMR spectrum also confirmed the presence of the ethyl ester group and two different quaternary methyl signals corresponding to the two epimers of (24) were seen. A mass measured molecular ion verified the molecular formula of (24).
This reaction has been tried under a number of different conditions, in order to achieve clean and complete alkylation of (20), with no success. Purification of the product (24) proved to be very difficult. Not only were the two epimers of (24) inseparable on TLC, they had surprisingly similar mobility to that of the starting material (20). In fact the only significant difference that was observed on TLC was their color development by the sulphuric acid reagent. The furan (20) gives a purple spot, while the alkylated ester (24) first turns purple, then changes rapidly to black on standing. It was decided to continue with the crude product and achieve purification at the next stage.

The initial attempts to reduce the ketoester (24) with a large excess of sodium borohydride in methanol at room temperature led to some surprising results. It was felt that the -CH₂CO₂Et group should control the stereochemistry of the reduction. Reduction should occur from the face opposite the -CH₂CO₂Et side chain due to steric factors and this should lead to the in situ formation of the lactone (25).

TLC showed the formation of one major product, which was less polar than
the starting material. The lactone (25) would be expected to be
definitely more polar on TLC than the ester (24). The IR and NMR spectra
of the crude product showed the presence of very little desired lactone
(25). The major product (55%) was isolated pure by preparative TLC. The
IR spectrum showed no -OH or lactone absorptions. The NMR spectrum
showed the presence of a AB quartet at δ 3.80 (2 H - corresponds to H_b
of (26)) and a doublet at δ 4.90 (1 H - Ha of (26)). The multiple signals
for the methoxyl groups and quaternary methyl groups indicated the product
to be approximately a 2:1 mixture of epimers. Careful analysis of the
spectral data showed the product to be an epimeric mixture of the over-
reduced lactone derivative (26). The mass measured molecular ion also
confirmed the assigned structure for (26).

Overreduction of the lactone (25) to (26) is surprising, and has
few precedents with sodium borohydride. A plausible mechanism for this
transformation is shown in Scheme 6.
The reduction of the enone (24) with sodium borohydride proceeds quite slowly. This is not surprising, as the enone is in fact a vinylogous ester, and hence the carbonyl group is quite deactivated. Several attempts to achieve the reduction of the ester (24) to the lactone (25) under a variety of conditions led to complex mixtures of products and the formation of (26) as a major by-product was seen on TLC. It was apparent that the lactone (25) had a comparable rate of reduction with sodium borohydride to the enone (24).

The ready formation of (26) in this reaction indicated that the desired stereochemistry of the reduction had been achieved. It is well known from the literature that cis-\(\gamma\)-lactones are formed readily under
the reduction conditions, while the formation of trans-γ-lactones requires more vigorous conditions. In fact, the hydroxy acid precursors of trans-γ-lactones can be usually isolated after the reduction and need fairly strong conditions for the subsequent lactonisation\textsuperscript{55} (eg. TsOH, benzene, reflux or DCC). This is because cis-γ-lactones are more stable than the trans-γ-lactones, and hence, form more easily.

The in situ formation of (26) in the reaction indicated the stereochemistry of the lactone ring to be cis. Confirmation of this shall be possible by comparisons in the end with the natural products.

To overcome the problem of over-reduction, it was decided to perform the sodium borohydride reductions in the presence of sodium hydroxide.\textsuperscript{56} Under these conditions, the reaction would be expected to go through the intermediate keto acid (27). The sodium salt of the hydroxy acid (28) should not undergo any further reduction. Cyclisation to the desired lactone (25) should occur only on the final acid work-up.
This prediction proved to be true. When the keto ester (24) was reduced with sodium borohydride in methanol in the presence of 3N sodium hydroxide an epimeric mixture of the lactones (25) was obtained after the acid work-up. The lactonisation of the hydroxy acid (28) was rapid under the work-up conditions.

\[
\begin{array}{c}
\text{OCH}_3 \\
\text{CO}_2\text{Et}^\text{0}
\end{array}
\xrightarrow{\text{NaBH}_4, \text{3N NaOH}}
\begin{array}{c}
\text{OCH}_3 \\
\text{0}
\end{array}
\]

(24) MeOH, H\textsubscript{2}O 3 days (25) 51%

When the reaction was followed by TLC, rapid formation of a more polar product, the acid (27), was seen. The reduction of the acid (27) to the less polar lactone (25) was slow and took 3 days.

The appearance of a strong absorption in the IR spectrum (1770 cm\textsuperscript{-1}) combined with the loss of the enone and the presence of a broad doublet at \(\delta 5.45\) (1 H, - ring proton \(\alpha\) to the oxygen of the lactone) confirmed the presence of the lactone ring. Multiplet signals in the NMR spectrum for the methoxyl and methyl groups showed (25) to be an epimeric mixture. Mass measurement of the molecular ion further verified the assigned structure of (25). The epimers had identical behavior on TLC and hence could not be separated by chromatography. However, one of the epimeric lactones was sparingly soluble in ether. After trituration with ether, a small quantity of one epimer (13%) was obtained pure (mp. 128\textdegree-130\textdegreeC). The NMR spectrum of this epimer showed a single set of signals for the various protons, attesting to its purity.
The ester (24) has also been successfully hydrolysed to the acid (27) with 3N sodium hydroxide. The acid (27) on reduction gave the lactone (25).

\[
\text{OCH}_3
\]
\[
\text{OCH}_3
\]

Having established the conditions for the construction of the \textit{cis}-lactone unit, one could proceed ahead with the synthesis. The demethylation of the lactone (25) was attempted under identical conditions as those used before with the methyl ether (20). The NMR spectrum of the product showed decomposition of the furan ring. The signals of the furan-H and -CH$_3$ groups were quite weak in the NMR spectrum of the product indicating that the lactone (25) was unstable under the demethylating conditions with boron tribromide. Other attempts to successfully demethylate (25) under different conditions have not proved successful.
Also efforts to synthesize the lactone (33) under rigid stereochanical controls by a completely different route (Scheme 7) proved unsuccessful. The lactone (33) should be a good precursor to isolinideralactone (2) and the proposed route should definitively establish the required stereochemistry. The conversion of (32) to (33) has little
precedence but it was a reaction well worth studying, since little is known about the relative rates of formation and stability of \( \gamma \)- versus \( \delta \)-lactones.

The lactone (30) was readily formed by the demethylation of (24) with BBr\(_3\). Lactonisation occurred in situ. An inseparable mixture of epimeric lactones with some of the demethylated alcohol (21) was formed. The NMR spectrum showed the loss of the ethyl ester group. The multiplet signals in the NMR spectrum and the strong absorption in the IR spectrum at 1740 cm\(^{-1}\) (6-membered lactone) showed in situ cyclisation had occurred to give an epimeric mixture of (30). Mass measurement of the molecular ion further attested to the assigned structure (30).

The preliminary experiments to equilibrate the epimeric mixture of \( \text{cis-} \) and \( \text{trans-} \) lactones (30) to pure \( \text{trans-} \) isomer (31), proved disappointing. The products isolated after stirring (30) with KOtBu in BuOH or NaOMe in MeOH for 24 h. were still epimeric mixtures of \( \text{cis-} \) and \( \text{trans-} \) lactones. No clear preference for one of the isomers could be detected. Also the \( \text{cis-} \) and \( \text{trans-} \) lactones (30) were inseparable on TLC. A study of molecular models of (30) failed to reveal any special thermodynamic preference for either the \( \text{cis} \) or \( \text{trans} \) lactones. At this stage investigations in this area were stopped as they did not appear to be promising.

The conversion of the vinylfuran (9) to the lactones (5a) and (5b) was examined. Since the methodology for the formation of the lactone unit in the case of the methoxymethylfuran ether (20) was already established, this proved to be a simple operation.
Alkylation of (9) with lithium diisopropylamide in THF at -70°C to -20°C and quenching with ethyl bromoacetate gave (6) as a mixture of epimers (ca 1:1 by NMR) at C-6, with traces of starting material.

The excess alkylation agent ethyl bromoacetate was removed by drying in vacuo for several hours. The IR spectrum of the product showed the presence of the newly introduced ester group (1730 cm⁻¹). The NMR spectrum also confirmed the presence of the ethyl ester group and two different quaternary methyl signals (δ 0.95 and 1.13), corresponding to the two epimers of (6) were seen. A mass measurement of the molecular ion verified the molecular formula.
Purification of the product proved to be difficult. The two epimers of (6) did not separate on TLC, and had very similar mobility to that of the starting material (9). It was decided to carry on with the crude product and achieve purification at the next stage.

Reduction of the ester (6) was achieved by using the identical conditions that had been developed previously. The keto ester (6), when treated with sodium borohydride in 3N NaOH/MeOH was reduced slowly (72 h.) via the keto acid (34) to the lactones (5a) and (5b).

The purification of the lactones was achieved by the following extraction procedure during work-up. The basic reaction mixture was diluted first with water and extracted with ether to remove the neutral by-products. The above solution was next cautiously acidified with dil. H₂SO₄ to form the neutral lactones (5a) and (5b) and extracted again with ether. Washing the extracts with a saturated solution of NaHCO₃ removed any unreacted keto acid (34) and other acidic impurities. The lactones (5a) and (5b) were obtained as a pure, pale yellow, oily solid (47% overall yield from (9)) and gave a single spot on TLC.

The IR spectrum showed a strong γ-lactone absorption at 1770 cm⁻¹ and absence of the enone carbonyl. The multiplet signals of the single vinyl proton (CH=CH₂, two quartets) showed the product to be about a 1:1 epimeric mixture of the lactones (5a) and (5b). Surprisingly, no difference was seen in the absorption of the quaternary methyl groups of (5a) and (5b). The NMR spectrum showed a singlet at δ 1.15 (3 H, -CH₃). The mass measured molecular ion further characterised the product. Having made (5a) and (5b) only one step remained for the synthesis of isolinderalactone (2) and epiisolinderalactone (4).
The ester (6) was also hydrolysed to the acid (34), which on reduction under the same conditions gave the lactones (5a and 5b).

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \xrightarrow{3\text{N NaOH}, \text{MeOH, H}_2\text{O}} \quad \text{COOH} \\
\text{CH}_3 & \quad \xrightarrow{\text{NaBH}_4, 3\text{N NaOH}, \text{MeOH, H}_2\text{O}} \quad \text{COOH}
\end{align*}
\]

The mixture of epimeric lactones (5a) and (5b) was treated with lithium diisopropylamide in THF at -70°C followed by Eschenmoser's salt and then slowly warmed to room temperature. The crude Mannich adduct (35) was stirred with methyl iodide in methanol for 1 h, and worked up with a solution of sodium carbonate and dichloromethane to give the α-methylenated lactones (2) and (4).
TLC of the product showed two close running, UV active products along with starting material. After preparative TLC a ~ 1:1 mixture of isolinderalactone (2) and epiisolinderalactone (4) was obtained in 20% yield. TLC comparisons with authentic isolinderalactone (2), kindly supplied by Professor Takeda, established the less polar of the two close running products to be isolinderalactone (2). Identical behavior was observed on UV, I₂ and sulphuric acid baking. The TLC Rf values of synthetic isolinderalactone were identical to those of the authentic (2) in different solvents.

The NMR spectrum of the mixture of products (2) and (4) also established the presence of isolinderalactone (2) and the success of the methylenation. The loss of the protons α- to the lactone carbonyl, and the appearance of the methylene protons in the NMR spectrum were definitive.
The NMR spectrum of the product showed two quaternary methyl singlets at δ 0.97 and 1.19 respectively. The value reported for isolinderalactone (2) is δ 0.98. All the signals reported for isolinderalactone (2) in the literature were seen in the NMR spectrum of the product. A strong absorption for the lactone unit (1759 cm⁻¹) was observed in the IR spectrum. A mass measured molecular ion confirmed the molecular formula of (2) and (4).

Having synthesised (2) and (4), their Cope rearrangement to linderalactone (1) and neolinderalactone (3) was attempted. When the mixture of (2) and (4) was heated at 160°C for 20 min. a clean Cope rearrangement was seen to give a mixture of 3 products, two of which were identified readily as isolinderalactone (2) and linderalactone (1) by comparison with authentic samples. The third product obtained from the conversion of (4) has to be neolinderalactone (3). Thus the preliminary results showed that the total synthesis of (1), (2) and (3) had been achieved.

Also a recent observation has solved the problem of separation of these natural products at the final stage. The mixture of vinyl lactones (5a and 5b), which behave identically on TLC can be easily separated by
use of their solubility characteristics. One of the epimers is very sparingly soluble in ether. On treatment with a small quantity of ether, one of the epimers dissolved readily leaving the other white crystalline epimer behind. Now separation was achieved by simple decantation of the solvent.

Each of the epimers (5a and 5b) was converted to the corresponding methylenated products by use of Danishefskey's procedure described before. Methylation of the white, crystalline epimer (5b) gave epiisolinderalactone (4), whose structure was deduced from the results of its subsequent Cope rearrangement. When epiisolinderalactone (4)
was heated at 160°-165°C for 30 min. it underwent Cope rearrangement to give neolinderalactone (3). TLC studies showed the disappearance of (4) to give one major product. The NMR spectrum of the product compared well with that of authentic neolinderalactone (3) supplied by Prof. Takeda.

The lactone (5a) on methylenation gave a product whose TLC behavior was identical with that of authentic isolinderalactone (2). Also the NMR spectrum of the methylenated product was identical with that of

![Chemical Structure](image)

1) LDA, THF
2) MeI, MeOH
3) NaHCO₃
isolnderalactone (2) reported in the literature. When synthetic isolnderalactone (2) was heated at 160°-165°C for 20 min., it underwent Cope rearrangement to give a mixture of two products, which were readily identified as (2) and (1) by comparison with authentic samples of isolnderalactone (2) and linderalactone (1), respectively. Thus the structure of synthetic isolnderalactone was conclusively established to be the same as that of the natural product.

The X-ray crystal structures of episolnderalactone (4) and neolinderalactone (3) are under investigation.

The above synthesis of (1), (2) and (3) is both short, and direct. The approach, because of its strategy, does not rely upon any stereochemical or regiochemical controls. The approach is quite general and should be applicable to the synthesis of other furanosesquiterpenes. This is the first direct synthesis of any complex germacronolide.
Synthesis of a key intermediate towards vernolepin (Part B)

Vernolepin (1) is a sesquiterpene tumor inhibitor and has been the subject of intense synthetic investigation. Four groups have achieved the total synthesis of this complex molecule and many others have published their approaches towards it.

Retrosynthetic analysis (Scheme 1) suggested (2) has a key synthetic intermediate. It was felt (2) could be made via a intramolecular alkylation of (3). Of course, the alcohol (4) was the obvious precursor to (3) and it became the immediate synthetic target.
The major problem in the synthesis of alcohol (4) was the construction of the quaternary carbon (C-5) carrying the vinyl and hydroxymethyl substituents.

Following the procedure of Bosch et al, 3,5-dimethoxybenzoic acid (5) was reduced with Li in liquid ammonia and the resultant dianion (6) was alkylated with 2-bromoethylphenylsulphide (7) to give the crystalline product (8). Elemental analysis confirmed the molecular formula and the presence of the phenyl and the methylene protons of the sidechain and singlet for the vinyl protons in the NMR spectrum confirmed the assigned structure (8). This alkylation procedure appears to be promising as a general route to angularly substituted ring junctions, a common feature of many naturally occurring polyoxygenated sesquiterpenes. Thus in one step, the problem of creating the quaternary center had been solved.
Great caution had to be exercised during the work-up of the Birch reduction to avoid hydrolysis of the acid sensitive bis-enol ether. The residue after the evaporation of ammonia was dissolved in water at 0°C and extracted once with dichloromethane to isolate neutral by-products. Evaporation of the dichloromethane gave vinylphenyl-sulphide (9), formed by elimination of the alkylating agent (7) under the reaction conditions.

\[
\text{PhSCH}_2\text{CH}_2\text{Br} \xrightarrow{-\text{HBr}} \text{PhS} \equiv 
\]

(9)

The aqueous layer was now cautiously acidified to pH 7 with conc. HCl at 0°C and then further acidified to pH 5.5 with a saturated solution of sodium dihydrogen phosphate before re-extraction with dichloromethane. Under these conditions no hydrolysis of bis-enol ether (8) was observed. The product (8) can be readily recrystallised from ether/pet ether.

The acid (8) was reduced to the alcohol (10) with LAH in THF/ether. Reduction was slow (6 h.), and TLC showed clean conversion to one major product. The new methylene group in the NMR spectrum and IR absorption
for the hydroxyl group confirmed the structure of (10).

The bis-enol ether (10) was converted to the monomethylether (12) in two steps as shown in Scheme 2.

Scheme 2

When (10) was stirred with 2N HCl/MeOH for 2 h., a mixture of (11) and (12) was produced, both considerably more polar than (10) on TLC. Treatment of the mixture with p-TsOH in dry methanol gave a single compound by TLC, readily identifiable as (12) from spectral data; particularly the single vinyl proton (δ 5.32, 1 H, s) and single methoxy group (δ 3.64, s) in the NMR spectrum were definitive.

Preliminary attempts to prepare the sulfoxide (13) from (12) with m-chloroperbenzoic acid gave a mixture of products. However, treatment of (12) with sodium metaperiodate under mild conditions gave a
clean reaction and the sulfoxide (13) was obtained homogeneous by TLC after separation from the polar residue by column chromatography. Although the mass spectrum did not give a parent molecular ion of sufficient intensity for mass measurement, this was considered encouraging for the subsequent sulfoxide elimination to form the vinyl group, especially as a fragment ion near the correct m/e (183) was observed. Little change was seen in the NMR spectrum of (13) in relation to the sulphide (12), except for a downfield shift of the aromatic protons (δ 7.52) due to the enhanced electron withdrawing effect of the sulfoxide compared to the sulfide group. Some line broadening which was observed may have been caused by the creation of a new asymmetric center on converting the sulfide to the chiral sulfoxide.
The thermal elimination of the sulfoxide\textsuperscript{40} to give the vinyl group of (14) required quite high temperatures. Prolonged heating at reflux in toluene gave none of the desired compound (14). However, heating (13) in xylene at reflux gave (14), which was isolated after separation from unreacted sulfoxide, and the polar residue by column chromatography. A mass measurement confirmed the molecular formula of (14) and the NMR spectrum showed a complex set of signals ($\delta$ 4.85-6.00) integrating to four vinyl protons. Other signals in the NMR and the IR spectra showed that the remainder of the molecule was intact.

At this point, a parallel to this work was published by another group. Birch reduction of 3,5-dimethoxybenzoic acid (5) followed by alkylation with 1,2-dibromoethane and elimination to give the vinyl group produced the dione (15) after hydrolysis. No further progress towards vernolepin has been reported by this group.

\[
\begin{align*}
\text{OH} & \\
\text{0} & \\
\text{0} & \\
\text{(15)} & \\
\end{align*}
\]

Schlessinger published his total synthesis of vernolepin, which proceeds through the same intermediate (4), which he made by a different route (6 steps). His success in the intramolecular alkylation of (16) to form (17) totally vindicated the validity of our approach and made it pointless for us to continue our own efforts in this area any further.
(4) \rightarrow \ce{CH3O} (16) \xrightarrow{\text{LiN (SiMe₃)}} \xrightarrow{-40^°C} (17) \xrightarrow{} \text{Vernolepin (1)}
General Experimental Information

All proton NMR spectra were obtained on either a Varian A-60 spectrometer or a Varian EM-360 spectrometer. Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 267 Grating Infrared Spectrophotometer. Elemental analyses were done by M-H-W Laboratories in Phoenix, Arizona. Mass spectral data were obtained on a Consolidated Electronic MS-9 Double Focusing mass spectrometer. Solvents and commercial reagents were distilled and dried by conventional methods before use. Room temperature refers to a temperature range of 22°C to 25°C.
1-Methyl-3,5-dimethoxy-1,4-dihydrobenzoic acid (11)

To anhydrous ammonia (2 l), 3,5-dimethoxybenzoic acid (48 g, 0.264 mol.) was added slowly to give a pale yellow solution. Lithium wire (5 g, 0.714 mol.) was added in small pieces until a persistent blue color was obtained. The solution was stirred for 20 min. and methyl iodide (171 g, 1.2 mol.) added. The ammonia was allowed to evaporate over 18 h.; the residue was treated with water (500 mL) and dichloromethane (500 mL), cooled to 0°C, and cautiously acidified to pH 7 with 12N HCl then further acidified to pH 5.5 with a saturated solution of sodium dihydrogen phosphate. The dichloromethane layer was separated and the solution reextracted with dichloromethane (3x400 mL). The combined dichloromethane extracts were washed with brine, dried (MgSO₄) and the solvent removed in vacuo to give acid (11) (45.4 g, 87%), as a pale yellow crystalline solid. The crude acid (pure by NMR and TLC) was used directly in the reduction, mp. 28-30°C. IR (CHCl₃) 3500-2500, 1700, 1610, 1405, 1155, 1030, 820 cm⁻¹; NMR (CDCl₃ int. TMS) δ 1.40 (3 H, s), 2.78 (2 H, bs), 3.60 (6 H, s), 4.73 (2 H, bs). Mass measured molecular ion: calculated for C₁₀H₁₄O₄ 198.0892; found 198.0895.

