SYNTHESIS AND REACTIONS OF A 2-CYCLOPENTEN-1-ONE d³ SYNTHON

by

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We accept this thesis as conforming
to the required standard

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This thesis describes the preparation of 3-trimethylstannyl-2-cyclopenten-1-one 14 via the higher order stannylcuprate 78, a new reagent prepared to convert 3-iodo-2-cyclopenten-1-one 75 to the desired product. The observations made from this chemistry led to the development of "one-pot" cuprate formation which was demonstrated to be a viable and practically convenient way to generate such species compared with traditional methods.

This thesis also describes the preparation of 3-tert-butyldimethylsiloxy-1-trimethylstannylcyclopentene 83, its conversion into the corresponding lithio species, and reaction of the latter reagent with electrophiles. Thus, transmetalation of 83 with methyllithium produced 1-lithio-3-tert-butyldimethylsiloxyocyclopentene 84, which reacted smoothly at -78°C in tetrahydrofuran with alkyl halides, aldehydes, and ketones, providing the corresponding products in good yield.

Treatment of the vinyllithium reagent 84 with 1 equiv. of phenylthiocopper or cuprous cyanide at -78°C for 1 h gave solutions of the corresponding cuprate reagents 103 and 104, respectively. Similarly the corresponding Grignard reagent 105 was made by addition of 1 equiv. of magnesium bromide to the solution of 84 at -78°C. The reagents thus produced reacted in a conjugate sense, the latter catalyzed by copper (I) bromide-dimethylsulphide complex, to enones such as 2-cyclopenten-1-one and 2-cyclohexen-1-one, affording the corresponding products 106 and 107 in excellent yields. β-Iodo enones such as 3-iodo-2-cyclopenten-1-one 75 and 3-iodo-2-cyclohexen-1-one 7 also reacted with the cuprate 103 in a conjugate sense to give the corresponding products 108 and 109 in excellent yields. The cyanocuprate 104 prepared by a "one-pot"
process also reacted with 3-iodo-2-cyclopenten-1-one 75 to give the enone 108 in good yield.

\[
[\text{Me}_2\text{Sn(Me)}\text{CuCN}]\text{Li}_2
\]

\[
78
\]

\[
75 \quad L = \text{I}
\]

\[
14 \quad L = \text{SnMe}_3
\]

\[
\text{OSi(Me)}_3\text{Bu}^t
\]

\[
83 \quad X = \text{-SnMe}_3
\]

\[
84 \quad X = \text{-Li}
\]

\[
103 \quad X = \text{-Cu(SPh)}_2\text{Li}
\]

\[
104 \quad X = \text{-Cu(CN)}_2\text{Li}
\]

\[
105 \quad X = \text{-MgBr}
\]

\[
106 \quad X = \text{-}
\]

\[
107 \quad X = \text{-}
\]

\[
108 \quad X = \text{-}
\]

\[
109 \quad X = \text{-}
\]

\[\text{iii}\]
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</tr>
<tr>
<td>AIBN</td>
<td>Azobisobutyronitrile</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>br.</td>
<td>broad</td>
</tr>
<tr>
<td>$^{13}$C nmr</td>
<td>carbon-13 nuclear magnetic resonance</td>
</tr>
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<tr>
<td>cat</td>
<td>catalytic</td>
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<td>DIBAH</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>E</td>
<td>electrophile</td>
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<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>ether</td>
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<td>h</td>
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<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>$^1$H nmr</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>i</td>
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<td>ir</td>
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<td>Me</td>
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</tr>
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<td>min</td>
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</tr>
<tr>
<td>Ms</td>
<td>Methanesulfonyl</td>
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<td>M</td>
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<td>n</td>
<td>normal</td>
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<td>Nuc−</td>
<td>nucleophile</td>
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<td>Pr</td>
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</tr>
<tr>
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<td>room temperature</td>
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<tr>
<td>t or tert</td>
<td>tertiary</td>
</tr>
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<td>tic</td>
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<tr>
<td>THF</td>
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</tr>
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</tr>
<tr>
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</tr>
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This thesis is dedicated to the memory of
my father
"If you do the experiment you may not be certain to get an answer, but
if you don't do it you can be certain not to get one."