1-Methyl-3,5-dimethoxy-1,4-dihydrobenzyl alcohol (12)

To a suspension of lithium aluminum hydride (14 g, 0.368 mol.) in anhydrous ether (700 mL) under nitrogen at 0°C was slowly added a solution of 1-methyl-3,5-dimethoxy-1,4 dihydrobenzoic acid (11) (45 g, 0.227 mol.) in ether (150 mL) over 30 min. The solution was stirred for 16 h.
The reaction was quenched by cautious addition of water (30 mL) at 0°C. The solution was stirred for 1 h., vacuum filtered and the precipitate washed with ether (200 mL). The combined ether extracts were washed with saturated sodium bicarbonate solution (100 mL), and brine (100 mL), dried (MgSO₄) and the solvent removed in vacuo to give the known alcohol (12), as a white crystalline solid. The alcohol (12), pure by NMR and TLC (6:3,pet ether:ethyl acetate), was directly used in the next step. mp 48-52°C. IR (film) 3400, 2950, 1660, 1690, 1610, 1450, 1040 cm⁻¹; NMR (CDCl₃ int. TMS) δ 1.08 (3 H, s), 2.75 (2 H, s), 3.30 (2 H, bs), 3.58 (6 H, s), 4.38 (2 H, s).

1-Methyl-1-methoxymethyl-1,4-dihydrobenzene (16)

To a mechanically stirred suspension of sodium hydride (9.3 g, 0.388 mol.) in dry THF (100 mL) under nitrogen at 0°C was added 1-methyl-3,5-dimethoxy-1,4-dihydrobenzyl alcohol (12) (34 g, 0.185 mol.) in THF (125 mL). The solution was allowed to warm up to room temperature and stirred for 3 h. To the above pale yellow solution was added iodomethane (182 g, 1.28 mol.) and the mixture heated at reflux for 72 h. Two more additions of iodomethane (2x46 g) were made after 24 and 48 h. The mixture was cautiously diluted with water (250 mL) and extracted with ether (3x250 mL). The ether extracts were washed with water (200 mL), brine (100 mL), dried (MgSO₄), and the solvent removed in vacuo to yield the methyl ether (16) (34.8 g, 95%), as a colorless oil. The methyl ether (16) (homogeneous by TLC 6:3 pet ether (60-110, C):ethyl acetate) was immediately hydrolysed to the β-diketone (17). IR (film) 1695, 1664, 1205, 950, 905, 825 cm⁻¹; NMR (CDCl₃ int. TMS) δ 1.13 (3 H, s), 2.73 (2 H, bs), 3.10 (2 H, s), 3.33 (3 H, s), 3.55 (6 H, s), 4.50 (2 H, bs).
To the enolether (16) (37 g, 0.187 mol.) in THF (600 mL) at room temperature was added 4N HCl (370 mL) and stirred for 6 h. The reaction mixture was extracted with ethyl acetate (3x300 mL). The ethyl acetate extract was washed with water (200 mL) and brine (150 mL), dried (MgSO₄) and the solvent was removed in vacuo to yield a viscous colorless oil. Drying overnight in vacuo gave the β-diketone (17) (27.9 g, 88%), as a white crystalline solid. The crude product was washed with a small amount of ether, filtered and dried to give (23.8 g, 75%) the pure β-diketone (17). A small sample was recrystallized from dichloromethane and petroleum ether (60°-110°C). mp. 92-93°C. IR (CHCl₃) 1705, 1610, 1450, 1110 cm⁻¹. NMR (CDCl₃ int. TMS) δ 1.02 (3 H, s), 2.34 (2 H, m), 2.54 (4 H, bs), 3.20 (5 H, s). Mass measured molecular ion: calculated 170.0942; found 170.0946. Analysis calculated for C₉H₁₄O₃: C, 63.50; H, 8.29; found: C, 63.78; H, 8.12.

Ethyl 3,6-dimethyl-4-oxo-6-methoxymethyl-4,5,6,7-tetrahydrobenzofuran-2-carboxylate (18).

The β-diketone (17) (10 g, 0.059 mol.) was added to a solution of potassium hydroxide (3.3 g, 0.059 mol.) in water (120 mL). After 5 min. ethyl 2-chloroacetoacetate (9.8 g, 0.059 mol.) in methanol (30 mL) was added and the reaction was stirred for 72 h. After acidification with 4N HCl, the mixture was extracted with ethyl acetate (3x150 mL.) The combined extracts were washed thoroughly with saturated sodium bicarbonate solution (3x100 mL) and brine (100 mL), dried (MgSO₄), and the
so solvent removed in vacuo to give the furan ester (18) (9.33 g, 57%), as a viscous, colorless oil (homogeneous by TLC 3:1 pet ether:ethyl acetate). The product was directly hydrolysed to the acid (19). IR (film) 2910, 1705, 1680, 1600, 1235, 1120, 1100 cm⁻¹; NMR (CDCl₃ int. CHCl₃) δ 0.94 (3 H, s), 1.23 (3 H, t, J=7 Hz), 2.00-3.10 (4 H, m), 2.40 (3 H, s), 2.08 (2 H, s), 3.20 (3 H, s), 4.22 (2 H, q, J=7 Hz). Mass measured molecular ion: calculated for C₁₅H₁₀O₃ 280.1310; found 280.1317.

3,6-Dimethyl-4-oxo-6-methoxymethyl-4,5,6,7-tetrahydrobenzofuran-2-carboxylic acid (19).

To a solution of the furan ester (18) (10.4 g, 0.037 mol) in methanol (42 mL) and water (16 mL) was added potassium hydroxide (14.5 g, 0.259 mol) and the mixture heated at reflux for 2 h. TLC in petroleum ether 60°-110°C: ethyl acetate (2:1) showed a clean conversion to a single product. The reaction mixture was cooled, diluted with water (80 mL), acidified cautiously with conc. HCl and extracted with ethyl acetate (3 x 25 mL). The ethyl acetate extract was washed with water (50 mL), and brine (50 mL), dried (MgSO₄) and the solvent removed in vacuo to give the furan acid (19) (7.98 g, 85%), as a pale yellow crystalline solid (pure by NMR and TLC). A small sample was recrystallised from ethyl acetate and petroleum ether 35°-60°C (1:2). mp. 140°-142°C. IR (CHCl₃) 3200-2700, 1675, 1455, 1100 cm⁻¹; NMR (CDCl₃ int. CHCl₃) δ 1.10 (3 H, s), 2.10-3.10 (4 H, m), 2.59 (3 H, s), 3.20 (2 H, s), 3.36 (3 H, s), 9.85 (1 H, bs). Mass measured molecular ion: Calculated 252.0997; found 252.1004. Analysis calculated for C₁₅H₁₆O₆: C, 61.90; H, 6.39; found C, 61.95; H, 6.38.
3,6-Dimethyl-4-oxo-6-methoxymethyl-4,5,6,7-tetrahydrobenzofuran (20).

The furan acid (19) (2.6 g, 10.3 mmol) was mixed with diethylene glycol (12.5 mL), copper powder (0.42 g) and dry pyridine (3 mL) and heated at 160°-165°C for 10 h. The reaction was cooled, diluted with water (15 mL) and acidified with 4N HCl (25 mL). The solution was then extracted with ether (3x30 mL). The combined ether extracts were washed with water (2x100 mL), saturated sodium bicarbonate solution (50 mL), and brine (25 mL), dried (MgSO₄), and the solvent removed in vacuo to give a brown oil. Bulb to bulb distillation (110°C at 0.1 mm/Hg) gave the furan (20) (1.83 g, 85%) as an analytically pure, colorless oil. IR (film) 2910, 1674, 1620, 1555, 1420, 1100 cm⁻¹. NMR (CDCl₃ in CH₃Cl₂) δ 1.13 (3 H, s), 2.23 (3 H, d J=1.5 Hz), 2.42 (2 H, q J=16 Hz), 2.81 (2 H, q J=18 Hz), 3.24 (2 H, s), 3.36 (3 H, s), 7.11 (1 H, bs). Mass measured molecular ion: calculated 208.1099; found 208.1104. Analysis calculated for C₁₂H₁₄O₃ C, 69.21; H, 7.74; found C, 69.47; H, 7.90.

3,6-Dimethyl-4-oxo-6-hydroxymethyl-4,5,6,7-tetrahydrobenzofuran (21).

To a solution of boron tribromide (2 mL) in dichloromethane (20 mL) at -70°C under argon was added a solution of the furan methylether (20) (2.0 g, 9.6 mmol) in dichloromethane (15 mL). The mixture was stirred at -70°C for 45 min. and slowly warmed to 0°C (over 45 min.), stirred at 0°-10°C for 2.5 h. and then at room temperature for 3h. The original yellow cloudy solution became clear red. The reaction mixture was carefully diluted with water (25 mL), and extracted with dichloromethane (3x25 mL). The dichloromethane extract was washed with
saturated sodium bicarbonate solution (25 mL), brine (25 mL), dried (MgSO₄) and the solvent was removed \textit{in vacuo} to give the demethylated furan alcohol (21), as a pale yellow gum (1.8 g, 96\%) pure by NMR and TLC (1:2 ethyl acetate : pet ether 60°-110°C). IR (film) 3430, 2930, 1670, 1565, 1050 cm⁻¹; NMR (CDCl₃), NMR (CDCl₃ int. TMS) δ 1.08 (3 H, s), 2.17 (3 H, d J=1.5 Hz), 2.38 (1 H, bs-OH), 2.40 (2 H, q J=16 Hz), 2.79 (2 H, q J=17 Hz), 3.47 (2 H, s), 7.09 (1 H, bs). Mass measured molecular ion: calculated for C₁₁H₁₄O₃ 194.0942; observed 194.0946.

3,6-Dimethyl-4-oxo-6-formyl-4,5,6,7-tetrahydrobenzofuran (22).

To a suspension of pyridinium chlorochromate (2.2 g, 10.2 mmol) in dichloromethane (5 mL) at room temperature was added dropwise the furan alcohol (21) (0.9 g, 5.84 mmol) in dichloromethane (4 mL). The mixture was stirred for 3 h., then diluted with ether (40 mL) and the ether decanted. The sticky black solid residue was washed thoroughly with ether (2x20 mL). The combined ether washings were filtered through a short column of silica gel and washed with additional ether (150 mL). The ether extract was dried (MgSO₄), and the solvent removed \textit{in vacuo} to give the furan aldehyde (22) (0.66 g, 74\%) as a pale yellow solid (mp. 70°-74°C) homogeneous by TLC (1:2 ethyl acetate : pet ether 60°-110°C). The aldehyde (22) was immediately used in the next step with no further purification. IR (CDCl₃) 2720, 1738, 1680, 1565, 1440, 1075 cm⁻¹. NMR (CDCl₃ int. TMS) δ 1.25 (3 H, s), 2.12 (3 H, d J=1.5 Hz), 2.58 (2 H, q J=17 Hz), 2.95 (2 H, q J=17 Hz), 7.03 (1 H, bs), 9.45 (1 H, s).
Mass measured molecular ion: calculated for C_{11}H_{12}O_3 192.0786; found 192.0791.

3,6-Dimethyl-4-oxo-6-vinyl-4,5,6,7-tetrahydrobenzofuran (7)

To a suspension of triphenylmethylphosphonium iodide (2.74 g, 6.77 mmol) in dry THF (10 mL) at 0°C under argon was added dropwise a 1.6 M solution of n-BuLi in hexane (4.2 mL, 6.72 mmol). The salt rapidly dissolved to give a orange red solution. After stirring for 5 min., the aldehyde (22) (1.3 g, 6.77 mmol) in THF (6 mL) was added rapidly. Immediate decoloration occurred and the ice bath was removed and the solution allowed to warm up to room temperature. After 35 min. there was a thick greyish white precipitate and TLC (petroleum ether 60°-110°C:ethyl acetate 3:1) showed no starting material. The reaction mixture was diluted with water (30 mL) and extracted with ether (3x50 mL). The ether extract was filtered through a column of silica gel and washed with additional ether (200 mL). The solution was dried (MgSO₄), and the solvent removed in vacuo to give a yellowish, oily, crystalline solid. The product was now separated from most of the residual triphenylphosphine oxide by washing the crude with a small quantity of a 1:1 ether:petroleum ether mixture. The solvent was removed in vacuo to give a reddish oil, which was purified by bulb to bulb distillation (110°C at 0.5 mm/Hg) to give the vinyl furan (7), as a colorless oil (0.88 g, 68%) pure by NMR and TLC. IR (film) 3090, 2960, 1675, 1436, 1070 and 920 cm⁻¹; NMR (CDCl₃, int. TMS) δ 1.15 (3 H, s), 2.12 (3 H, d, J=1.5 Hz), 2.41 (2 H, d), 2.78 (2 H, d), 4.90 (1 H, d)
J=18 Hz), 4.70-6.0 (3 H, Js 18 Hz, 10 Hz - ABX). Mass measured molecular ion: calculated 190.0993; found 190.0997. Analysis calculated for C_{12}H_{14}O_2: C, 75.76; H, 7.42; found C, 75.55; H, 7.63.

3,6-Dimethyl-4-oxo-5-ethoxycarbonylmethyl-6-vinyl-4,5,6,7-tetrahydrobenzofuran (6)

To a solution of diisopropylamine (0.6 g, 5.9 mmol) in dry THF (3 mL) under argon at 0°C was added dropwise a 1.6 M solution of n-BuLi in hexane (3.8 mL, 6.08 mmol). After 10 min. the mixture was cooled to -70°C. A solution of the vinylfuran (7) (0.88 g, 4.63 mmol) in THF (4 mL) was added slowly over 5 min. The resulting clear yellow solution was stirred at -70°C for 40 min., slowly warmed to -20°C and stirred for 30 min. Ethyl bromoacetate (2.26 g, 13.5 mmol) was added rapidly and the solution was maintained at -20°C for 45 min. and then allowed to warm up to room temperature and stirred for 2 h. Water (20 mL) was added and the mixture extracted with ether (3x25 mL). The combined ether extracts were washed with brine (25 mL), dried (MgSO4) and the solvent removed in vacuo.

The product was dried in vacuo to remove excess ethyl bromoacetate and the alkylated furan (6) obtained as a mixture of epimers ca 1:1 by NMR at C-6 (1.15 g, 90%). Due to difficulties in purification at this step, the crude product was directly used in the next step. IR (film) 3080, 2960, 1730, 1675, 1560, 1425, 920 cm^{-1}. NMR (CDCl3, int. TMS) δ 0.95 (3 H, s), 1.13 (3 H, s)-epimers at C-6, 1.20 (3 H, t J=7 Hz), 2.08 (3 H, d J=1.5 Hz), 2.18-3.18 (5 H, m), 4.08 (2 H, q J=7 Hz), 4.75-6.10 (3 H, m), 7.0 (1 H, bs). Mass measured molecular ion: calculated for C_{12}H_{20}O_4 276.1361; found 276.1368.
(4α,5α)-3,6-dimethyl-4-hydroxy-6-vinyl-4,5,6,7-tetrahydro-5-benzo-furanacetic acid γ-lactone (5a) and (5b)

To a solution of sodium borohydride (0.78 g, 20.5 mmol) in methanol at room temperature was added a solution of 3N sodium hydroxide (5 mL). To this, the crude furan ester (6) (1.15 g, 4.16 mmol) in methanol (7 mL) was added. After 24 h. of stirring at room temperature some more sodium borohydride (.8 g, 21 mmol) was added and the reaction allowed to proceed for 48 h. The reaction was worked up by addition of water (20 mL) and extracted once with ether (20 mL) to remove all neutral impurities. The aqueous layer was cautiously acidified with dil. H₂SO₄, stirred for 10 min. and extracted with ethyl acetate (35+20+20 mL). The combined ethyl acetate extracts were washed with saturated sodium bicarbonate solution (2x20 mL) to remove all acidic impurities, brine (20 mL), dried (MgSO₄) and the solvent was removed in vacuo. After drying in vacuo for a few hours, the mixture of epimeric lactones (5a) and (5b), ca 1:1 was obtained as an oily, pale yellow crystalline solid (0.5 g, 47% from vinylfuran (7), pure by NMR and TLC (1:2 pet ether 60°-110°C : ethyl acetate). IR (CDCl₃) 3080, 2960, 1770, 1638, 1332, 1250, 1170 and 955 cm⁻¹. NMR (CDCl₃ int. TMS) δ 1.09 (3 H, bs), 1.97 (3 H d J=1.2 Hz), 2.10-3.00 (5 H, m), 4.80-5.20 (2 H, m), 5.32 (1 H, bd), 5.48-6.02 (1 H, two quartets), 7.00 (1 H, bs). Mass measured molecular ion: C₁₄H₁₆O₃, 232.1099, found 232.1105. The epimeric mixture of lactones (5a and 5b) was treated with small quantities of ether. The ether layer was separated from the white crystalline residue. The combined ether washings, after removal of the solvent, gave the lactone (5a) (276 mg) as a pale yellow gum. The lactone (5b) (220 mg) was obtained as a solid: mp 137°-141°C.
Preparation of isolarinderalactone (2) and epiisolarinderalactone (4)

To a solution of diisopropylamine (0.1 mL, 0.71 mmol) in THF (1 mL) at 0°C under argon, was added a 1.6 M solution of n-BuLi in hexane (0.47 mL, 0.75 mmol) dropwise. After 10 min. at 0°C, the solution was cooled to -70°C. The epimeric mixture of lactones (5a and 5b) (70 mg, 0.30 mmol) was added dropwise. The near colorless solution turned reddish brown after the addition. After 20 min. at -70°C, the solution was warmed to -40°C (20 min.) and cooled back to -70°C. Eschenmoser's salt (110 mg, 0.54 mmol) was added. After about 25 min., the salt had completely dissolved to give a red clear solution. The solution was allowed to warm up to room temperature. TLC (ethyl acetate : pet ether 1:2) showed the presence of still some residual unreacted starting material. The solution was cooled back to -70°C and one more addition of Eschenmoser's salt (100 mg, 0.54 mmol) was made and then allowed to warm up to room temperature. After 30 min., the mixture was quenched with water (10 mL) and extracted with ethyl acetate (3x10 mL). The combined ethyl acetate extracts were washed with brine, dried (MgSO₄) and the solvent removed in vacuo to give a yellowish gum, which was directly used in the next step.

The Mannich adduct was dissolved in methanol (1 mL) and added excess methyl iodide (1 mL). After stirring for 1 h., the methanol was removed under vacuum and the residue partitioned between saturated sodium bicarbonate solution (10 mL) and dichloromethane (10 mL) and stirred for 10 min. The organic layer was removed and the aqueous
layer reextracted with dichloromethane (2x10 mL). The dichloromethane extract was dried (MgSO₄) and the solvent removed to give a pale yellow semi-crystalline product. The product was purified by preparative TLC on silica gel, using benzene:ethyl acetate 9:1 as eluant. TLC of the isolated material (15 mg, 20%) showed two very close running UV active products, the less polar of which, exhibited identical behavior when compared with an authentic sample of *isolinderalactone* (2). IR of (2) and (4) (CDCl₃) 1759, 1640, 1430, 1258 and 1145 cm⁻¹. NMR (CDCl₃ int. CHCl₃) δ 0.97 (3 H, s - assigned to (2), reported literature value δ 0.98), 1.19 (3 H, s - assigned to (4)), 2.07 (3 H, bs), 2.55-3.20 (3 H, m), 4.85-5.45 (3 H, m), 5.55-6.15 (2 H, m), 6.27 (1 H, m), 7.08 (1 H, bs). Mass measured molecular ion: calculated for C₁₅H₁₆O₃ 244.1099, found 244.1105.

**Cope rearrangement of isolinderalactone (2) and epiisolinderalactone (4)**

The mixture of isolinderalactone (2) and epiisolinderalactone (4) (6 mg) was heated at 160°-165°C for 20 min. under argon. TLC (benzene: ethyl acetate 9:1) showed the disappearance of epiisolinderalactone (4) and appearance of two new Cope rearrangement products along with isolinderalactone (2). Two of the three products were easily identified as linderalactone (1) and isolinderalactone (2) by direct TLC comparisons with authentic samples of (1) and (2) respectively. The third product obtained by the Cope rearrangement of epiisolinderalactone (4) has to be neolinderalactone (3), authentic sample of which was not available.
Preparation of epiisolinderalactone (4) and its Cope rearrangement to neolinderalactone (3).

To a solution of diisopropylamine (0.45 mL, 3.21 mmol) in THF (2 mL) at 0°C under argon was added dropwise a 1.5 M solution of n-BuLi in hexane (2.15 mL, 3.2 mmol). After 10 min. at 0°C, the solution was cooled to -76°C and stirred for another 10 min. The crystalline lactone (5b) (105 mg, 0.45 mmol) in THF (2 mL) was added dropwise. After stirring for 20 min. at -76°C, the solution was warmed to -40°C over 25 min., and then cooled back to -76°C. Eschenmoser's salt (0.53 g, 2.85 mmol), which had been dried prior to use by heating at 80°C at 0.5 mm of Hg for 18 h., was added to the mixture. The solution was stirred at -76°C for 10 min. and then at -42°C for 45 min. The mixture was slowly allowed to warm up to room temperature. The white suspension dissolved to give a reddish clear solution. The mixture was stirred at room temperature for 45 min. The mixture was worked up by addition of water (15 mL) and extraction with ethyl acetate (3x20 mL). The combined ethyl acetate extracts were filtered through a short column of silica gel, dried (MgSO₄) and the solvent was removed in vacuo to give a yellowish gum, which was directly used in the next step.

The Mannich adduct was dissolved in methanol (3 mL) and methyl iodide (6 mL) was added. The mixture was stirred for 18 h. and the solvent removed in vacuo. The residue was partitioned between saturated sodium bicarbonate solution (15 mL) and ethyl acetate (20 mL) and
vigorously stirred for 30 min. The organic layer was removed and more ethyl acetate (20 mL) was added. Vigorous stirring was continued for 30 min. and the ethyl acetate layer once again removed. The mixture was extracted once more in a similar fashion with ethyl acetate (20 mL). The combined organic layers were dried (MgSO₄) and the solvent removed in vacuo to give a gummy solid. The product was purified by preparative TLC on silica gel, using benzene:ethyl acetate 9:1 as eluant. After purification, epiisolinderalactone (15 mg, 14%) was obtained as a gummy solid.

NMR (CDCl₃ int. TMS) δ 1.20 (3 H, s), 2.06 (3 H, d J=1.2 Hz), 2.44-3.24 (3 H, m), 4.84-5.40 (3 H, m), 5.66-6.14 (1 H, m), 5.76 (1 H, d J=1.5 Hz), 6.24 (1 H, d J=1.5 Hz), and 7.06 (1 H, bs).

Epiisolinderalactone (12 mg) was heated at 160°-165°C for 30 min. under argon. TLC analysis (benzene:ethyl acetate 9:1) showed the disappearance of the starting material and formation of a slower running major product. The NMR spectrum of the Cope rearranged product compared well with that of neolinderalactone (3) kindly supplied by Prof. Takeda. An authentic sample of (3) was not available for TLC comparisons.
Preparation of isolinderalactone (2) and its Cope rearrangement to linderalactone (1).

To a solution of diisopropylamine (0.45 mL, 3.21 mmol) in THF (2 mL) at 0°C under argon was added dropwise a 1.5 M solution of n-BuLi in hexane (2.15 mL, 3.2 mmol). After 10 min. at 0°C, the solution was cooled to -76°C and stirred for another 10 min. The crystalline lactone (5b) (107 mg, 0.46 mmol) in THF (2 mL) was added dropwise. After stirring for 20 min. at -76°C, the solution was warmed to -40°C over 25 min., and then cooled back to -76°C. Eschenmoser's salt (0.6 g, 3.26 mmol), which had been dried prior to use by heating at 80°C at 0.5 mm of Hg for 18 h., was added to the mixture. The solution was stirred at -76°C for 10 min. and then at -42°C for 25 min. The mixture was slowly allowed to warm up to room temperature. The white suspension dissolved to give a reddish clear solution. The mixture was stirred at room temperature for 45 min. The mixture was worked up by addition of water (15 mL) and extraction with ethyl acetate (3x20 mL). The combined ethyl acetate extracts were filtered through a short column of silica gel, dried (MgSO₄) and the solvent was removed in vacuo to give a yellowish gum, which was directly used in the next step.

The Mannich adduct was dissolved in methanol (3 mL) and methyl iodide (6 mL) was added. The mixture was stirred for 18 h. and the solvent removed in vacuo. The residue was partitioned between saturated
sodium bicarbonate solution (15 mL) and ethyl acetate (20 mL) and vigorously stirred for 30 min. The organic layer was removed and more ethyl acetate (20 mL) was added. Vigorous stirring was continued for 30 min. and the ethyl acetate layer once again removed. The mixture was extracted once more in a similar fashion with ethyl acetate (20 mL). The combined organic layers were dried (MgSO₄) and the solvent removed in vacuo to give a gummy solid. The product was purified by preparative TLC on silica gel, using benzene:ethyl acetate 9:1 as eluant. After purification, isolinderalactone (38 mg, 34%) was obtained as a gummy solid: NMR (CDCl₃, int. TMS) δ 0.98 (3 H, s), 2.09 (3 H, d J=1.2 Hz), 2.50-2.71 (2 H, m), 2.92-3.12 (1 H, bd), 4.95-5.30 (3 H, m), 5.65 (1 H, d, J=1.5 Hz), 5.68-6.00 (1 H, m), 6.32 (1 H, d, J=1.5 Hz) and 7.12 (1 H, bs).

A small sample (2 mg) of synthetic isolinderalactone (2) was heated at 160°-165°C for 20 min. under argon. TLC (benzene:ethyl acetate 9:1) analysis showed the presence of two products, which were readily identified as (2) and (1) by comparison with authentic samples of linderalactone (2) and linderalactone (1) respectively.
3,6-Dimethyl-4-oxo-6-vinyl-4,5,6,7-tetrahydro-5-benzofuranacetic acid (34)

To the furan ester (6) (76 mg, 0.27 mmol) in methanol (1.5 mL), 3N sodium hydroxide (1.5 mL) was added. After stirring at room temperature for 10 h., the reaction mixture was diluted with water (10 mL) and extracted once with ether (20 mL) to remove all neutral impurities. The aqueous layer was acidified with 4N HCl and extracted with ether (3x10 mL). The combined ether extracts were washed with water (10 mL) and brine (10 mL), dried (MgSO₄) and the solvent removed in vacuo. After drying in vacuo for a few hours, the furan acid (34) was obtained as a pale yellow gum (50 mg, 73%). The product was further purified by preparative TLC on silica gel (ethyl acetate : petroleum ether (60°-110°C) 1 : 2). IR (CHCl₃) 3500-2600, 1710, 1670, 1425, 1250, 925 cm⁻¹. NMR (CDCl₃ int. CHCl₃) δ 1.05 (3 H, s), 1.33 (3 H, s - epimers at C-6 ca:7:15), 2.19 (3 H, d J=1.5 Hz), 2.25-3.25 (5 H, m), 4.80-6.25 (3 H, m - two ABX systems), 7.05 (1 H, bs), 9.95 (1 H, bs). Mass measured molecular ion: C₁₅H₁₄O₄ 248.1048; found 248.1054.

3,6-Dimethyl-4-oxo-5-ethoxycarbonylmethyl-6-methoxymethyl-4,5,6,7-tetrahydrobenzofuran (24)

To a solution of diisopropylamine (0.47 g, 4.6 mmol) in dry THF (3 mL) under nitrogen at -78°C was added a 1.6 M solution of n-BuLi in hexane (3.1 mL, 4.96 mmol). The mixture was warmed to -5°C and cooled back to -78°C. A solution of the furan (20) (0.8 g, 3.85 mmol) in THF (2 mL) was added dropwise. The solution became reddish brown and was maintained at -78°C for 45 min. and then at -20°C for 45 min. The mixture was quenched with
ethylbromoacetate (1.96 g, 11.7 mmol), stirred at -20°C for 45 min., slowly warmed to room temperature and stirred for 2 h. The mixture was diluted with water (25 mL) and extracted with ethyl acetate (3x25 mL). The combined ethyl acetate extracts were washed with brine (30 mL), dried (MgSO₄) and the solvent removed in vacuo. The crude product was dried for several hours in vacuo to remove excess ethylbromoacetate and the furan ester (24) was obtained as a pale yellow oil (1.08 g, 95%), a mixture of epimers at C-6 with traces of starting material. Due to difficulties in purification, the crude was directly used in the next step. IR (film) 2910, 1730, 1675, 1560, 1105, 930 cm⁻¹. NMR (CDCl₃ int. TMS) δ 0.80 (s) and 1.00 (s) - epimers at C-6 (3 H), 1.20 (3 H, t J=7 Hz), 2.06 (3 H, d J=1.5 Hz), 2.25-2.90 (5 H, m), 3.13 (2 H, s), 3.26 (3 H, s), 7.00 (1 H, bs). Mass measured molecular ion: calculated for C₁₆H₂₂O₂ 294.1467; found 294.1473.

3,6-Dimethyl-4-oxo-6-methoxymethyl-4,5,6,7-tetrahydro-5-benzofuran-acetic acid (27)

The furan ester (24) (0.16 g, 0.54 mmol) in methanol (1 mL) was added to a solution of 3N sodium hydroxide (2 mL) in methanol (2 mL). The mixture was stirred at room temperature for 7 h. The mixture was diluted with water (10 mL) and extracted with ether (20 mL) to remove all neutral impurities. The aqueous layer was acidified with 4N HCl and then extracted with ethyl acetate (3x10 mL). The combined ethyl acetate extracts were washed with water (15 mL), brine (15 mL), dried (MgSO₄) and the solvent removed in vacuo to give the furan acid (27) (100 mg, 69% homogeneous on TLC
1:2 ethyl acetate : pet ether 60°-110°C, as a pasty yellow solid. IR (CHCl₃) 3500-2500, 1710, 1675, 1560, 1420, 1105 cm⁻¹; NMR (CDCl₃ int. TMS) δ 0.85 (s), 1.20 (s) (3 H, epimers at C-6 ca 2:1), 2.15 (3 H, d J=1.5 Hz), 2.05-3.05 (5 H, m), 3.10 and 3.25 (2 H, s), 3.20 and 3.35 (3 H, s), 7.05 (1 H, bs), 9.40 (1 H, bs). Mass measured molecular ion: calculated for C₁₄H₁₈O₂ 266.1154; observed 266.1161.

To a large excess of sodium borohydride (0.5 g, 13.2 mmol) in methanol (4 mL) was added a solution of furan ester (24) (0.27 g, 0.92 mmol) in methanol (2 mL). After 6 h. sodium borohydride (0.2 g, 5.3 mmol) was added to ensure complete reaction. TLC showed the formation of one major product. After 7 h. of stirring at room temperature, the reaction was acidified with 4N HCl (5 mL), and extracted with ethyl acetate (3x10 mL). The combined ethyl acetate extracts were washed with saturated sodium bicarbonate solution, brine, dried (MgSO₄) and the solvent removed in vacuo to give the crude product (0.22 g). The major product (0.12 g, 55%) was isolated pure by preparative TLC on silica gel using 1:2 ethyl acetate : petroleum ether (60°-110°C) as eluant. Spectroscopic data clearly showed this to be an epimeric mixture at C₆ of the overreduced, tetrahydrofuranono-derivative (26). IR (CDCl₃) 2910, 1440, 1190, 1100 cm⁻¹; NMR (CDCl₃ int. CHCl₃) δ 1.05 and 1.15 (3 H, s - epimers at C-6 ca 2:1), 1.5-2.6 (5 H, m), 2.05 (3 H, s) 3.15-3.35 (5 H, m), 3.8 (2 H, q), 4.9 (1 H, bd), 7.03 (1 H, bs). Mass measured molecular ion: calculated for C₁₄H₂₀O₃ 236.1412; found 236.1416.
(4α,5α)-3,6-dimethyl-4-hydroxy-6-methoxymethyl-4,5,6,7-tetrahydro-5-
benzofuranacetic acid γ-lactone (25)

To a solution of sodium borohydride (0.14 g, 3.7 mmol) in methanol (4 mL) and 3N sodium hydroxide (2 mL) at room temperature was added the furan ester (24) (0.5 g, 1.7 mmol) in methanol (2 mL). After 30 h. another addition of sodium borohydride (0.14 g, 3.7 mmol) was made. After 72 h. the reaction was diluted with water (5 mL) and extracted once with ether (15 mL) to remove neutral impurities. Then the aqueous layer was acidified with 4N HCl (5 mL), stirred for a few minutes and extracted with ethyl acetate (3x10 mL). The ethyl acetate extract was washed with saturated sodium bicarbonate solution (10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed in vacuo to yield the mixture of epimeric lactones (25) as a pasty yellow solid (0.34 g). The crude lactone was fractionally crystallised from ether to give one of the epimeric lactones as a pure white crystalline solid (58 mg, 13.6%, m.p. 128°-130°C).

The rest of the crude product obtained after the evaporation of the mother liquor was purified by preparative TLC on silica gel using 1:2 ethyl acetate:petroleum ether (60°-110°C). An epimeric mixture of the lactones (25) (160 mg, 38%) was obtained as a pale yellow semi solid. IR (CDCl₃) 2940, 1740, 1645, 1425, 1340, 1175, 1115 and 965 cm⁻¹; NMR for the epimeric mixture (CDCl₃ int. TMS) δ 1.03 and 1.08 (3 H, s epimers at C-6), 2.05 (3 H, d J=1.5 Hz). 2.2-3.0 (5 H, m), 3.15 and 3.20 (2 H, s), 3.30 and 3.35 (3 H, s), 5.45 (1 H, bs), 7.08 (1 H, bs). NMR for isolated pure epimer (CDCl₃ int. TMS) δ 1.10 (3 H, s), 2.03 (3 H, s), 2.25-3.00 (5 H, m), 3.13 (2 H, s), 3.30 (3 H, s), 5.38 (1 H, bd J=7 Hz), 7.08 (1 H, bs).
Mass measured molecular ion: calculated for \( \text{C}_{14}\text{H}_{18}\text{O}_{4} \) 250.1204, found 250.1207.

(4\(\alpha,5\alpha\))-3,6-dimethyl-4-hydroxy-6-methoxymethyl-4,5,6,7-tetrahydro-5-benzofuranacetic acid \( \gamma \)-lactone (25)

To a solution of sodium borohydride (75 mg, 1.97 mmol) in methanol (2 mL) and 3N sodium hydroxide (2 mL) was added the furan acid (27) (85 mg, 0.32 mmol) in methanol (1 mL). After stirring for 24 h. at room temperature sodium borohydride (100 mg, 2.6 mmol) was added and the reaction allowed to proceed for 24 h. The reaction was diluted with water (5 mL) and cautiously acidified with dil HCl and stirred for a few minutes. The mixture was extracted with ethyl acetate (2x10 mL) and the combined ethyl acetate extracts were washed with saturated sodium bicarbonate solution (10 mL), brine (10 mL), dried (MgSO\(_4\)) and the solvent removed in vacuo. The crude was dried in vacuo to give the furan lactone (25) (40 mg, 57\%) as a pale yellow crystalline solid, mixture of epimers at C-6. The IR, NMR and TLC of the product were identical to the lactone (25) made by direct reduction of the furan ester (24).

Attempted demethylation of lactone (25)

To a solution of boron tribromide (0.04 mL, 0.1 g, 0.4 mmol) in dichloromethane at -78°C under nitrogen was added the furan lactone (25) (36 mg, 0.14 mmol) in dichloromethane (1 mL). The solution was stirred at -78°C for 35 min. and then at -5° to 5°C for 1.5 h. The reaction was
quenched by addition of water (10 mL) and extracted with dichloromethane
(2x10 mL). The dichloromethane extract was washed with saturated sodium
bicarbonate solution (10 mL), brine (10 mL), dried (MgSO₄) and the
solvent removed in vacuo to give a gum. Although IR spectrum showed a
hydroxyl absorption, the NMR spectrum showed decomposition of the furan (very
weak signals for the furan-H and -CH₃ group); very little, if any, of
the desired product (29) was obtained.

6-Hydroxymethyl-3,6-dimethyl-4-oxo-4,5,6,7-tetrahydro-5-benzofuran-
acetic acid δ-lactone (30)

To a solution of boron tribromide (0.26 mL, 0.69 g, 2.75 mmol) under
nitrogen at -78°C was added the alkylated furan (24) (0.52 g, 1.77 mmol)
in dichloromethane (4 mL). The red brown solution was stirred at -78°C for
1 h., warmed to 0°C and stirred for 2 h. The reaction was quenched by
addition of water (10 mL) and extracted with dichloromethane (3x15 mL).
The combined dichloromethane extracts were washed with saturated
sodium bicarbonate solution (25 mL), brine (25 mL), dried (MgSO₄)
and the solvent removed to give a viscous oil (0.41 g). NMR and IR spectra
showed the product to be a mixture of the desired epimeric lactones
(30) (~ 70%) and the demethylated furan (21) (~ 30%). Due to difficulty
in purification the mixture was directly used in the preliminary
equilibration experiments. IR (film) 3480, 2920, 1740, 1675, 1425 and
1035 cm⁻¹. NMR (CDCl₃ int. CH₂Cl₂) δ 1.13 (3 H, s of (2D)), 1.16 and
1.33 (3 H, s corresponding to the two epimeric lactones (30)), 2.20
(3 H, d J=1.3 Hz), 2.35-3.1 (m), 3.23 (2 H, s of (21)), 4.10-4.40
(2 H, m), 7.10 (1 H, bs), 7.20 (1 H, bs). Mass measured molecular ion for the lactone (30): C_{13}H_{14}O_{4}, 234.0892; found 234.0897.

Attempted equilibration of epimeric lactones (30) with KOTBu/t-BuOH

To a solution of potassium t-butoxide (0.2 g) in dry t-BuOH (4 mL) was added a solution of the lactone (30) (0.36 g, 1.22 mmol) in t-BuOH (4 mL). The solution was stirred at room temperature for 24 h. The reaction was acidified with 4 N HCl and extracted with ethyl acetate (3x15 mL). The combined ethyl acetate extracts were washed with saturated sodium bicarbonate solution (2x15 mL), brine (20 mL) and dried (MgSO_{4}). After removal of the solvent in vacuo, a viscous oil was obtained which was purified by column chromatography on silica gel using ethyl acetate and pet ether, to give the demethylated furan (21).

The sodium bicarbonate layer was now re-acidified and stirred for a few minutes. It was extracted with ethyl acetate (2x15 mL). The extracts were washed with brine (15 mL), dried (MgSO_{4}) and the solvent removed in vacuo to yield a gum. This was heated at reflux for 18 h. in benzene (2 mL) with p-toluenesulfonic acid (0.1 g) to ensure complete lactonisation. The product was worked up with saturated sodium bicarbonate solution and ethyl acetate. The gum that was obtained was purified by preparative TLC on silica gel (1:1 ethyl acetate:petroleum ether (60°-110°C)). The mixture of epimeric lactones (30) was isolated as a pale yellow gum in a ratio of ca 4:3. The TLC behavior of the epimer epimers was identical and no clear preference for any one was observed after the equilibration. IR (CDCl_{3}) 2920, 1740, 1675, 1555, 1425, 1200, 1135 cm\(^{-1}\). NMR (CDCl_{3} int. TMS) δ 1.08 and 1.20
(3 H, s-epimers), 2.15 (3 H, d J=1.2 Hz), 2.40-3.0 (5 H, m), 4.10 (2 H, dd), 7.15 (1 H, bs). Mass measured molecular ion: calculated for C_{13}H_{14}O_{4} 234.0892; found 234.0897.

Attempted equilibration of epimeric lactones (30) with NaOMe/MeOH

To a solution of sodium (0.1 g, 4.3 mmol) in dry methanol (5 mL, distilled from Mg(OMe)_2) was added the mixture of epimeric lactones (30) 0.2 g, 0.85 mmol) in methanol (2 mL). The solution was stirred for 24 h. under nitrogen. The reaction was acidified with 4N HCl, diluted with water (10 mL) and extracted with ethyl acetate (10x3 mL). The ethyl acetate extract was washed with a saturated sodium bicarbonate solution (15 mL), brine, dried (MgSO_4) and the solvent removed in vacuo to give predominantly the demethylated furan (21). Now the sodium bicarbonate extract was cautiously re-acidified with 4N HCl, stirred for a few minutes and extracted with ethyl acetate (2x15 mL). The combined extracts were dried (MgSO_4) and the solvent removed in vacuo to give the mixture of epimeric lactones (30) (ca 7:5 by NMR). No clear preference for any one epimer was seen.