Lord Howard Florey (1898–1968)
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INTRODUCTION

1.1 General

During the twentieth century, our knowledge of organic chemistry has increased to an extent which would have been inconceivable a hundred years ago. Among the various classes of organic molecules, $\alpha,\beta$-unsaturated carbonyl compounds have for some time occupied a special position, and have received a fair share of attention from practicing organic chemists. These compounds owe their synthetic utility mainly to the presence of the carbon-oxygen double bond. As a result, the $\beta$-carbon of the $\alpha,\beta$-unsaturated system is an acceptor site for nucleophiles and free radicals, but not for electrophiles.

\[ \begin{align*}
\text{K} & \quad \text{Nuc}^- \\
\text{Nuc} & \quad \text{K} \\
\end{align*} \]

$\beta$-Alkylated-$\alpha,\beta$-unsaturated carbonyl compounds 1 are useful precursors in organic synthesis. This important family of compounds is usually prepared by nucleophilic attack of suitable organometallic reagents on $\alpha,\beta$-unsaturated carbonyl compounds substituted with a $\beta$-heteroatom (cf. species 2). The latter substances behave synthetically as equivalents of the $\beta$-acylvinyl cations or $\alpha$ synthons\textsuperscript{1} 3 [1]. Thus, starting from 1,3-dicarbonyl compounds 4, the alkenones 1 can be prepared in good yields via the corresponding enaminoines [2], enol ethers [3], enol phosphates [4], enol acetates [5], thioenol ethers [6] as well as

---

\textsuperscript{1} Corey defines synthons as "structural units within a molecule which are related to possible synthetic operations" [E. J. Corey, Pure. Appl. Chem., 14, 19 (1967)].
vinyl halides [7] (equation 1). This strategy has been successfully applied to the
total synthesis of more complex molecules [8-10].

\[
\begin{align*}
\text{4} & \xrightarrow{\text{O}} \text{2} \xrightarrow{\text{X}} \text{1} + \text{X}^\ominus \\
\end{align*}
\]

Although there have been numerous examples of nucleophilic attack on
\(\alpha,\beta\)-unsaturated systems, it would be interesting to attempt electrophilic attack on
these systems. To effect this one must reverse the pattern of "normal reactivity". This may be achieved via "reactivity umpolung" [1], which involves conversion of
normal electrophilic [acceptor (a)] character of the \(\beta\)-carbon atom into
nucleophilic [donor (d)] reactivity \(^2\) (equation 2). This can be realized through the
intermediacy of masked \(\alpha,\beta\)-unsaturated carbonyl (or latent) compounds, which
behave as equivalents of the \(\beta\)-acylvinyl anions or d\(^3\) synthons 5. This type of
methodology has greatly extended the synthesis and synthetic utility of
\(\alpha,\beta\)-unsaturated carbonyl compounds.

\(^2\) Hetero atoms, present in many organic molecules, impose alternating acceptor
properties (attack by donor species) at carbons C\(^1\), C\(^3\), C\(^5\), and donor properties
(attack by acceptor reagents) at carbons C\(^2\), C\(^4\), the heteroatom itself being a
donor center (d\(^6\)), see reference 1.
where $Y = \text{CN, NO}_2, \text{SPh, SO}_2\text{Ph}$; $RX = \text{alkyl halide}$

Scheme 1

In recent years there have been a number of reports concerning the development and use of synthetic equivalents of $\beta$-acylvinyl anions. An extensive survey of these reports is beyond the scope of this thesis. However, in general, four strategies have been employed to generate $\beta$-acylvinyl anion equivalents.