1-(2-Phenylthio)ethyl-3,5-dimethoxy-1,4-dihydrobenzoic acid (8) - Part B

Ammonia (1 L) was distilled from sodium into a reaction flask fitted with a mechanical stirrer and Dewar condensers and cooled in an acetone/dry ice bath. 3,5-Dimethoxybenzoic acid (25 g, 0.137 mole) was added slowly. Lithium wire (3 g, 0.42 mol.) was added in small portions until a permanent blue color was obtained. To this solution 2-bromoethylphenylsulphide (41.2 g, 0.19 mol.) was added dropwise. The
ammonia was allowed to evaporate over 20 h. The yellow residue was cooled to 0°C and treated with ice cold water (400 mL) and cooled dichloromethane (300 mL). After vigorous stirring, the dichloromethane layer was removed and discarded. The aqueous layer was cooled in an ice bath and treated with dichloromethane (400 mL) and cautiously acidified with a saturated solution of sodium dihydrogen phosphate to pH 5.5. The dichloromethane layer was removed and the solution reextracted twice with dichloromethane (2x300 mL). The combined extracts were dried (MgSO₄) and the solvent removed in vacuo to give a pale yellow crystalline solid. This was washed with a small amount of ether and the acid (8) (22 g, 50%) was obtained as a pure, white crystalline solid. Recrystallisation from petroleum ether (40°-50°C) : ether (1:1) gave 1-(2-phenylthio)ethyl-3,5-dimethoxy-1,4-dihydrobenzoic acid (8) as large prisms. mp 125°-126°C. IR (Nujol) 1700, 1205, 1155, 825, 740 cm⁻¹ ; NMR (CDCl₃, int. TMS) δ 1.78-2.12 (2 H, m), 2.50-3.0 (4 H, m), 3.53 (6 H, s), 4.69 (2 H, s), 7.26 (5 H, bs) : Mass measured molecular ion : calculated 320.1082; found 320.1086. Analysis : calculated for C₁₇H₂₀O₄S : C, 63.73; H, 6.29; S, 10.00; found C, 63.40; H, 6.29; S, 9.97.

Preparation of 1-(2-phenylthio)ethyl-3,5-dimethoxy-1,4-dihydrobenzyl Alcohol (10)

1-(2-phenylthio)ethyl-3,5-dimethoxy-1,4-dihydrobenzoic acid (8) (5.0 g, 15.6 mmol) in dry THF (100 mL) was added slowly to a stirred suspension of LAH (1.21 g, 24.3 mmol) in dry THF (40 mL) at -5°C.
When the initial vigorous evolution of hydrogen ceased, the reaction was allowed to warm up to room temperature, and stirred for 6 h., when no starting acid (8) was observable by TLC in petroleum ether (60°-110°): ethyl acetate : ethanol (12 : 6 : 1). The reaction mixture was poured into saturated aqueous sodium sulphate (250 mL) and ether (250 mL) at 0°C. The ether layer was separated and the aqueous phase extracted with ether (2x150 mL). The combined extracts were dried (anhyd. MgSO₄) and solvent removed to give 1-(2-phenylthio)ethyl-3,5-dimethoxy-1,4-dihydrobenzyl alcohol (10) as a clear, colorless oil, ca 95% pure by TLC (4.2 g, 89%), after drying in vacuo. IR (neat liquid) 3450 (broad), 1650, 1605, 1585, 1400, 1205, 1150, 888, 830, 740, 690 cm⁻¹. NMR (CDCl₃, int. TMS) δ 1.50-1.90 (3 H, m), 2.67-2.95 (4 H, m), 3.32 (2 H, s), 3.56 (6 H, s), 4.26 (2 H, s) and 7.22 (5 H, bs). Mass spectrum, M⁺=306. The product was used without purification in subsequent reactions.

Preparation of 5-(2-phenylthio)ethyl-5-hydroxymethyl-3-methoxy-2-cyclohexen-1-one (12)

1-(2-phenylthio)ethyl-3,5-dimethoxy-1,4-dihydrobenzyl alcohol (10) (4.0 g, 13.1 mmol) was stirred at room temperature with 2M hydrochloric acid (20 mL) and methanol (80 mL). After 2 h. no starting material remained and two lower-Rf hydrolysis products were observed on TLC in petroleum ether (60°-110°C): ethyl acetate : ethanol (6 : 3 : 1). The solution was poured into water (200 mL), extracted with dichloromethane (3x120 mL), the combined extracts washed with water (50 mL) and dried (anhyd. MgSO₄). Solvent was removed to give an oil (3.92 g) which
was dissolved in absolute methanol (75 mL), p-toluenesulphonic acid (ca 15 mg) added, and the solution stirred at room temperature for 90 min. when TLC showed a single compound, all of intermediate (11) having been monomethylated. The solution was poured into dilute aqueous sodium bicarbonate (100 mL), extracted with dichloromethane (4x50 mL), the combined extracts washed with water (40 mL) and dried (anhyd. MgSO₄). Solvent was removed to give 5-(2-phenylthio)ethyl-5-hydroxymethyl-3-methoxy-2-cyclohexen-1-one (12) as a colorless oil (3.14 g, 82%) after drying and sufficiently pure to be directly used in the next step. The product was purified by column chromatography on silica gel using pet ether: ethyl acetate (7:4) as eluant and subsequent bulb to bulb distillation (250°C at .13 mm). IR (neat) 3600, 2930, 1590-1640, 1600, 1375, 1160, and 740 cm⁻¹; NMR (CDCl₃, int. TMS) δ 1.65-2.10 (3 H, m), 2.25-2.50 (4 H, m), 2.75-3.05 (2 H, m), 3.50 (2 H, s), 3.64 (3 H, s), 5.32 (1 H, s) and 7.22 (5 H, bs). Mass measured molecular ion: calculated 292.1133; found 292.1138.

Analysis: C₁₆H₂₀O₃S: C, 65.73; H, 6.88; Found: C, 65.56; H, 6.90.

Preparation of 5-(2-phenylsulphphynl)ethyl-5-hydroxymethyl-3-methoxy-2-cyclohexen-1-one (13)

Sodium metaperiodate (1.20 g, 3.81 mmol) in water (8 mL) was added slowly to 5-(2-phenylthio)ethyl-5-hydroxymethyl-3-methoxy-2-cyclohexen-1-one (12) (1.02 g, 3.49 mmol) in methanol (10 mL) at 0°C. After stirring for 4 h., during which time the reaction was allowed to warm to room temperature, no starting material could be detected by
TLC in petroleum ether (60°-110°: ethyl acetate: ethanol (6: 3: 1). The reaction mixture was diluted with water (50 mL), extracted with dichloromethane (3x30 mL), the combined extracts washed with dilute sodium carbonate solution (20 mL), and water (20 mL), and dried (anhyd. MgSO₄). Solvent was removed to give a pale yellow viscous oil which was purified by column chromatography on silica gel eluting with petroleum ether (40°-50°C): ethyl acetate (20%) to give 5-(2-phenyl sulphonyl)-ethyl-5-hydroxymethyl-3-methoxy-2-cyclohexen-1-one (13) as a colorless oil (0.55 g, 51%) homogeneous by TLC. IR (neat liquid) 3460, 1650, 1610, 1225, 830, 755, 690 cm⁻¹. NMR (CDCl₃ int. TMS) 1.65-2.00 (2 H, m), 2.15-2.45 (4 H, m), 2.70-3.00 (2 H, m) 3.42 (2 H, s), 3.62 (3 H, s), 5.29 (1 H, s), 7.52 (5 H, bs). Mass spectrum M⁺ (308) very weak.

Thermal Elimination of (13) to give 5-hydroxymethyl-5-vinyl-3-methoxy-2-cyclohexene-1-one (14)

5-(2-phenylsulphonyl)ethyl-5-hydroxymethyl-3-methoxy-2-cyclohexene-1-one (13) (0.50 g, 1.62 mmole) was heated at reflux in anhydrous xylene (10 mL) for 8 h., after which time TLC in petroleum ether (60°-110°C): ethyl acetate (3:2) showed almost complete conversion of the sulphoxide to a single new compound. The cool solution was poured into dilute aqueous sodium bicarbonate (40 mL), extracted with dichloromethane (3x30 mL), the combined extracts washed with water (10 mL) and dried (anhyd. MgSO₄). Solvent was removed under reduced pressure at 50°C to give a yellow oil which was purified by column chromatography on silica gel eluting with petroleum ether (60°-110°C): ethyl acetate (0-5%) to give two fractions; a small amount of starting sulphoxide (13)
and 5-hydroxymethyl-5-vinyl-3-methoxy-2-cyclohexen-1-one (14) as a colorless oil (0.12 g, 41%). IR (neat liquid) 3400, 1650, 1605, 1225, 1000, 920, 825 cm⁻¹. NMR (CDCl₃ int. TMS) δ 2.44-2.68 (4 H, m), 3.46-3.67 (2 H, s), 3.67 (3 H, s), 4.85-6.00 (4 H, m). Mass measured molecular ion: calculated for C₁₀H₁₄O₃ 182.0943; found 182.0945.
CHAPTER 3
Review - Chemistry of Allylsilanes

Electron deficient allylsilanes are a hitherto unknown class of compounds. It was decided to examine their chemistry and possible synthetic applications.

In the past decade there has been an explosive growth in organosilicon chemistry. There is growing awareness of the considerable synthetic utility of silicon to the organic chemist and several good reviews attest to this. A complete discussion of the numerous applications of organosilicon chemistry is beyond the scope of this review. Only the chemistry of allylsilanes, a key class of silicon compounds of increasing synthetic interest is discussed.

Atomic Properties of Silicon

To understand the chemistry of silicon compounds, it is important for us to understand the special properties of silicon which make it so interesting to the organic chemist.

Silicon has the outer electronic configuration of $3s^2 3p^2 3d^0$, differing from carbon in its possession of vacant d-orbitals, which can be used to expand the valency as in $SiF_6^{2-}$ or to allow backbonding. The $3p$ orbitals are of too high an energy to give adequate $\pi$ overlap with $2p$ orbitals, so silaethylenes such as ($\text{Si}=\text{CH}_2$) are very unstable.

Silicon's utility in organic synthesis derives from three main factors.
1) **Relative bond strengths**

Silicon bonds to fluorine and oxygen are much stronger than the bonds between carbon and these elements. (Table 1). Such characteristics give rise to a wide range of thermodynamically favorable processes.

<table>
<thead>
<tr>
<th>Bond Strengths</th>
<th>Bond Strengths</th>
</tr>
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<tbody>
<tr>
<td>kcal/mole</td>
<td>kcal/mole</td>
</tr>
<tr>
<td>Si-F 129.3</td>
<td>Si-O 88.2</td>
</tr>
<tr>
<td>C-F 105.4</td>
<td>C-O 84.0</td>
</tr>
<tr>
<td>Si-C 69.3</td>
<td>C-C 83.1</td>
</tr>
<tr>
<td>Si-H 70.4</td>
<td>C-H 98.8</td>
</tr>
</tbody>
</table>

**Vacant d-orbitals**

The vacant d-orbitals of silicon are capable of backbonding with a filled 2p orbital of an adjacent atom of the first row element, enabling silicon to stabilise for example an adjacent carbanion; these orbitals also increase the facility of nucleophilic reactions at the silicon.

**Relative electronegativity**

Silicon has a Pauling electronegativity of 1.8 and carbon has a value of 2.5, making silicon-carbon bonds polarised and therefore susceptible to nucleophilic attack at silicon. This leads to heterolysis

\[
\delta^+ \quad \delta^- \\
Si - C \quad 12\% \text{ polarity}
\]
especially when the carbon fragment being expelled is a good leaving group.

\[
\text{Nu : } \begin{array}{c}
\text{Nu : } \begin{array}{c}
\text{Nu : } \begin{array}{c}
\text{Nu : }
\end{array}
\end{array}
\end{array}
\]

\[
\text{Si-O} \rightarrow \text{C} \rightarrow \text{O}
\]

\[
\text{Nu : } \begin{array}{c}
\text{Nu : } \begin{array}{c}
\text{Nu : } \begin{array}{c}
\text{Nu : }
\end{array}
\end{array}
\end{array}
\]

\[
\text{Si-C-C} \rightarrow \text{C=C}
\]

\[
\text{Si-C} \rightarrow \text{C}\]

Scheme I

**β-Stabilising effect**

The factor that controls most of the electrophilic reactivity of allylsilanes and vinylsilanes, is the β-carbonium ion stabilising effect of silicon. The electropositive nature of silicon results in the observable capacity of a carbon-silicon bond to stabilise a carbonium ion β- to it either by bridging or by hyperconjugation. An elegant example of bridging was reported by Eaborn and Jarvie. They reisolated the starting material from the partial solvolysis of 2-bromo-2,2-dideuterio-1-trimethylsilyl methane (1) and obtained material in which deuterium had been extensively scrambled between C-1 and C-2, consistent with the mechanism involving an anchimerically assisted ionisation of the C-Br bond to give a bridged carbonium ion. (Scheme 2).
The principal evidence for the stabilisation of a β-carbonium ion by a Si-C bond comes from the study of electrophilic aromatic substitution of silylarenes. The Hammett electrophilic para substitution constant for the Me₃SiCH₂- group is -0.66. This closely approximates to the value for the -OMe group viz -0.74 implying that in general terms a Me₃Si group β to a carbonium ion stabilises that ion to about the same extent as does a -OMe group α to it. Under normal conditions of electrophilic aromatic substitution such substitution on silylarenes will take place at the site of the silyl group, even when other substituents do not favor such regiospecificity.
The stabilising effect is also evidenced by the fact that vinylsilanes undergo regiospecific electrophilic substitution and the intermediate carbonium ion rapidly loses the silyl group (Scheme 3).

\[
\begin{align*}
\text{Ph} & \quad \text{SiMe}_3 \quad \xrightarrow{\text{Br}_2} \quad \text{Ph} \quad \text{SiMe}_3 \quad \xrightarrow{\text{MeCOCl}^{12} \quad \text{AlCl}_3} \quad \text{OMe} \\
\text{MeCOCl}^{12} \quad \text{AlCl}_3 & \\
\text{OMe} & \\
\end{align*}
\]

Scheme 3

Clear evidence for the effect of silicon is observed in the cyclization of the olefins (2a) and (2b).

\[
\begin{align*}
\text{R} & \quad \text{OMe} \quad \text{OMe} \quad \xrightarrow{\text{R=SiMe}_3} \quad \text{OMe} \\
\text{OMe} & \\
\end{align*}
\]

(2a) R=SiMe₃  
(2b) R=H

5 products

(3)
When R=SiMe₃ only the alkene (3) was obtained in good yield.

When R=H a mixture of 5 products was obtained.

Another example of the directing effect of silicon in systems can be seen in a preparation of synthetically versatile allyl sulfides by acid catalysed rearrangement of the more accessible β-hydroxyalkyl phenyl sulfides. Here with silicon's assistance, migration from a secondary to a tertiary cationic site is observed (Scheme 4).

\[
\begin{align*}
\text{PhS} & \quad \text{SiMe₃} \\
\text{OH} & \quad + \\
\text{H} & \quad \rightarrow \quad \text{[Nu]} \quad \text{SiMe₃} \\
\text{Ph} & \quad \downarrow \\
\text{PhS} & \quad \rightarrow \quad \text{hv} \\
\end{align*}
\]

Scheme 4

In conclusion, the β-carbonium ion stabilising effect of silicon makes allylsilanes useful synthetic intermediates. Before discussing the reactivity of allylsilanes, let us first consider their methods of preparation and accessibility.
Preparation of allylsilanes.

Allyltrimethylsilane is commercially available. Other substituted allylsilanes can be made by methods with very limited applications; in particular for multifunctional situations.

Silylation of allyl-metal compounds.

The most common way for the preparation of allylsilanes is the silylation of allyl metal compounds. Sommer and Marans\textsuperscript{15} prepared 1-(trimethylsilyl)indene (4) in 55% yield by quenching 1-indenylsodium (prepared by treating indene with sodium) with chlorotrimethylsilane.

\[
\begin{array}{c}
\text{Na,Me}_3\text{SiCl,Et}_2\text{O} \\
r.t \text{ 72 hours}
\end{array}
\]

Fleming\textsuperscript{16} made the allylsilane (6) in 68% yield from the corresponding allyl chlorides (5) in a similar manner.

With symmetrical allyl halides there are no problems but with a unsymmetrical allyl chloride like crotyl (7), Sakurai\textsuperscript{17} obtained a mixture of allylsilanes in 60-90% yield, due to rapid equilibration of the organometallic intermediate (8).
However, Calas has shown when steric factors are very different at the two ends of the allylic anion, one product usually predominates.

Sarkar and Andersen prepared the allylsilane (11) via treatment of the dilithio derivative (10) with chlorotrimethylsilane and hydrolysis of the silyl ether in refluxing methanol and water.
Alkoxide coordination at the allyllithium as shown in (10) appears essential for the facile C-silylation and does not occur when \( n = 2 \) or 3.

**From dienes by hydrosilylation**

Allylsilanes have been prepared from the hydrosilylation of dienes in the presence of various catalysts. Ojima prepared 3-trimethylsilylcyclopentene-1 (13) by hydrosilylation of cyclopentadiene catalyzed by a phosphine-palladium complex. The 1,4 adduct (12) was obtained exclusively and was methylated with methylmagnesium bromide in moderate yields to give 3-TMS-cyclopentene-1 (13).
Wrighton has reported that chromium hexacarbonyl photocatalysed 1,4-hydrosilylation of 1,3-dienes yields allylsilanes in near quantitative yields.

\[
\text{HSiMe}_3 \xrightarrow{\text{cat. Cr (CO)}_6, \text{hv}} \text{SiMe}_3
\]

r.t

Allylsilanes have been also prepared from 1,3-dienes by metal reductions. Calas has found that the action of Li/Me₃SiCl in THF or Mg/Me₃SiCl/HMPT on 1,3-dienes results in 1,4-disilylation.

From Diels-Alder reactions

Fleming has used the Diels-Alder reaction of 1-trimethylsilyl-butadiene with dienophiles for the preparation in moderate yields of allylsilanes. This method however gives mixtures of products with unsymmetrical dienophiles, decreasing its utility. 1-Trimethylsilyl-butadiene (14) reacts with maleic anhydride to give 74% of the allylsilane (15).

\[
\text{SiMe}_3 \xrightarrow{\text{Mg, Me}_3\text{SiCl}} \text{SiMe}_3
\]

\[
\text{SiMe}_3
\]
Fleming has also reported that trimethylsilylcyclopentadiene reacts with dichloroketene at 0°-5°C to give the crystalline adduct (16) in 70% yield. Less reactive ketenes however react to give adducts that are vinyl- and not allylsilanes.

![Chemical structure](image)

**From Wittig reactions**

A method which promises to have wide applications in the incorporation of the allylsilane unit in complicated molecules has been developed by Seyferth. It involves the reactions of \( \beta \)-trimethylsilylethyltribenzylphenylphosphonium salt derived ylids (18) and (20) with aldehydes and ketones. The \( \beta \)-silylsubstituted phosphonium salts (17) and (19) are prepared by the action of iodomethyltrimethylsilane on the corresponding Wittig reagents and they are readily deprotonated with methyllithium to give the ylids.

\[
\text{Ph}_3\text{P=CH}_2 + \text{Me}_3\text{SiCH}_2\text{I} \xrightarrow{\text{r.t.} 12-15 \text{ h.}} \begin{cases} 
\text{Ph}_3\text{P-CH}_2 \\
\text{CH}_2-\text{SiMe}_3
\end{cases}
\]

(17)

\[
\text{CH}_3\text{Li}
\]

(18)
The ylids (18) and (20) react readily with aldehydes and somewhat less well with ketones to give the expected allylsilanes (Scheme 5).

Scheme 5
Other methods

Pillot and Calas\textsuperscript{26} have prepared the allylsilane (21) by the hydrosilylation of $\beta$-pinene with trichlorosilane using azobis (isobutyrionitrile) (AIBN) as initiator, followed by further methylation. The allylsilane (21) was obtained in 70\% yield from $\beta$-pinene.

\[ \text{HSiCl}_3 \xrightarrow{\text{AIBN}} \begin{array}{c} \text{HSiCl}_3 \\ \text{AIBN} \end{array} \xrightarrow{48 \ \text{h., reflux}} \]

1) MeMgCl, Et\textsubscript{2}O
2) H\textsubscript{3}O\textsuperscript{+}

\[
\begin{array}{c}
\text{SiCl}_3 \\
\text{SiMe}_3
\end{array}
\]

(21)

The ene reaction of N-sulfinyl benzenesulfonamide (PhSO\textsubscript{2}NSO) has been used by Calas\textsuperscript{26} in the synthesis of terpenylsilanes.
In conclusion, although several methods exist for the synthesis of allylsilanes, most of them are limited in their applications. Incorporation of the allylsilane unit into complicated molecules in an effective manner, and the synthesis of substituted allylsilanes remains a difficult operation.

Reactions of allylsilanes

Electrophilic chemistry:

 Allylsilanes undergo regiospecific electrophilic attack, the electrophile bonding to the $\gamma$-carbon atom, which results in a net shift of the position of the double bond (Scheme 6). Attack at the $\gamma$-position by an electrophile results in a cation stabilised by the $\beta$-silicon.

$\text{E}^+ \rightarrow [\text{E}^+\underset{\text{SiMe}_3}{}] \rightarrow \text{E}$

Scheme 6
This specific property of allylsilanes has made them useful synthetic intermediates in several transformations. A large number of electrophiles have been successfully reacted with allylsilanes.

Carbon electrophiles

The chemistry of allylsilanes with a large array of carbon electrophiles has been studied. Allylsilanes can be induced to transfer the allyl group readily to several electrophiles in the presence of Lewis acids. Some of the electrophiles that have been reacted with allylsilanes are acid chlorides, ketones, enones, and quinones. The Lewis acids that have been most frequently used as catalysts are TiCl₄, SnCl₄ and AlCl₃. The solvent of choice for these reactions is dichloromethane. Allylsilanes are reactive species and most of the reactions are best performed at -78° to 0°C. The Lewis acids in general coordinate with the electrophilic component increasing their electrophilicity and hence facilitating ready attack by the nucleophilic allylsilanes.

Pillot and Calas used the selective acylation in high yield at the more hindered site of the allylsilane (22) to give artemesia ketone (23), whereas the corresponding Grignard reagent is silylated at the less hindered end.

\[
\begin{align*}
\text{OCCl} + \text{SiMe}_3 & \xrightarrow{\text{AlCl}_3, -60°C} \text{O} \\
(22) & \quad 90% 
\end{align*}
\]
Sakurai has reacted allylsilanes successfully with ketones, enones, quinones and ketals. The allylsilane (24) when treated with an equimolar amount of acetone in the presence of TiCl₄ afforded the adduct (25) in 45% yield.

\[
\text{Me}_3\text{Si}\quad  \underset{\text{CH}_2\text{Cl}_2, \text{r.t}, 30 \text{ sec.}}{\xrightarrow{\text{TiCl}_4}} \quad \text{Me}_3\text{Si}\quad \text{CH}_2\text{Cl}_2, \text{r.t}, 30 \text{ sec.}
\]

(24)  (25)

Allyltrimethylsilane undergoes 1,4 addition to enones in the presence of TiCl₄ as the Lewis acid. In such a transformation a quaternary allyl group that can be further modified, has been introduced in the bicyclic enone (26).

\[
\text{Me}_3\text{Si} \quad \underset{\text{TiCl}_4}{\xrightarrow{\text{CH}_2\text{Cl}_2, -30^\circ \text{C}}}
\]

It has been found that treatment of allylsilanes with various quinones activated by a Lewis acid in dichloromethane produces the corresponding allylsubstituted hydroquinones and/or p-allylquinols in moderate yield. Although the type of the product depends on the substrate employed, the reaction is quite general.
In a nice illustration of the versatility of allylsilane chemistry, Ojima et al. have studied the reaction of 3-TMS-1-cyclopentene with aldehydes, ketones, α,β-unsaturated ketones, α-keto-esters, and acyl-chlorides in the presence of TiCl₄. The yields of the expected adducts are good to moderate. (Scheme 7).
Fleming\textsuperscript{32} has found that allylsilanes when treated with ethylene oxide and tertiary halides in the presence of TiCl\textsubscript{4} give the expected adducts shown below. It is important to note that alkylation of allyl-lithium derivatives is not so highly regioselective\textsuperscript{33} and is not possible at all using tertiary halides.

\[ \text{SiMe}_3 \text{CO} + \text{TiCl}_4 \xrightarrow{\Delta} \text{C}_8\text{H}_{18} \text{OH} \]

\[ \text{SiMe}_3 \text{CO} + \text{TiCl}_4 \xrightarrow{R-X, \text{TiCl}_4} \text{C}_8\text{H}_8 \text{R} \quad 83-98\% \]

R=t-Bu

The allyltrimethylsilane,\textsuperscript{34} (28) when treated with chlorosulfonyl isocyanate gave the adduct (29) which can be further modified.

\[ \text{SiMe}_3 \xrightarrow{\text{CISO}_2\text{NCO}} \text{CCl}_4, 0^\circ\text{C} \quad 30\text{ min.} \]

\[ \text{SiMe}_3 \xrightarrow{0^\circ\text{C}} \text{pyridine} \]

(28) (29)
An advantage of using allylsilane rather than allylmetal compounds is that they are relatively unreactive in a wide variety of reaction conditions, yet quite reactive when treated with an electrophile capable of attacking the olefin. This is most vividly demonstrated in a synthesis of loganin by Fleming where an allylsilane survived a sequence of seven reactions from (30) to (31) intact, but cleanly reacts with the electrophile chlorosulfonyl isocyanate to give (32).

\[ \text{loganin} \]
Fleming has also converted the allylsilane (30) to a known prostaglandin intermediate (33) of the A and F series.

![Chemical reaction diagram]

Sarkar and Anderson have reported a facile intramolecular cyclization of the allylsilyl aldehyde (34) and showed evidence for a non-concerted process. The cyclization can be effected with SnCl₄ or BF₃·Et₂O and gives a mixture of the alcohols (35) and (36).

![Chemical reaction diagram]

total yield 78%
**F-catalysed reactions of allylsilanes**

Chemoselective allylation of carbonyl compounds with allylsilanes promoted by catalytic amounts of tetra-n-butylammonium fluoride has been reported. Nitriles, esters and epoxides do not react with this reagent even on prolonged heating and this permits selective alkylation at the keto group. The ketoester (37) reacts with allyltrimethylsilane in presence of catalytic (n-Bu)_4NF to give the lactone (38).

\[
\text{Me}_3\text{Si} + \overset{\theta}{\text{CH}}\text{C}-\text{CH}_2-\text{CH}_2\text{CO}_2\text{CH}_3 \rightarrow \overset{\theta}{\text{CH}}\text{C}-\text{CH}_2-\text{CH}_2\text{CO}_2\text{CH}_3
\]

With alkyl-substituted allylsilanes allylation of the carbonyl group occurs favorably at the less substituted carbon end of the allylic group.

\[
\overset{\theta}{\text{SiMe}} + \overset{\theta}{\text{CH}}\text{C} + \overset{\theta}{\text{n-But}}_4\text{NF} \rightarrow \overset{\theta}{\text{Ph}}\text{CH}_2\text{C}_3\text{H}_3\text{H} \overset{\theta}{\text{OH}}
\]
This method of allylation is carried out under very mild and neutral conditions and is complementary to the reported allylation via allylsilane-Lewis acid in acidic media.

With electrophiles other than carbon

Fleming has demonstrated the wide range of electrophiles that can be reacted with allylsilanes to give useful synthetic intermediates. The allylsilane (39) and its simple derivatives (40) and (41) have been reacted successfully with acids to give protodesilylation, and peracids to give the allyl alcohol (43).

Treatment of the allylsilane (41) with PhSBF₄ gives the allylsulfide (44) which can be further transformed to the allyl alcohol (45) using Evan's procedure.
Protodesilylation is a facile reaction of allylsilanes and several acids and even basic conditions have been used to achieve this transformation. In a recent paper Fleming reported that $\text{BF}_3|\text{AcOH}$ is an excellent reagent for this transformation.

$$\text{BF}_3|\text{AcOH} \quad 5 \text{ min.}$$

87%

The epoxidation of simple allylsilanes is not a straightforward reaction. The $\beta,\gamma$-epoxysilanes are not readily isolable intermediates and may lead to rearranged products (Scheme 8).

![Scheme 8](image)
Ene reactions of allylsilanes

The ene reaction of allyltrimethylsilane with some common enophiles has been studied by Laporterie, Dubac and Lestre. These reactions occur with transfer of hydrogen and not silicon. Allyltrimethylsilane on treatment with maleic anhydride at 200°C under pressure gave ~ 35% of the cis- and trans-adducts (46).

\[
\begin{align*}
\text{Me}_3\text{Si} & + \text{O} & \rightarrow \text{Me}_3\text{Si} & + \text{O} \\
(46)
\end{align*}
\]

Diethyl diazodicarboxylate reacts more readily at 100°C at atmospheric pressure with allyltrimethylsilane to give a mixture of the cis- and trans-adducts (47).

\[
\begin{align*}
\text{Me}_3\text{Si} & + \text{EtOOC} & \rightarrow \text{Me}_3\text{Si} & + \text{EtOOC} \\
6:4 & \text{ cis : trans} \\
(47)
\end{align*}
\]

N-Phenyl-1,2,4-triazoline-3,5-dione reacts in quantitative yields at 20°C in benzene with allyltrimethylsilane to give the urazole adduct (48). The geometry of the double bond in (48) has not been established convincingly but it is probably cis \( (J_{CH=CH} = 14 \text{ Hz}) \). In general, nitrogen enophiles are far more reactive with allylsilanes than carbon enophiles.
The reaction of 1-silacyclopent-3-ene with several enophiles has been studied. 1-Silacyclopent-3-ene (49) reacts with PhSO₂NSO, a highly reactive enophile to give the adduct (50), which can be easily reduced to the thiol (51).

\[
\begin{align*}
\text{Me}_3\text{Si} & + \overset{\text{PhSO}_2\text{NSO}}{\text{PhSO}_2\text{NSO}} \\
\text{Me} & \quad \text{Me} \quad \overset{\text{Me}}{\text{Si}} \\
(49) & \rightarrow \quad \text{Me} \quad \text{Me} \quad \text{Si} \quad \overset{\text{HN}}{\text{N}} \\
\end{align*}
\]

The silacyclopentene (52) reacts with N-phenyl-1,2,4-triazoline-3,5-dione to give exclusively the adduct (53).
No reports have been published on the regiochemical outcome of ene reactions with substituted and unsymmetrical allylsilanes. In fact only the reactivity of allyltrimethylsilane which can react by only one pathway has been explored.

**Allylsilane anions**

The first report of the successful deprotonation and reaction of allylsilane anions was by Corriu and Masse. Treatment of allylsilane (54) and (55) with n-BuLi in the presence of TMEDA resulted in the formation of the allylsilane anion (56) or (57) respectively. They also made the corresponding Grignard reagent (58) by treatment of the allylsilane (55) with NBS and reaction of the resulting bromide with magnesium.
Both the lithioallylsilane (57) and the allyl Grignard (58) react with various electrophiles. The site of attack by an electrophile depends on the electrophile and the metal. The lithium species (57) reacts readily with Me₃SiCl to give exclusively the product of β-attack in about 95% yield. It was found that the lithium anion (57) prefers β attack while the Grignard (58) prefers α-attack. The results of the treatment of (57) and (58) with various electrophiles are summarised in Scheme 9.

Scheme 9
Chan\textsuperscript{43} has reported that allyltrimethylsilane anion gives regioselective $\alpha$-attack with ketones and aldehydes in the presence of magnesium bromide and HMPA at $-78^\circ\text{C}$ (Scheme 10).

\[
\begin{array}{c}
\text{SiMe}_3\underset{\text{HMPA, } -78^\circ\text{C}}{\text{t-BuLi}}\rightarrow\text{Li}^+\text{SiMe}_3 \\
\end{array}
\]

Scheme 10

Magnus and Ehlinger\textsuperscript{44} have reported a new $\beta$-acylcarbanion equivalent based on allyltrimethylsilane chemistry. The allylanion (54) reacts readily with ketones and aldehydes to give $\delta$-hydroxyvinylsilanes which can be readily converted to $\gamma$-lactols and $\gamma$-lactones.

\[
\begin{array}{c}
\text{Me}_3\text{Si}\underset{-78^\circ\text{C} \rightarrow -40^\circ\text{C}}{\text{s-BuLi, THF}}\text{Me}_3\text{Si} \\
\text{OH}^\text{-BuLi, THF} \\
\end{array}
\]

1) MCPBA, CH\textsubscript{2}Cl\textsubscript{2}, 0°C

2) BF\textsubscript{3}.OEt\textsubscript{2}-MeOH

\[
\begin{array}{c}
\text{CH}_3\text{C-O-OH, CH}_3\text{COOH} \\
\text{conc. } \text{H}_2\text{SO}_4 \\
\end{array}
\]
In conclusion, allylsilanes are continuing to grow in importance as useful reagents and convenient synthetic intermediates for key transformations.
CHAPTER 4

Discussion

Electron deficient allylsilanes of the type (1) are a class unknown compounds. At present no methodology exists for their preparation. The preparation of substituted allylsilanes remains a difficult operation. In continuation of our group's research in organosilicon chemistry, it was decided to examine the chemistry of electron deficient allylsilanes and their possible synthetic applications.

\[
\begin{align*}
\text{R}(\text{1}) & \quad X = \text{CN, CO}_2\text{Et or other electron}\nonumber \\
\text{R} & \quad \text{SiMe}_3
\end{align*}
\]

While the electrophilic chemistry of simple allylsilanes has been extensively investigated, very little is known of the effect of an \(\alpha\)-electron withdrawing substituent on their electrophilic reactivity (Scheme 1).

When \(X=\text{H or an alkyl group, allylsilanes react with electrophiles to give products of the type (4). The intermediate carbonium ion (3) is stabilised by the \(\beta\)-silicon and energetically the whole transformation is favorable. But if } X=\text{CN or CO}_2\text{Et or any other electron withdrawing group the situation is quite different. The intermediate carbonium}\nonumber
ion (3) should be destabilised by the α-electron withdrawing substituent while stabilised by the β-trimethylsilyl group. No data are available on such relative substituent effects on the reactivity of allylsilanes. A transformation of the type shown in Scheme 1 is not facile when X is an electron withdrawing group but would be very useful if achieved. The intention at the outset was two-fold.

1) To develop a general synthetic route to electron deficient allylsilanes of the type (1) and to study their chemistry.

2) Application of their electrophilic chemistry to develop a functionality present in several natural products, specifically the acrylate unit. A large number of naturally occurring compounds contain acrylate units and related groups.
Ambrosic acid

Damsinic acid (6)

At present, there are no good methods for the generation of such functionality from the corresponding cyclic ketones. Both Marshall in his synthesis of costic acid (5) and Wender in his synthesis of damsinic acid (6) have used multistep procedures to achieve such transformations. It was felt a method based on allylsilane chemistry could efficiently solve this problem.

The transformations seen in Scheme 2 were the immediate synthetic goal.
First, one needed reagents that could generate in one step the
electron deficient allylsilanes (7) and (8). The obvious way to achieve
such a transformation is to use a suitably substituted Wittig reagent.
It is known that alkylidene triphenylphosphoranes react poorly with cyclo-
hexanone due to substantial enolisation. It has been found that Wittig-
Horner reagents are more nucleophilic and give substantially better
yields of the olefin products. It was decided to develop a suitably
substituted Wittig-Horner reagent which would react with ketones to
give allylsilanes of the type (7) and (8).

Only a few examples are known for the condensation of α-substituted
triethylphosphonoacetates. The reagent (9) made by the alkylation of
diethoxyphosphonoacetate is commercially available and reacts with a
wide variety of ketones to form tetrasubstituted acrylates in good
yields (40-85%).

Triethylphosphonoacetate was readily deprotonated (NaH/glyme) and
alkylated with iodomethyltrimethylsilane (50°C, 16 h.) to give the
reagent (10), as a colorless, pure liquid (56% after distillation).
The alkylation was found to be fairly slow and proceeded best at around 50°C. NMR (δ 0.15, 9 H, s) and IR (1250 cm⁻¹ (s), 850 cm⁻¹ (s)) spectra showed the successful incorporation of silicon in the molecule. The reagent (10) was completely characterised. Attempts to synthesize the methyl analog (11) using similar conditions met with no success. The NMR spectrum of the product showed no incorporation of silicon and loss of the methyl group. It was clear that the methyl ester was too labile to the iodide ion that is generated in this reaction leading to degradation.

The reagent (13) was prepared by the alkylation of cyanomethyl-diethylphosphonate (12). The anion from (12) proved to be quite reactive and was readily alkylated with iodomethyltrimethylsilane at room temperature over 24 h. The reagent (13) was obtained as a pure colorless oil after distillation (70%).

Having successfully made the reagents (10) and (13), their reactivity with cyclic ketones was examined. The phosphonate (10) when added to a suspension of sodium hydride in glyme at r.t. underwent deprotonation. The reaction was stirred until all the effervescence ceased and quenched with distilled cyclohexanone and allowed to proceed for 16 h. TLC (8:1 pet ether:ethyl acetate) showed the formation of a fast running UV active product. The α,β-unsaturated ester (14) would be expected to be strongly UV active on TLC. However, the reaction was not clean and TLC
showed presence of other undesired products and also the phosphonate (10), which can arise due to enolization of the cyclohexanone. The long reaction time indicated the lack of reactivity of the carbanion derived from the reagent (10), possibly due to its bulk and stability. The allylsilane (14) was obtained in a modest yield of 42% after fractional distillation. IR spectrum (1710 cm$^{-1}$) showed the presence of the α,β-unsaturated ester functionality in the molecule.

The silylphosphonate (10) was also treated under similar conditions with norcamphor, cyclopentanone and β-tetralone. While TLC, NMR, IR and mass spectral data indicated the presence of some of the desired allylsilanes in the crude product of these reactions, the yields were undoubtedly poor. Complex mixtures of undesired by-products, the desired allylsilane and the phosphonate (10) were formed. The reagent (10) proved in general to be fairly unreactive. An attempt to use zinc as a counter-ion to decrease enolisation only managed to further reduce the reactivity of (10) and led to very little of the desired allylsilane product (14).

\[
\begin{align*}
(\mathrm{EtO})_2P & \quad \text{COOEt} \\
\text{SiMe}_3 & \quad \stackrel{1) \text{NaH, glyme}}{\longrightarrow} \\
(10) & \quad \text{COOEt} \\
\text{SiMe}_3 & \quad \stackrel{2) \text{ZnCl}_2}{\longrightarrow} \\
(14) & \quad \text{COOEt} \\
\end{align*}
\]

The cyanophosphonate (13) proved to be far more reactive. It was deprotonated with NaH in glyme at room temperature. The phosphonate carbanion (15) reacted rapidly when cyclopentanone was added. A thick gum formed immediately and the reaction was complete in 30 min. by TLC.
As the product is strongly UV active, the reaction could be easily monitored. Cyclohexanone when reacted similarly with (15) gave the allylsilane (17). The allylsilane products (16) and (17) were easily purified by fractional distillation under vacuum. The IR (2210 cm\(^{-1}\)) spectrum showed the presence of a \(\alpha,\beta\)-unsaturated nitrile functionality in these molecules.

The route for the preparation of electron deficient allylsilanes had been established. Their electrophilic chemistry was now examined. The prototropic desilylation\(^{32,38}\) of these allylsilanes should generate the desired acrylic acid functionality (Scheme 1).

The allylsilane (14) was heated at reflux in benzene with p-toluene-sulphonic acid for 4 h. with no change. Compound (14) was recovered unchanged (NMR and TLC) after heating at reflux for 3 h. in CF\(_3\)COOH (Scheme 3).
The cyanoallylsilane (16) also proved to be stable under a variety of acid conditions (Scheme 4).

The results clearly showed, that the -CN and -COOEt groups completely govern the reactivity rather lack of reactivity of these allylsilanes. The development of a positive charge to these electron withdrawing groups is energetically too unfavorable. The β-carbonium ion stabilising ability of silicon is quite weak in relation to these groups. Electron deficient allylsilanes of the type (14) and (16) hence are quite stable to electrophilic attack, even under harsh conditions.

The reduction of the allylsilane (14) to the alcohol (18) posed no problems. This reaction was easily followed by TLC, as the UV active spot corresponding to the starting material slowly disappeared to give
a slower running UV-inactive spot. Appearance of an alcohol absorption in the IR spectrum with the disappearance of the ester absorption confirmed the formation of the alcohol.

\[
\text{COOEt} \xrightarrow{\text{LAH}} \text{Et}_2\text{O at } 0^\circ\text{C, } 2 \text{ h.} \xrightarrow{\text{(18) } 81\%} \text{OH}
\]

As the allylsilane alcohol (18) has no destabilising \(\alpha\)-electron withdrawing substituent, this compound was expected to show the usual electrophilic reactivity of allylsilanes. The prototropic desilylation of the alcohol (18) to give (19) was attempted under a variety of conditions. The allylsilane (18) proved to very labile and extensive polymerisation occurred under the different conditions that were tried for the protodesilylation (Scheme 5).

\[
\text{Polymer} \xrightarrow{\text{CF}_3\text{COOH, } 0^\circ\text{C, } 1 \text{ h.}} \text{Polymer} \xrightarrow{\text{BF}_3\text{Et}_2\text{O, } 0^\circ\text{C}} \xrightarrow{\text{CH}_2\text{Cl}_2, 5 \text{ min.}} \text{Polymer}
\]

\[
\text{Polymer} \xrightarrow{\text{TsOH, } C_6\text{H}_6 \text{ reflux}} \xrightarrow{\text{TsOH, } 0^\circ\text{C}} \text{OH} + \text{Polymer}
\]
When the allylsilane alcohol (18) was treated with BF₃·Et₂O in CH₂Cl₂ or CF₃COOH, or heated at reflux in benzene containing p-toluene-sulfonic acid decomposition occurred. The NMR spectrum showed loss of silicon and no vinylic protons. Of the variety of conditions that were tried, p-toluenesulphonic acid at 0°C proved to be most effective and gave a low yield of the desired allylic alcohol (19). The allylsilane (18) was stable to TsOH at -78°C. When stirred for 2 h. at 0°C with 0.5 eq of TsOH·H₂O in benzene, TLC showed formation of a slow running product and disappearance of the starting material. The NMR spectrum of the product showed loss of silicon and the presence of some of the desired product\(^{36} (19) \quad \delta 4.10 (2 \text{ H}, \text{ d } J=8 \text{ Hz} - \text{vinylic protons, } \delta 4.10 (2 \text{ H}, \text{ s-CH₂OH}). \text{ However, predominantly polymeric material was obtained. An attempt to isolate the allylic alcohol (19) pure by preparative TLC on silica gel resulted in its decomposition. The acid sensitivity of the allylsilane (18) is due to the fact is is also an allylic alcohol. Protonation of the product occurs readily as it results in a tertiary carbonium ion (20) which is also stabilised by the β-OH group. Both the starting substrate (18) and the product (19) are very acid sensitive and it is not surprising that extensive polymerisation occurred under mild reaction conditions.
Having met with little success with the protodesilylation of the allylsilane (18), it was decided to try protected derivatives.

The acetate (21) was easily formed when the alcohol (18) was heated at reflux with acetic anhydride in pyridine for 1 h. TLC showed clean conversion of the slow running alcohol to the faster running acetate derivative. After purification by column chromatography the acetate (21) was obtained as a colorless oil (62%).

Attempts to protodesilylate the allylsilane (21) to give the allylic acetate (22) met with no success. The NMR spectrum of the products showed loss of the acetate group, no vinylic protons, and also loss of silicon.

At this point, it was apparent that acidic conditions to achieve the desired protodesilylation were not effective. The electron deficient allylsilanes were extremely stable to acids while the allylsilane alcohol (18) and its acetate derivative (21) were too labile!

Neutral conditions to achieve the protodesilylation were tried. It is known that simple allylsilanes undergo desilylation with \((n-Bu)_4N^+F^-\).
in refluxing THF while they are stable to potassium fluoride. Cesium fluoride in dimethyl sulfoxide has been reported to be an excellent desilylating agent although its use with allylsilanes has not been reported. Cesium fluoride is commercially available and is far less hygroscopic than tetra-n-butylammonium fluoride, and hence more convenient to handle.

The carboethoxyallylsilane (14) in DMSO reacted with anhydrous cesium fluoride (1.1 eq.) when heated at 100°C for 1 h. No reaction was observed at room temperature. TLC showed clean conversion to a slightly more polar product. The NMR spectrum of the product showed desilylation had occurred. But the absence of vinyl protons and the appearance of a sharp singlet at δ 1.75 (3 H, allylic-CH₃) indicated that simple desilylation had been achieved to give (23). No rearranged products were seen.

\[
\text{[Diagram: Reaction of (14) with CsF, DMSO under heating]}\]

\[
(14) \xrightarrow{\text{CsF, DMSO, 100°C, 1 h.}} (23)
\]

The allylsilanes (18) and (21) also underwent clean desilylation on heating with cesium fluoride (1.1 eq.) in DMSO at ~100°C to give (24) and (25) respectively. The cyanoallylsilane (16) underwent ready desilylation on stirring with cesium fluoride at room temperature for 6 h to give (26) (Table 1). Cyclohexylallylsilane (27) when heated in a sealed NMR tube with cesium fluoride in D₆-DMSO at 100°C underwent desilylation to give ethylidencyclohexane (28). An NMR spectrum run directly on the reaction mixture showed desilylation and a quartet at δ 5.10 (1 H, J=6 Hz)
<table>
<thead>
<tr>
<th>Allylsilane</th>
<th>Products</th>
<th>Isolated Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="14" alt="Image" /></td>
<td><img src="23" alt="Image" /></td>
<td>77%</td>
</tr>
<tr>
<td><img src="18" alt="Image" /></td>
<td><img src="24" alt="Image" /></td>
<td>71%</td>
</tr>
<tr>
<td><img src="21" alt="Image" /></td>
<td><img src="25" alt="Image" /></td>
<td>78%</td>
</tr>
<tr>
<td><img src="16" alt="Image" /></td>
<td><img src="26" alt="Image" /></td>
<td>83%</td>
</tr>
<tr>
<td><img src="27" alt="Image" /></td>
<td><img src="28" alt="Image" /></td>
<td>NO RXN after 6 h. at 90°C.</td>
</tr>
<tr>
<td><img src="45" alt="Image" /></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**

Desilylations with CSF/DMSO
corresponding to the vinylic proton of ethylidene cyclohexane (28). In comparison the starting material (27) exhibits a triplet at δ 5.04 (1 H, J=8 Hz) in its NMR spectrum.

In order to determine whether the reaction was catalytic with CsF, the cyanoallylsilane (16) was heated at 90°C with 0.1 eq. of CsF for 5 h. TLC and NMR spectrum of the product showed near complete desilylation had occurred to give (26). The reaction was found to be catalytic with CsF in DMSO.

The first step in the mechanism is probably the displacement of silicon by F to give an allylic carbanionic species of the type (29).

\[
\text{COOEt} \quad \text{SiMe}_3 \quad \text{F} \quad \xrightarrow{\text{H}^+} \quad \text{COOEt} \quad \text{Cs} \quad \text{H}^+ \\
\text{CH}_3-S-\text{CH}_3 + \text{Me}_3\text{SiF} \quad \rightarrow \quad \text{CH}_3-S-\text{CH}_3 + \text{F} + \text{O-SiMe}_3
\]

The allylic carbanion (29) prefers to react through its primary site and proton abstraction possibly from the solvent leads to the product (23). The fluoride ion could be regenerated by the reaction of DMSO on Me₃SiF, making the reaction catalytic.
It was hoped that CsF in acetic acid would achieve the desired protodesilylation, reasoning on a simultaneous push-pull mechanism (Scheme 6).

When the allylsilanes (14) and (21) were heated with CsF (1.1 eq.) in glacial acetic acid at 95°C for 3 h., there was no change. Addition of DMSO at this point and further heating for 16 h. caused no desilylation and the starting material was recovered unchanged. This showed that the conditions for the desilylation with CsF were quite specific. Desilylation did not occur in the presence of AcOH. CsF is effective only in pure DMSO, a polar solvent in which it is sufficiently soluble to be reactive.
The epoxidation of the allylsilanes\textsuperscript{38,39} (18) and (21) under different experimental conditions were also examined. Peracetic acid in acetic acid at room temperature appeared to be most effective and the loss of silicon and appearance of vinylic protons in the NMR spectrum showed the formation of some of the desired products (30) and (31).

\[
\begin{array}{c}
\text{OH} \\
\text{SiMe}_3
\end{array}
\xrightarrow{\text{O}}
\begin{array}{c}
\text{OH} \\
\text{OH}
\end{array} \\
\begin{array}{c}
\text{CH}_3\text{C}-\text{O-O-H} \\
\text{CH}_3\text{COH, r.t}
\end{array}
\]

(18) \quad (30)

\[
\begin{array}{c}
\text{OAc} \\
\text{SiMe}_3
\end{array}
\xrightarrow{\text{O}}
\begin{array}{c}
\text{HO} \\
\text{OAc}
\end{array} \\
\begin{array}{c}
\text{CH}_3\text{C}-\text{O-OH} \\
\text{CH}_3\text{COOH, r.t}
\end{array}
\]

(21) \quad (31)

The IR and NMR of spectra of the product from the epoxidation of (18) compared well with that of the known allyl alcohol\textsuperscript{59} (30). However, once again these reactions were accompanied by substantial decomposition. These transformations could not be achieved in a clean, high yielding manner.

The electrophilic chemistry of these allylsilanes proved to be disappointing. The overall synthetic objective (Scheme 1) was not achieved in a meaningful manner. However, methodology was developed to provide access to electron deficient allylsilanes and the effect of \(\alpha\)-electron withdrawing substituents on their reactivity was shown. It was clear from the studies that certain substituents can severely limit the applications of allylsilane chemistry.
It was decided to explore the regiospecificity of the ene reaction of substituted allylsilanes and its application to certain synthetic transformations. This led to the discovery of some other interesting chemistry.

Study of the ene-reactivity of substituted allylsilanes.

Introduction of amine functionality at a tertiary carbon is a difficult synthetic operation.\(^6\) It was decided to investigate the applicability of the ene-reaction of allylsilanes\(^6\) with the potent electrophile N-phenyl-1,2,4-triazoline-3,5-dione (TAD) to introduce nitrogen functionality at a highly substituted carbon atom. While TAD has been used extensively in organic synthesis, and its reaction with allyltrimethylsilane and cyclic allylsilane documented, no studies have described how substituents can effect the regiospecific outcome of ene-reactions between TAD and allylic systems capable of at least two modes of reaction (Scheme 7).

\[\text{(A)} \quad (E=H \text{ or } \text{CN})\]
throughout, \( \text{N NH} \) \( \xrightarrow{\text{PhN}} \) \( \text{N NH} \) \( \equiv \) \( \text{PhN} \) \( \text{O} \) \( \text{N NH} \) \( \equiv \) \( \text{PhN} \) \( \text{O} \) \( \equiv \) \( \text{TAD} \)

Scheme 7

The allylsilane of cyclohexanone (27) was prepared in a one-pot reaction by a slight modification of the Seyferth procedure, which avoided isolation of the intermediate \( \beta \)-trimethylsilylphosphonium salt (32).

Triphenylphosphonium methyldide was alkylated with iodomethyltrimethylsilane at room temperature over 4 h. to give (32). The new phosphonium salt (32) was not isolated but deprotonated by addition of one more equivalent of \( \text{n-BuLi} \) to give a deep red solution of the ylid (33). The ylid (33) was treated with cyclohexanone over 16 h. and after purification by column chromatography the cyclohexylallylsilane (27) was obtained pure and homogeneous by GLC in 59% yield. The same procedure
was used for the formation of adamantylallylsilane (34) in 25% yield after distillation. No efforts have been made to optimize the yields in these reactions. This one pot in-situ procedure has been effectively used for the preparation of several other substituted allylsilanes.

Having now access to several substituted allylsilanes, capable of two modes of reactivity, their reactions with TAD were examined.

When a slight excess of the cyclohexylallylsilane (27) in dichloromethane was added to a solution of TAD in dichloromethane at room temperature, it reacted rapidly.

Rapid decolorisation occurred and the initial deep red TAD solution became pale yellow on completion of the addition, indicating clearly all the triazolinedione had been consumed. After evaporation of the
solvent, the ene adduct (35) was obtained pure in 95% yield. Careful scrutiny of the NMR spectrum showed no traces of any isomeric products.

The compounds (35) and (36) can be easily differentiated by means of NMR. Signals at δ 5.85 (1 H, bs, vinylic proton), 4.70 (1 H, t J=7 Hz, allylic proton α- to nitrogen), 1.15 (2 H, dd, J=7 Hz, allylic protons α to silicon) and 0.05 (9 H, s - SiMe₃) easily identified the adduct to be (35). The TAD-adduct (35) was completely characterised by means of IR, 'H and ¹³C NMR and elemental analysis. As a comparison, ethylidenecyclohexane (28) reacted with TAD (4 h., r.t) to give only the ene adduct (37) in 92% yield. Once again characteristic signals in the NMR left no room for doubt regarding the structure of the adduct (37). The adamantylallylsilane (37), which can only react in mode b gave the adduct (38) in 80% yield. These results are summarised in Table 2.

The cyanoallylsilane (16) reacted slowly with TAD at room temperature over several hours. The absence of any allylic protons and a 1 H vinyl absorption at δ 6.65 in the NMR spectrum easily identified the adduct to be (39).
Table 2
Ene Reaction of TAD with Allylsilanes

<table>
<thead>
<tr>
<th>Allylsilanes</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 27" /></td>
<td><img src="image" alt="Structure 35" /></td>
<td>95%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 28" /></td>
<td><img src="image" alt="Structure 37" /></td>
<td>92%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 34" /></td>
<td><img src="image" alt="Structure 28" /></td>
<td>80%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 16" /></td>
<td><img src="image" alt="Structure 39" /></td>
<td>98%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 17" /></td>
<td><img src="image" alt="Structure 42" /></td>
<td>100%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 40" /></td>
<td><img src="image" alt="Structure 41" /></td>
<td>92%</td>
</tr>
</tbody>
</table>
The IR spectrum (2220 cm\(^{-1}\) - unsaturated nitrile) also verified the structure. For a comparison, the compound (40) obtained as shown in the equation was reacted with TAD to give exclusively (41) in 92% yield. The presence of a vinylic doublet at \(\delta = 6.00\) (J=6 Hz) in the NMR spectrum clearly supported the structure.

These results show when \(E=H\), pathway a is followed and when \(E=CN\) pathway b prevails.

These regiochemical reversals can be rationalized by considering a polar transition state in which TAD removes a hydride ion from the substrate; the two transition states (Scheme 8) are \(T_1\) and \(T_2\). In \(T_1\) there is a build-up of positive charge \(\beta^+\) to the trimethylsilyl group, an energetically favorable situation, leading to the observed products, (35) and (37). The alternative mode would cause a build-up of positive charge \(\alpha^+\) to the trimethylsilyl group. The cyano group completely overwhelms the trimethylsilyl group and the transition state \(T_2\) involves the build-up of positive charge \(\beta^+\) to the cyano...
group and $\alpha$- to the trimethylsilyl group. Furthermore the double bond in mode b remains in conjugation with the cyano group. The alternative mode would produce a build-up of positive charge $\alpha$- to the cyano group; an exceedingly high energy intermediate.

These ene reactions can be easily followed visually by the disappearance of the red color of initial triazolinedione solution. Work-up is simple. Evaporation of the solvent gives the ene adducts in excellent yields. The purification of the ene adducts also proved to be trivial. The crystalline TAD adducts in general were sparingly soluble in ether and after trituration with small quantities of ether the adducts usually were obtained in $> 95\%$ purity and in high yields. The products were easily characterised by means of their NMR and IR spectra. In no cases, were traces of any isomeric products detected. The adducts without the $-\text{CN}$ group, proved to be unstable to mass spectral conditions and gave no $M^+$ peaks. Strong $M^+-15$ peaks,
corresponding to the loss of a methyl group from the molecular ion were obtained. Accurate mass measurements and/or elemental analysis were obtained on all adducts. In the cases of adducts (39), (41) and (42) the NMR spectra suggested the presence of only one isomer, and the exact geometry of the double bonds was not conclusively determined.

In summary, the electron deficient \( \alpha, \beta \) unsaturated cyano compounds (16), (18) and (40) provide, because of electronic reasons, access to the adducts (39), (41) and (42) where a nitrogen functionality has been introduced at a hindered tertiary carbon atom.

Deprotonation of substituted allylsilanes

There are no reports of deprotonation of substituted allylsilanes in literature. The deprotonation of cyclohexylallylsilane (27) under a variety of conditions to give (43) was attempted.

\[
\begin{align*}
\text{(27)} & \quad \rightarrow \quad \text{(43)}
\end{align*}
\]

The reactivity of the resultant allylsilane anion with electrophiles would be of interest, if it specifically occurred either at the \( \alpha \) or \( \gamma \) positions. Several bases have been tried (Scheme 9) to achieve this deprotonation to give (43) with no success. In general, the allylsilane (27) was recovered unchanged.
Treatment of the allylsilane (27) with t-BuLi in HMPA, led to desilylation and its complete decomposition. Very little success has been achieved in the deprotonation of other allylsilanes of the type (44).

The results clearly indicate in these cases, that the protons α- to silicon are not sufficiently acidic to be removed. This shows the weak nature of the ability of silicon to stabilise an adjacent carbanion. The deprotonation of (27) may also be resisted by the fact that the allylic anion (43) is secondary at one end and tertiary at the other.

All these factors combine and make the pKa of the allylsilane (27) sufficiently high, to prevent its deprotonation.

The conclusions are further supported by the observation that the cyanoallylsilane (16) underwent ready deprotonation with LDA and was alkylated with methyl iodide in excellent yields to give exclusively (45).
The cyano group, completely directs the reaction. The ease of deprotonation is clearly due to the strong stabilising effect of the cyano group.

An interesting observation made during these studies was that the cyclohexylallylsilane (27) undergoes ready epoxidation on treatment with MCPBA in CH₂Cl₂ at 0°C. It was surprising to find that a clean
conversion to the easily isoslab β,γ-epoxyallylsilane (46) had
occurred. It has been previously reported that epoxyallylsilanes are
unstable intermediates\(^3\) and not readily isoslab. The structure of
(46) was easily deduced from its NMR spectrum - \(\delta 0.00\) (9 H, s – SiMe\(_3\)),
0.75 (2 H, d, J=7 Hz, protons α to silicon), 2.70 (1 H, t, J=7 Hz,
proton on the epoxide ring). The epoxyallylsilane (46) when treated
with BF\(_3\)\(\cdot\)Et\(_2\)O in methanol gave the alcohol (47).\(^6\)\(^5\) Appearance of
a typical vinyl pattern in the NMR spectrum and -OH absorption in the
IR spectrum supported the conclusions.

In conclusion, the extension of simple allylsilane chemistry to its
substituted derivatives is difficult. All the studies show that
silicon has only a weak directing effect and the nature of other
substituents in the allylsilane makes significant differences in its
reactivity. In fact, attempts to broaden the application of
allylsilane chemistry have proved a trifle disappointing!
General Experimental Information

All proton NMR spectra were obtained on either a Varian A-60 spectrometer or a Varian EM-360 spectrometer. Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 267 Grating Infrared Spectrophotometer. Elemental analyses were done by M-H-W Laboratories in Phoenix, Arizona. Mass spectral data were obtained on a Consolidated Electronic MS-9 Double Focusing mass spectrometer. Solvents and commercial reagents were distilled and dried by conventional methods before use. Room temperature refers to a temperature range of 22°C to 25°C.
Triethyl 2-phosphono-3-trimethylsilylpropionate (10)

To a suspension of sodium hydride (2.64 g, 110 mmol) in dry glyme (20 mL) under nitrogen was added dropwise triethoxyphosphonoacetate (22.6 g, 100 mmol). After stirring for 2 h, iodomethyltrimethylsilane (23.6 g, 110 mmol) was added. The solution was stirred at 50°C for 16 h. The mixture was diluted with water (510 mL) and extracted with ether (3x250 mL). The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo to give the phosphonate reagent (10) (25 g, 81%) as an oil. The crude was distilled in vacuum (bp 104-105°C at 0.35 mm/Hg) to give the pure phosphonate ester (10) (17.3 g, 56%) as a colorless liquid. IR (film) 3460, 2980, 2900, 1735, 1320, 1250, 1025, 965, 850 cm⁻¹. NMR (CDCl₃ int. CHCl₃) δ 0.15 (9 H, s), 0.8-1.3 (11 H, m), 2.3-2.95 (1 H, m), 3.65-4.15 (6 H, quintuplet J=7 Hz). Analysis calculated for C₁₁H₂₇O₅SiP C, 46.43; H, 8.77; found C, 46.36; H, 9.01.

Attempted preparation of methyl diethyl 2-phosphono-3-trimethylsilyl-propionate (11)

To a suspension of sodium hydride (0.14 g, 5.83 mmol) in glyme (2 mL) under nitrogen was added dropwise a solution of methyl diethylphosphonoacetate (1 g, 4.76 mmol) in glyme (1 mL). After stirring at room temperature for 2 h, iodomethyltrimethylsilane (1.2 g, 5.6 mmol) in glyme (1 mL) was added and the mixture heated at reflux for 16 h. The reaction was worked up with saturated ammonium chloride solution and ether. The NMR spectrum showed no desired product (11), loss of methoxyl group and very little silicon incorporation.
(1-Ethoxycarbonyl-2-trimethylsilyl)ethylidene cyclohexane (14).

To a suspension of sodium hydride (0.82 g, 34 mmol) in glyme (10 mL) under nitrogen at room temperature was added the phosphonate reagent (10) (10 g, 32.2 mmol) in glyme (5 mL) in drops. After stirring for 3 h. at room temperature, freshly distilled cyclohexanone (3.17 g, 32 mmol) was added to the above mixture. The reaction was allowed to proceed for 16 h. Water (200 mL) was added and the mixture extracted with ether (3x200 mL). The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo to give the α-ethoxycarbonyl allylsilane (14) (8.6 g). The crude product was fractionally distilled under vacuum to give the pure, desired allylsilane (14) (3.44 g, 42%) as a colorless liquid (bp 94-98°C at 0.5 mm of Hg). IR (film) 2920, 1710, 1630, 1450, 1205, 1150, 850 cm⁻¹. NMR (CHCl₃) δ 0.00 (9 H, s), 1.25 (3 H, t J=7 Hz), 1.55 (6 H, bs), 1.75 (2 H, s), 1.9-2.55 (4 H, envelope), 4.15 (2 H, q J=7 Hz). Mass measured molecular ion: calculated for C₁₄H₂₆O₂Si 245.1701; found 254.1709.

Attempted preparation of (1-ethoxycarbonyl-2-trimethylsilyl)ethylidene cyclohexane (14) using sodium hydride and zinc chloride.

To a suspension of sodium hydride (0.08 g, 3.55 mmol) in glyme (3 mL) was added the phosphonate reagent (10) (1 g, 3.23 mmol) in glyme (2 mL). The mixture was stirred for 1 h. under nitrogen and zinc chloride (0.5 g, 3.7 mmol) was added. All the zinc chloride went into solution giving a pale yellow solution. After 20 min. cyclohexanone (0.38 g, 3.87 mmol) was added in drops and the mixture stirred for 16 h. The mixture was worked up by acidification with 4N HCl and extraction with ether. NMR and TLC comparisons showed that no desired product (14) was present.
(1-Hydroxymethyl-2-trimethylsilyl)ethylidenecyclohexane (18)

To a suspension of lithium aluminum hydride (0.5 g, 13 mmol) in glyme (4 mL) at 0°C under nitrogen was added the ester (14) (2 g, 7.9 mmol) in glyme (1.5 mL) slowly. The solution was stirred at 0°C for 2 h. The mixture was carefully quenched by dropwise addition of water (2 mL). The product was extracted by several additions of ether (total 80 mL) and subsequent decantation of the ether from the solid residue. The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo to give the alcohol (18) (1.36 g, 81%) as a viscous colorless oil. NMR and TLC (8:1 pet ether, 60°-110°C: ethyl acetate) showed the alcohol was sufficiently pure to be used directly in the subsequent steps. The product was fully characterised as its acetate (21). IR for alcohol (18) (neat) 3340, 2860, 1450, 1245, 845 cm⁻¹. NMR (CDCl₃) δ -0.05 (9 H, s), 1.45 (6 H, bs), 1.60 (2 H, s), 2.15 (4 H, envelope), 4.0 (2 H, s).

(1-Acetoxyethyl-2-trimethylsilyl)ethylidenecyclohexane (21)

The alcohol (18) (0.95 g, 4.5 mmol) was dissolved in dry pyridine (3 mL) and acetic anhydride (0.9 g, 8.8 mmol) was added. The mixture was heated to near reflux (ca. 100°C). After 1 h. TLC (1:5 ethyl acetate: pet ether, 60°-110°C) showed clean conversion to a single product. The solution was cooled, diluted with ether (100 mL), washed with 3N H₂SO₄ (50 mL) and saturated sodium bicarbonate solution (20 mL), dried (MgSO₄) and the solvent removed in vacuo to give the acetate (21) (0.9 g, 79%). The
product was purified by column chromatography on silica gel using ethyl acetate and petroleum ether (0-15%) as eluant. The acetate (21) was obtained as a colorless oil (0.7 g, 62%): IR (film) 2930, 2860, 1740, 1450, 1250 and 850 cm\(^{-1}\); NMR (CDCl\(_3\) int. CDCl\(_3\)) \(\delta\) 0.00 (9 H, s), 1.55 (8 H, broad singlet with shoulder at 1.50), 1.95 (3 H, s), 2.05-2.35 (4 H, envelope), 4.45 (2 H, s). Mass measured molecular ion: calculated for C\(_{14}\)H\(_{26}\)O\(_2\)Si 254.1701; found 254.1706.

Diethyl 2-phosphono-3-trimethylsilylpropionitrile (13)

To a suspension of sodium hydride (3 g, 0.12 mol) in glyme (20 mL) under nitrogen at 0°C was added dropwise cyanomethyldiethoxyphosphonate (20 g, 0.11 mol). After stirring for 3 h. at room temperature iodomethyltrimethylsilane (27 g, 0.13 mol) was added and the mixture left at room temperature for 24 h. Water (150 mL) was added and the mixture extracted with ether (3x20 mL). The combined ether extracts were dried (MgSO\(_4\)) and the solvent was removed in vacuo to give the phosphonate reagent (13) (28 g, 94%). The crude product was fractionally distilled under vacuum (bp 111°-112°C at 0.45 mm of Hg) to give the pure phosphonate reagent (13) (20.8 g, 70%) as a colorless liquid. IR (film) 3480, 2960, 1395, 1260, 1030 and 850 cm\(^{-1}\). NMR (CDCl\(_3\)) \(\delta\) 0.05 (9 H, s), 0.95-1.40 (8 H, m), 2.40-3.10 (1 H, m), 3.90-4.40 (4 H, quintuplet). Analysis calculated for C\(_{10}\)H\(_{22}\)O\(_3\)SiPN: C, 45.61; H, 8.42; N, 5.32; found C, 45.42; H, 8.62; N, 5.13.
(l-Cyano-2-trimethylsilyl)ethylidenecyclopentane (16)

To a suspension of sodium hydride (0.95 g, 39.6 mmol) in glyme (10 mL) under nitrogen at 0°C was added dropwise the phosphonate reagent (13) (10 g, 38 mmol) in glyme (7 mL). After stirring for 30 min. at room temperature distilled cyclopentanone (3.25 g, 38.6 mmol) was added. A very thick gum formed immediately after addition of the ketone. After 30 min., the mixture was quenched by addition of water (250 mL), extracted with ether (3x150 mL), dried (MgSO₄) and the solvent was removed in vacuo to give the α-cyanoallylsilane (16) (8.5 g). After vacuum distillation the allylsilane (16) was obtained as a pure, colorless liquid. (4.9 g, 67%, bp. 65°-68°C at 0.25 mm of Hg). IR (film) 2950, 2880, 1635, 1160 and 840 cm⁻¹. NMR (CHCl₃) δ 0.05 (9 H, s), 1.15-1.80 (6 H, m), 2.00-2.70 (4 H, envelope). Mass measured molecular ion: calculated for C₁₅H₁₉NSi 193.1286; found 193.1290.

Attempted protodesilylation of (l-ethoxycarbonyl-2-trimethylsilyl)-ethylidenecyclohexane (14) with p-TsOH.

A solution of allylsilane (14) (0.2 g, 0.79 mmol) in benzene (1 mL) was heated at reflux with p-toluenesulfonic acid monohydrate (0.1 g, 0.79 mmol) for 4 h. The mixture was stirred at room temperature for 16 h, and worked-up with saturated sodium bicarbonate solution and ether. NMR of the product showed it to be mostly unreacted starting material (14) and absence of any vinylic protons clearly indicated that no desired product was present.
Attempted protodesilylation of (1-ethoxycarbonyl-2-trimethylsilyl)-
ethylidene-cyclohexane (14) with trifluoroacetic acid.

A solution of allylsilane (14) (100 mg, 0.43 mmol) in trifluoro-
acetic acid (0.5 mL) was stirred at room temperature for 2 h. No
change was observed on TLC (1:8 ethyl acetate:pet ether). The mixture
was heated at reflux for 3 h. The mixture was worked up with
saturated sodium bicarbonate solution and ether. NMR showed no loss
of silicon and the starting material (14) was recovered unchanged.

Attempted protodesilylation of (1-cyano-2-trimethylsilyl)ethylidene-
cyclopentane (16) with trifluoroacetic acid.

The allylsilane (16) (0.11 g, 0.57 mmol) was heated at reflux in
trifluoroacetic acid (1 mL) for 24 h. The mixture was worked up by
removal of the trifluoroacetic acid in vacuo. NMR and TLC of the
product showed it to be starting material (16).

Attempted protodesilylation of (1-cyano-2-trimethylsilyl)ethylidene-
cyclopentane (16) with TsOH/H₂O

To the allylsilane (16) (105 mg, 0.54 mmol) in xylene (1 mL) was
added p-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmol). The
mixture was heated at 110°C for 24 h. The mixture was worked up with
saturated sodium bicarbonate solution and ether. NMR and TLC of the
product were identical with that of the starting material (16).
Attempted protodesilylation of (1-cyano-2-trimethylsilyl)ethylidene-cyclopentane (16) with dil. sulfuric acid

To the allylsilane (16) (60 mg) in methanol (1 mL) was added 20 drops of 2.3N sulfuric acid. The mixture was stirred at room temperature for a few hours. No change was seen on TLC (8:1 pet ether:ethyl acetate). The reaction was heated at reflux for 3 h. (no change on TLC). To this mixture 7 drops of conc. H₂SO₄ was added and even after heating for a further 16 h. TLC of the reaction product was identical to that of the starting material (16).

Protodesilylation of (1-hydroxymethyl-2-trimethylsilyl)ethylidene-cyclohexane (18) with p-TsOH at 0°C

The allylsilane (18) (0.3 g, 1.4 mmol) in dichloromethane (2 mL) was treated with TsOH.H₂O (0.13 g, 0.68 mmol) at 0°C. The solution was stirred at 0°C for 2.5 h. and TLC (5:1 pet ether 60°-110°C : ethyl acetate) showed no starting material. The reaction was worked up by addition of saturated sodium bicarbonate solution (20 mL) and extracted with dichloromethane (3x20 mL). The combined dichloromethane extracts were dried (MgSO₄) and the solvent removed in vacuo to give a oil. NMR showed loss of silicon, presence of some of the known desired alcohol (19)\(^{46}\) (δ 4.90, 2 H, d J=8 Hz - vinylic protons; δ 4.10, 2 H, s - CH₂OH; IR - 3340 cm\(^{-1}\) - broad - OH) but mostly polymeric material. An attempt to isolate the desired product (19) pure by preparative TLC on silica gel resulted in decomposition.
Attempted protodesilylation of (1-hydroxymethyl-2-trimethylsilyl)-
ethylidenecyclohexane (18) with p-TsOH in refluxing benzene

The allylsilane (18) (150 mg, 0.71 mmol) in benzene (2 mL) was heated
at reflux with TsOH H₂O (0.2 g, 1 mmol) for 2 h. The mixture was worked
up with saturated sodium bicarbonate solution and ether. The NMR spectrum
of the product had no vinylic absorptions and indicated polymerisation
of the starting material had occurred under the reaction conditions.

Attempted protodesilylation of (1-hydroxymethyl-2-trimethylsilyl)-
ethylidenecyclohexane (18) with BF₃·Et₂O

To a solution of the allylsilane (18) (0.1 g, 0.47 mmol) in dichloro-
methane (1 mL) at 0°C was added BF₃·Et₂O (0.12 mL, 0.94 mmol). The
solution became immediately yellowish brown. After stirring for 5 min.
the mixture was quenched with water (10 mL) and extracted with dichloro-
methane (10x2 mL). The dichloromethane extract was dried (MgSO₄) and the
solvent removed in vacuo. The NMR spectrum of the product indicated
that the starting material (18) had decomposed under the reaction conditions.

Attempted protodesilylation of (1-hydroxymethyl-2-trimethylsilyl)-
ethylidenecyclohexane (18) with trifluoroacetic acid.

To the allylsilane (18) (0.1 g, 0.47 mmol), trifluoroacetic acid
(1 mL) was added at 0°C. The solution was stirred for 60 min. and
worked up with saturated sodium bicarbonate solution and ether. The NMR
spectrum of the product had no vinylic absorptions and indicated
polymerisation of the starting material had occurred under the reaction
conditions.
Attempted protodesilylation of (1-acetoxyethyl-2-trimethylsilyl)-
ethyldenecyclohexane (21) with p-toluenesulfonic acid.

The allylsilane (21) (0.1 g, 0.4 mmol) in benzene (1 mL) was stirred
at room temperature with p-toluenesulfonic acid monohydrate (90 mg, 0.45
mmol) for 1 h. No reaction was seen on TLC (8:1 pet ether:ethyl acetate).
The reaction was heated at reflux for 45 min. and worked up with saturated
sodium bicarbonate solution and ether. The NMR spectrum of the product
showed loss of silicon and extensive decomposition of the starting material.

Attempted protodesilylation of (1-acetoxyethyl-2-trimethylsilyl)ethyl-
idenecyclohexane (21) with methanesulfonic acid.

To a solution of the allylsilane (21) (0.1 g, 0.47 mmol) in dichloro-
methane (1 mL) was added two drops of methanesulfonic acid at 0°C. After
45 min. two drops of the acid was added and the mixture was stirred for
45 min. The mixture was worked up with saturated sodium bicarbonate
solution and ether. The NMR spectrum of the product indicated decomposition
of allylsilane (21).

Desilylation of (14) with cesium fluoride to give (1-ethoxycarbonyl)-
ethyldenecyclohexane (23)

To a solution of allylsilane (14) (150 mg., 0.6 mmol) in DMSO (1 mL).
was added anhydrous cesium fluoride (100 mg, 0.65 mmol). TLC (8:1 pet
ether : ethyl acetate) showed unreacted starting material after 45 min.
of stirring at room temperature. The mixture was heated at 100°C for
1 h. and allowed to stir at room temperature for 16 h. It was worked-up by addition of water (80 mL) and extraction with ether (3x25 mL). The ether extract was dried (MgSO₄) and the solvent was removed in vacuo to give the desilylated ester (23) as a pale yellow oil. (83 mg., 77%).

IR (film) 2940, 1715, 1450, 1210, 1110 cm⁻¹. NMR (CDCl₃ int. CHCl₃) δ 1.25 (3 H, t J=7 Hz), 1.55 (6 H, bs), 1.75 (3 H, s), 2.05-2.65 (4 H, envelope), 4.15 (2 H, q J=7 Hz). Mass measured molecular ion: calculated for C₁₁H₁₆O₂ 182.1306; found 182.1309.

Desilylation of (18) with cesium fluoride to give (1-hydroxymethyl)-ethyldienecyclohexane (24)

The allylsilane (18) (150 mg, 0.70 mmol) was dissolved in DMSO (1.5 mL). Anhydrous cesium fluoride (130 mg, 0.85 mmol) was added and the mixture warmed to 95°C over 45 min. The mixture was cooled to room temperature and the solution stirred for 16 h. The mixture was worked up by addition of water (80 mL) and extraction with ether (3x20 mL). The combined ether extracts were dried (MgSO₄) and the solvent was removed in vacuo to give a pale yellow oil. After bulb to bulb distillation, the allyl alcohol (24) was obtained as a colorless oil (70 mg., 71%). IR (film) 3450, 2930, 1450, 1000 cm⁻¹. NMR (CDCl₃ int. CHCl₃) δ 1.50 (6 H, bs), 1.70 (3 H, s), 2.0-2.4 (4 H, envelope), 4.00 (2 H, s). Mass. measured molecular ion: calculated for C₉H₁₆O 140.1201, found 140.1204.
Desilylation of (21) with cesium fluoride to give (1-acetoxyethyl)-
ethylidenecyclohexane (25).

To a solution of the allylsilane (21) (0.1 g, 0.4 mmol) in DMSO
(1 mL) was added anhydrous cesium fluoride (67 mg, 0.44 mmol). The mix-
ture was heated at 100°C for 2 h. TLC (8:1 pet ether (60°-110°C):ethyl
acetate showed clean conversion to a single slow running product. The
mixture was poured into water (60 mL) and extracted with ether (3x15 mL).
The combined ether extracts were washed with brine (10 mL), dried (MgSO₄)
and the solvent removed in vacuo to give the desilylated allylacate
(25) (56 mg, 78%), homogeneous by TLC. IR (film) 2920, 1470, 1450,
1380, 1230 and 1020 cm⁻¹. NMR (CCl₄ int. CHCl₃) δ 1.55 (6 H, bs), 1.70
(3 H, s), 2.00 (3 H, s), 2.10-2.40 (4 H, envelope), 4.55 (2 H, s).
Mass measured molecular ion: calculated for C₁₁H₁₈O₂ 182.1306, found
182.1309.

Desilylation of (16) with cesium fluoroide to give (1-cyano)ethylidene-
cyclopentane (26).

To the allylsilane (16) (0.23 g, 1.2 mmol) in DMSO (1 mL) was added
anhydrous cesium fluoride (0.2 g, 1.31 mmol) and the mixture stirred at
room temperature for 6 h. The mixture was worked up by addition of water
(50 mL) and extraction with ether (3x20 mL). The combined ether extracts
were dried (MgSO₄) and the solvent removed in vacuo to give an oil. The
crude product was bulb to bulb distilled to give (1-cyanoethylidenecyclo-
pentane (26)ab (120 mg, 83%) as a colorless oil. IR (film) 2950, 2220, 1650,
1450, 1055 cm$^{-1}$, NMR (CCl$_4$ int. CHCl$_3$) $\delta$ 1.55-1.90 (7 H, m), 2.10-2.80 (4 H, envelope). Mass measured molecular ion: calculated for C$_6$H$_{11}$N 121.0891, found 121.0894.

Desilylation of (16) with catalytic cesium fluoride to give (1-cyano)-ethyldenecyclopentane (26).

To the allylsilane (16) (0.2 g, 1.0 mmol) in DMSO (1 mL) was added cesium fluoride (15 mg, 0.1 mmol). The solution was heated at 90°C under nitrogen for 5 h. The mixture was worked up as before with water and ether. The NMR spectrum and TLC of the product showed near complete conversion of the allylsilane (16) to (1-cyano)ethyldenecyclopentane (26). Hence the reaction is catalytic with respect to cesium fluoride.

Desilylation of (2-trimethylsilyl)ethyldene)cyclohexane (27) with cesium fluoride

To the allylsilane (27) (0.2 g, 1.1 mmol) dissolved in d$_6$-DMSO (0.5 mL) was added anhydrous cesium fluoride (185 mg., 1.2 mmol). The solution was heated at 100°C under nitrogen for 4 h. An NMR spectrum run directly on the reaction mixture, showed that desilylation had occurred to give the known, commercially available ethyldenecyclohexane.

NMR (d$_6$-DMSO, ext. TMS) 1.40-1.80 (9 H, m), 1.80-2.20 (4 H, bs), 5.10 (1 H, bq J=6 Hz). No attempt was made to isolate the volatile product.
Attempted desilylation of 1-(1-cyano-1-trimethylsilylmethy)ethyl-
cyclopentene (45) with cesium fluoride.

To a solution of the silane (45) (0.1 g, 0.48 mmol) in DMSO (0.5 mL) was added anhydrous cesium fluoride (90 mg, 0.59 mmol). The mixture was heated at 90°C for 6 h. under nitrogen. The mixture was worked up by addition of water and extraction with ether. The NMR spectrum and TLC comparisons of the product clearly showed it to be starting material.

Attempted protodesilylation of (1-acetoxyethyl-2-trimethylsilyl)ethylidenecyclohexane (21) with cesium fluoride in acetic acid.

The allylsilane (21) (0.1 g, 0.4 mmol) was dissolved in glacial acetic acid (1 mL) and anhydrous cesium fluoride (67 mg, 0.44 mmol) was added. After stirring at 50°C for 1 h. no change on TLC (8:1 pet ether: ethyl acetate) was observed. After heating at 90°-95°C for 3 h. TLC still showed only unreacted starting material. DMSO (0.5 mL) was added to the mixture and heating continued at 95°C for 16 h. After work up with saturated starting sodium bicarbonate solution and ether, the starting material was recovered unchanged by NMR and TLC.

Attempted protodesilylation of (1-ethoxycarbonyl-2-trimethylsilyl)-ethylidenecyclohexane (14) with cesium fluoride in acetic acid.

To the allylsilane (14) (0.1 g, 0.4 mmol) in glacial acetic acid (1 mL) was added anhydrous cesium fluoride (70 mg, 0.46 mmol) and the mixture heated at reflux for 2 h. No reaction was seen on TLC (8:1 pet ether: ethyl acetate). DMSO (0.15 mL) was added and the mixture heated at 100°C for for 8 h. After work up with saturated sodium bicarbonate solution
and ether, the starting material was recovered unchanged by NMR and TLC.

Epoxidation of (18) with peracetic acid to give 2-(1-hydroxy)cyclo-
hexylallyl alcohol (30)

To the allylsilane (18) (0.1 g, 0.47 mmol) in glacial acetic acid (1 mL) was added peracetic acid (0.06 mL of a 40% solution, 0.46 mmol) and stirred for 2 h. at room temperature. TLC (1:5 ethyl acetate: petroleum ether) showed one major product with several minor ones. The mixture was worked-up with saturated sodium bicarbonate solution and ether. The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo to give a viscous oil. The NMR spectrum of the product showed loss of silicon and presence of the desired and known 2-(1-hydroxy)-cyclohexylallyl alcohol (30) (ca 50% of the product) along with some polymeric material. IR (film) 3380 broad OH, 2930, 2855, 1640, 1030, 960 and 905 cm⁻¹. NMR (CCl₄ int. CHCl₃) δ 1.40-2.10 (10 H, bs), 3.40 (2 H, bs), 4.23 (2 H, bs), 5.05 (2 H, bs). The NMR and IR spectra of the product compared well with those reported in the literature for the same compound (30).

Epoxidation (21) with peracetic acid to give 2-(1-hydroxy)cyclohexyl-
allyl acetate (31)

To the acetate (0.1 g, 0.39 mmol) in glacial acetic acid (0.5 mL) was added peracetic acid (0.07 mL of a 40% solution, 0.54 mmol) which was saturated with anhydrous sodium acetate prior to use. After 2 h. seven more drops of peracetic acid were added to drive the reaction to
completion. The mixture was worked up after 30 min. with saturated sodium bicarbonate solution and ether. The NMR spectrum showed loss of silicon and that some of the desired product (31) was present—δ 5.25 (2 H, d, vinyl protons), 4.75 (2 H, s –CH₂OAc); IR 3480 cm⁻¹ – broad –OH). Most of the product was however decomposed starting material.

(2-trimethylsilyl)ethylidenecyclohexane (27)

To a suspension of methyltriphenylphosphonium iodide (13.20 g, 32.6 mmol) in dry THF (60 mL) at 0°C under nitrogen was added a 1.6 M solution of n-BuLi in hexane (22.2 mL, 35 mmol). The mixture was stirred for 30 min. at 0°C. To the red orange solution was added iodomethyltrimethylsilylbutane (6.6 g, 35 mmol) in THF (5 mL). The solution was warmed to room temperature and stirred for 4 h. One more equivalent of n-BuLi (22.2 mL, 35 mmol) was added to the mixture at 0°C. A dark red solution resulted, which was stirred at 0°C for 30 min. and quenched by dropwise addition of cyclohexanone (3.52 g, 36 mmol). The solution was now allowed to warm to room temperature slowly and stirred for 16 h. The color was discharged and a thick white precipitate formed. The mixture was worked up by addition of a saturated solution of ammonium chloride (100 mL) and extraction with ether (3x75 mL). The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo. The crude product was chromatographed on silica gel to give the known cyclohexylallylsilane³ (3.5 g., 59%), pure by NMR and GLC (bp. 90°-92°C/17 mm of Hg). IR 3040, 2920, 1450, 1250 and 855 cm⁻¹. NMR (CCl₄ int. CHCl₃)
δ 0.00 (9 H, s), 1.38 (2 H, d J=8 Hz), 1.40-1.67 (6 H, m), 1.88-2.20 (4 H, envelope), 5.04 (1 H, bt J=8 Hz). Mass measured molecular ion: calculated for C11H22Si 182.1490, found 182.1493.

(2-trimethylsilyl)ethylidene-2-adamantane (34).

To a suspension of methyltriphenylphosphonium iodide (6.6 g, 16.3 mmol) in THF (25 mL) at 0°C under nitrogen was added n-BuLi (2.45 M) in hexane (7.34 mL, 18 mmol). After stirring at 0°C for 30 min., iodomethyltrimethysilane (3.3 g, 17.5 mmol) in THF (5 mL) was added to the red orange solution. The mixture was stirred at room temperature for 6 h. and one more equivalent of n-BuLi (7.34 mL, 18 mmol) added at 0°C. After stirring at 0°C for 30 min., adamantanone (2.57 g, 17.1 mmol) was added. The mixture was stirred for 16 h. and then worked up by addition of a saturated solution of ammonium chloride (100 mL) and extracted with ether (3x80 mL). The combined ether extracts were dried (MgSO4) and the solvent removed in vacuo to give an oil. The product was fractionally distilled in vacuum to give the adamantylallylsilane (34) (1 g, 25% bp 98°-103°C at 0.4 mm of Hg). IR (film) 2920, 2860, 1455, 1250, 890 and 860 cm⁻¹. NMR (CDCl3 int. CHCl3) δ 0.10 (9 H, s), 1.48 (2 H, d J=8 Hz), 1.95 (12 H, broad singlet with shoulder at 2.08), 2.28-2.73 (1 H, envelope), 2.73-3.00 (1 H, envelope), 5.13 (1 H, t J=8 Hz). Mass measured molecular ion: calculated for C11H26Si 234.1803, found 234.1816.
**N-phenyl-2-[1-(1-cyclohexen-1-yl)-2-(trimethylsilyl)ethyl]bicarbamimide**

(35)

To a solution of N-phenyl-1,2,4-triazoline-3,5-dione (2 g, 11.4 mmol) in dichloromethane (15 mL) was added dropwise a solution of the cyclohexylallylsilane (27) (2.15 g, 11.8 mmol) in dichloromethane (5 mL). Rapid decolorisation occurred and the red solution became pale yellow on completion of the addition. The solution was stirred for 30 min. diluted with dichloromethane and filtered. The solvent was removed in vacuo to give one adduct of cyclohexylallylsilane (35) (3.9 g, 96%) as a pale yellow crystalline solid. The product was found to be pure and no traces of isomeric by-products were seen in the NMR spectrum.

An analytical sample was prepared by recrystallisation from ethyl acetate and hexane (mp. 147-149°C). IR (nujol) 3260-3060, 2920, 1770, 1690, 1600, 1460, 1380, 850 and 770 cm⁻¹. NMR (CDCl₃ int. TMS) δ 0.05 (9 H, s), 1.15 (2 H, dd J=7 Hz), 1.60 (4 H, bs), 2.05 (4 H, bs), 4.70 (1 H, t J=7 Hz), 5.85 (1 H, bs), 7.50 (5 H, bs), 9.40 (1 H, bs). No parent peak seen in mass spectra. Mass measured M⁺-15 (CH₃): calculated for C₁₉H₂₆N₅O₂Si 342.1637, found 342.1645. Analysis calculated for C₁₉H₂₆N₅O₂Si: C, 63.87; H, 7.61; found C, 63.73; H, 7.63.

**N-phenyl-2-[1-(1-cyclohexen-1-yl)ethyl]bicarbamimide** (37)

To a solution of N-phenyl-1,2,4-triazoline-3,5-dione (0.1 g, 0.57 mmol) in dichloromethane (1 mL) at room temperature was added ethylidene cyclohexane (70 mg, 0.63 mmol) in dichloromethane (1 mL).
The solution was stirred for 4 h. The solvent was removed in vacuo to give a pale yellow crystalline solid (150 mg., 92%). The triazoline-dione adduct (37) was found to be pure by NMR and also no traces of isomeric products seen. mp. 135°-138°C. IR (nujol) 3440, 3140, 2920, 1760, 1695, 1425, 1130, 880, 690 cm⁻¹. NMR (CDCl₃ int. TMS) δ 1.35 (3 H, d J=7 Hz), 1.60 (4 H, bs), 1.95 (4 H, bs), 4.60 (1 H, q J=7 Hz), 5.70 (1 H, bs), 7.45 (5 H, bs), 9.30 (1 H, bs).

N-Phenyl-2-[2-(trimethylsilyl)vinyl]-2-adamantylbicarbamimide (38)

To a solution of N-phenyl-1,2,4-triazoline-3,5-dione (0.42 g, 2.4 mmol) in dichloromethane (3 mL) at room temperature, was added in drops the adamantylallylsilane (34) (0.6 g, 2.56 mmol) in dichloromethane (2 mL). The red color of the solution slowly changed to pale yellow. The mixture was diluted with dichloromethane, filtered and the solvent was removed in vacuo to give a pale yellow solid. After trituration with a small amount of ether the adamantylallylsilane ene adduct (38) was isolated as a pure, white crystalline solid (0.77 g, 80%). No traces of isomeric products were seen in the NMR spectrum.

An analytical sample was prepared by recrystallisation from ethyl acetate. mp. 207°-209°C. IR (nujol) 3170, 3070, 2920, 1760, 1710, 1500, 1420, 1250, 1005 and 840 cm⁻¹. NMR (CDCl₃ int. CH₂Cl₂) δ 0.16 (9 H, s), 1.83-3.00 (14 H, m), 6.13 (2 H, s), 7.43 (5 H, s), 8.73 (1 Hm bs). M⁺-409 (small). Mass measured M⁺-15 (CH₃) calculated for C₂₂H₂₈N₃O₂Si 394.1950, found 394.1955. Analysis calculated for C₂₃H₃₁N₃O₂Si C, 67.44; H, 7.63; found C, 66.96; H, 7.89.

To a solution of N-phenyl-1,2,4-triazolene-3,5-dione (0.2 g, 1.14 mmol) in dichloromethane (2 mL) at room temperature was added the allylsilane (16) (0.23 g, 1.19 mmol) in dichloromethane (1 mL). The mixture was stirred for 16 h. The solvent was removed in vacuo to give the ene adduct (39) (0.41 g, 98%), as a pure, pale yellow solid. No traces of isomeric products were seen in the NMR spectrum.

An analytical sample was prepared by recrystallisation from ether, mp. 127°-128°C (white needles). IR (nujol) 3140, 1770, 1705, 1495, —ı 1440, 1250 and 850 cm⁻¹. NMR (CDCl₃ int. CH₂Cl₂) δ 0.25 (9 H, s), 1.5 1.55-2.65 (8 H, envelope), 6.65 (1 H, s), 7.45 (5 H, s), 8.90 (1 H, bs). Mass measured molecular ion: calculated 368.1668, found 368.1674. Analysis: calculated for C₁₉H₂₄N₄O₂Si C, 61.93; H, 6.56; found C, 61.69; H, 6.47.

(1-cyano-2-trimethylsilyl)ethylidenecyclohexane (17)

To a suspension of sodium hydride (0.3 g, 12.5 mmol) in THF (6 mL) under nitrogen, was added in drops the phosphonate reagent (13) (3 g., 11.4 mmol) in THF (2 mL). The mixture was stirred at room temperature for 40 min. and distilled cyclohexanone (1.23 g, 12.55 mmol) was added slowly. A thick gum formed at the bottom of the flask soon after addition. After 1 h., the mixture was worked up by addition of water (100 mL) and extraction with ether (3x40 mL). The combined ether extracts were washed with brine (25 mL), dried (MgSO₄) and the solvent removed in vacuo to give a colorless oil (2.3 g.). The product was
fractionally distilled in vacuum to give the allylsilane (17) (1.36 g., 57%, bp. 110°-116°C at 1.7 mm of Hg). IR (film) 2935, 2210, 1620, 1250, 1165 and 850 cm⁻¹. NMR (CCl₄ int. CHCl₃) δ 0.00 (9 H, s), 1.60 (8 H, bs with shoulder at 1.55), 2.00-2.30 (2 H, envelope), 2.3-2.6 (2 H, envelope). Mass measured molecular ion: calculated for C₁₂H₂₁NSi 207.1443, found 207.1448.

2-[1-[1-cyano-2-(trimethylsilyl)vinyl]cyclohexyl]-N-phenylbicarbamimide (42)

To a solution of N-phenyl-1,2,4-triazoline-3,5-dione (0.2 g, 1.14 mmol) in dichloromethane (1 mL) at room temperature was added in drops the allylsilane (17) (0.25 g, 1.2 mmol) in dichloromethane (1 mL). After 5 h., the red color was completely discharged and the solution became pale yellow. The solvent was removed in vacuo to give a pale yellow crystalline solid. The crude product was triturated with a small quantity of ether to give the ene adduct (42), (0.42 g, ~ 100%), as a pure, white crystalline solid in near quantitative yield. No traces of isomeric products were seen in the NMR spectrum. mp.161°-164°C. IR (nujol) 3150, 3050, 2860, 2220, 1765, 1695, 1460, 1250, 910, 865, 770 cm⁻¹. NMR (CDCl₃ int. CH₂Cl₂) 0.32 (9 H, s), 1.50-1.90 (6 H, bs), 1.90-2.90 (4 H, envelope), 6.70 (1 H, s), 7.50 (5 H, bs), 9.70 (1 H, bs). Mass measured molecular ion: calculated for C₂₀H₂₆N₄O₂Si 382.1824, found 382.1831.
(1-cyano)ethylidenecyclopentane (40)

To a suspension of sodium hydride (0.15 g, 6.25 mmol) in THF (2 mL) under nitrogen at room temperature was added cyanomethyldiethoxy-phosphonate (1 g., 5.65 mmol) slowly. The mixture was stirred for 30 min. and methyliodide (1.8 g., 12.6 mmol) added. After 3 h. one more equivalent of sodium hydride (0.15 g, 6.25 mmol) was added and the mixture stirred for 30 min. before the dropwise addition of cyclopentanone (0.52 g, 6.18 mmol). The mixture was worked up after 6 h. by addition of water (50 mL) and extraction with ether (3x25 mL). The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo to give a crude oil. The product was vacuum distilled (bp. 43°-45°C at 0.25 mm of Hg) to give (1-cyano)ethylidenecyclopentane (140 mg, 20%) as a pure, colorless oil. IR (film) 2950, 2220, 1650, 1450, 1055 cm⁻¹. NMR (CCl₄ int. CHCl₃) δ 1.55-1.90 (7 H, m), 2.10-2.80 (4 H, envelope). Mass measured molecular ion: calculated for C₁₈H₂₁N 121.0891, found 121.0894.

2-[1-[1-cyanovinyl]cyclopentyl]-N-phenylbicarbamimide (41)

To a solution of N-phenyl-1,2,4-triazoline-3,5-dione (90 mg., 0.51 mmol) in dichloromethane (0.5 mL) at room temperature was added (1-cyano)ethylidenecyclopentane (65 mg., 0.55 mmol) in dichloromethane (0.5 mL) and the mixture stirred for 16 h. The mixture was worked up by evaporation of the solvent in vacuo. The crude product was purified by preparative TLC on silica gel using ethyl acetate and gave
the ene adduct (41) as a pale yellow solid. The product was tritutated with a small quantity of ether to give the pure adduct (41) (140 mg., 92%) as a white crystalline solid. No traces of isomeric products were seen in the NMR spectrum. IR (neat) 3460, 3170, 2220, 1780, 1710, 1600, 1430, 1025 and 770 cm\(^{-1}\). NMR (CDCl\(_3\), int. TMS) \(\delta\) 1.60-2.70 (8 H, envelope), 6.00 (2 H, d J=6 Hz), 7.42 (5 H, bs), 9.20 (1 H, bs). Mass measured molecular ion: calculated for C\(_{16}\)H\(_{16}\)O\(_2\)N\(_2\), 296.1273, found 296.1280.

Attempted deprotonation of (2-trimethylsilyl)ethylidene cyclohexane (27) with s-BuLi/TMEDA.

To a solution of (2-trimethylsilyl)ethylidene cyclohexane (27) (0.15 g, 0.82 mmol) in THF (3 mL) at -78°C under nitrogen was added a 1 M solution of s-BuLi in hexane (0.9 mL, 0.9 mmol) in drops. TMEDA (0.14 mL, 0.9 mmol) was added and the solution slowly warmed to -30°C. The mixture was cooled to -78°C and quenched with methyl iodide (0.23 g, 1.6 mmol) and slowly warmed to room temperature. On work up with saturated ammonium chloride solution and ether, the starting material was recovered unchanged.

Attempted deprotonation of (2-trimethylsilyl)ethylidene cyclohexane (27) with n-BuLi.

To a solution of the allylsilane (27) (0.15 g, 0.82 mmol) in THF (2 mL), TMEDA (0.3 mL, 2.0 mmol) was added. A solution of n-BuLi in hexane (1.05 mL, 1.64 mmol) was added at room temperature and the mixture
stirred for 1.5 h. The mixture was quenched with benzaldehyde (0.1 g, 0.9 mmol) and stirred for 2 h. The mixture was worked up with ammonium chloride solution and ether. The starting material was recovered unchanged by NMR and TLC (8:1 pet ether:ethyl acetate).

Attempted deprotonation of (2-trimethylsilyl)ethylidene cyclohexane (27) with s-BuLi/HMPA in THF.

To THF (1 mL) at -78°C under nitrogen was added a 1.43 M solution of s-BuLi in hexane (0.7 mL, 1.0 mmol). HMPA (0.17 mL, 0.9 mmol) was added and the allylsilane (27) (0.15 g, 0.82 mmol) in THF (0.5 mL) was also added dropwise. The mixture was warmed slowly to 0°C over 45 min., cooled back to -78°C and quenched with methyl iodide (0.5 mL, 8.0 mmol) and slowly warmed to room temperature. The mixture was worked up with water and ether. No alkylated products were seen in the NMR spectrum.

Attempted deprotonation of (2-trimethylsilyl)ethylidene cyclohexane (27) with t-BuLi/HMPA.

To HMPA (1 mL) at 0°C under nitrogen was added a 1.85 M solution of t-BuLi in pentane (0.9 mL, 1.66 mmol). After stirring for a few minutes the allylsilane (27) (0.15 g, 0.82 mmol) in HMPA (0.5 mL) was added in drops. The near colorless solution rapidly turned deep red. The mixture was stirred at 0°C for 1 h. and quenched with distilled acetone (0.5 mL, 6.8 mmol). The mixture decolorised rapidly. After stirring for a few more minutes, the mixture was worked up with water and ether. The NMR spectrum of the product showed desilylation and decomposition of the allylsilane (27).
1-(1-cyano-1-methyl-2-trimethylsilyl)ethylcyclopentene (45)

To a solution of diisopropylamine (0.32 g, 3.14 mmol) in THF (4 mL) under N₂ at -78°C was added a 1.6 M solution of n-BuLi in hexane (1.95 mL, 3.12 mmol). The mixture was warmed to 0°C and cooled back to -78°C. The α-cyano allylsilane (16) (0.5 g, 2.6 mmol) in THF (1 mL) was added dropwise. The solution was slowly warmed to -20°C over 20 min. and quenched with methyl iodide (9.9 g, 6.34 mmol). The mixture was warmed to room temperature, and stirred for 1 h. Water (5 mL) and brine (10 mL) were added and the mixture extracted with dichloromethane (25×3 mL). The dichloromethane extract was dried (MgSO₄) and solvent removed in vacuo. The crude oil was bulb to bulb distilled (125°C at 0.8 mm of Hg) to give the alkylated silane (45) (0.44 g, 82%), homogeneous by TLC. IR 3060, 2240, 1640, 1450, 1250, 850 cm⁻¹. NMR (CHC₃) δ 0.05 (9 H, s), 1.10 (2 H, s), 1.50 (3 H, s), 1.75-2.10 (2 H, m), 2.15-2.5 (4 H, m), 5.7 (1 H, bs). Mass measured molecular ion: calculated for C₁₁H₂₂NSi 207.1443, found 207.1448.

2-[(trimethylsilyl)methyl]-1-oxaspiro[2,5]octane (46)

To a solution of the allylsilane (165 mg, 0.9 mmol) in dichloromethane (1.5 mL) at 0°C was added m-chloroperbenzoic acid (0.2 g, 1.0 mmol). After stirring at 0°C for 2 h., TLC (8:1 pet ether:ethyl acetate) showed clean conversion to a single product. The mixture was worked up with saturated sodium bicarbonate solution (10 mL) and extracted with ether (3×15 mL). The ether extract was dried (MgSO₄) and solvent
removed in vacuo to yield the epoxysilane (46) (120 mg., 66%) as an oil, homogeneous on TLC. IR (film) 2930, 1850, 1250, 855, 700 cm⁻¹.

NMR (CHCl₃) δ 0.00 (9 H, s), 0.75 (2 H, d J=7 Hz), 1.15-1.70 (10 H, bs), 2.70 (1 H, t J=7 Hz). Mass measured molecular ion: calculated for C₁₁H₂₂OSi 198.1439, found 198.1444.

**Reaction of (46) with BF₃·Et₂O to give 1-vinylcyclohexanol (47)**

To the β,γ-epoxysilane (46) (0.1 g, 0.5 mmol) dissolved in methanol (2 mL), BF₃·Et₂O (0.14 g, 0.98 mmol) was added. After stirring at 0°C for 2 h., the mixture was slowly warmed to room temperature. The mixture was worked up with saturated sodium bicarbonate solution and dichloromethane. The dichloromethane extract was dried (MgSO₄) and the solvent removed in vacuo to yield a product (40 mg.), whose IR and NMR spectra corresponded well with the known (1-vinyl)cyclohexanol (47).
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57. 2-Bromoethylphenylsulphide (7) is readily prepared by the following reaction.

\[ \text{PhSH} \xrightarrow{\text{NaH}} \text{PhS} \xrightarrow{\text{Toluene, reflux}} \text{PhS} \xrightarrow{\text{Br}} \text{PhS} \xrightarrow{\text{Br}} \]


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55. We have found in our labs, that Zn⁺⁺, when used as a counterion, reduces substantially the enolisation of ketones with allylsilane-anions, leading to excellent yields of desired adducts.


58. a) Although compound (23) itself appears to be unknown, similar compounds have been prepared by using a modified Wittig-Horner reagent by Vig, O. P.; Salota, J. P.; Sharma, M. P.; Sharma, S. D. J. Ind. Chem. Soc., 1968, 45;5. b) Ono, N.; Tamura, R.; Hayami, J.; Kaji, A. Tet. Lett., 1978, 763.


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64. Corey has developed a three step procedure for the conversion of the urazole moiety to the corresponding amine derivative - Corey, E. J.; Snider, B. B. Tet. Lett., 1973, 3091. However, no simple methods exist for the degradation of the urazole adducts to amines and our own efforts to achieve this transformation effectively have not been successful.