In one (Method A), the $\beta$-position of a latent $\alpha,\beta$-unsaturated carbonyl system is activated toward proton abstraction by an electron withdrawing group (cyano [12], nitro [13], phenylseleno [14], phosphino [15], thio [16], sulfonyl [17]), the resulting carbanion is reacted with an electrophile, and the activating

---

3 For reviews on this subject, see reference 11.
group is subsequently eliminated to introduce the required unsaturation \[18\] (Scheme 1).

\[
\begin{align*}
\text{Base} & \quad \rightarrow \\
\text{Y}X & \quad \rightarrow \quad \text{E}^+ \\
\text{Y}X & \quad \rightarrow \\
\text{allylic rearrangement} & \\
\text{Y}X & = \text{dithiocarbamate, sulfoxide or selenoxide where } Y = S \text{ or } Se \text{ and } X = O; E^+ = \text{alkyl halide (electrophile)}
\end{align*}
\]

Scheme 2

The second method (Method B) which has a close relationship to the work described in this thesis, involves generation of a donor center $\beta$- to a latent carbonyl group via lithiation of a vinyl substituent\(^4\) (halo \([19-20]\), trialkylstanny)

\(^4\) For reports of acyclic counterparts used mainly in the field of prostaglandin synthesis, see references 19b, 21d-e, and 22.
followed by reaction of the resulting organometallic compound with electrophiles (Schemes 4, 6, and 7) \textit{(vide infra)}.

\begin{align*}
\text{Scheme 3}
\end{align*}

In the third method (Method C), the $\alpha$- position of an S-allyl system (dithiocarbamate [24], sulfoxide [25]) or an Se-allyl system (selenoxide [26]) is deprotonated, the resulting carbanion is reacted with an electrophile, and the activating group is subsequently made to undergo an allylic rearrangement to introduce the unsaturation and become the latent carbonyl system (Scheme 2) [27].

\textsuperscript{5} For examples of direct deprotonation of, (a) heteroatom activated $\beta$-vinyl center of mainly $\alpha,\beta$-unsaturated acrylic acid derivatives, see reference 23; (b) propargylic ethers, see reference 22b.
The fourth method (Method D) involves the generation of an allenic carbanion \( \beta^- \) to a latent carbonyl group from heteroatom substituted propargyl or allenyl precursors followed by reaction with electrophiles [28] (Scheme 3).

1.2 Previous work

Previous work in our laboratories had shown that \( \beta^- \)-bromo- and \( \beta^- \)-iodo-\( \alpha,\beta \)-unsaturated ketones 2 [7] are excellent synthetic equivalents of \( \beta^- \)-acylvinylic cations (\( \alpha^3 \) synthons) 3 [8-9].

\[
\begin{align*}
X = \text{Br, I} \\
2 & \quad \equiv \\
3
\end{align*}
\]

Thus, reaction of \( \beta^- \)-halo enones 2 with variety of nucleophilic reagents, such as alkyl cuprates, afforded, in excellent yields, \( \beta^- \)-substituted enones 6, in which the organic halide has been replaced by a nucleophilic species (equation 3). A certain number of these \( \beta^- \)-substituted enones 6 have proven to be very useful for the synthesis of functionalized five [8b] and seven [8c] membered ring systems.

We were also intrigued by the possibility that \( \beta^- \)-halo enones 2 might serve as suitable precursors of synthetic equivalents of \( \beta^- \)-acylvinylic anions (\( \alpha^3 \) synthons) 5. It was found that this could be successfully achieved via \( \beta^- \)-trialkylstannylic-\( \alpha,\beta \)-unsaturated ketones [21a] (Scheme 4).
1) LDA

\[ (R)(L)\text{CuLi} \]

\[ \text{X} = \text{Br, I} \]

2

where \( E^* = \) electrophile

Scheme 4
Thus, 3-iodo-2-cyclohexen-1-one 7 reacted smoothly with lithium (phenylthio)(trimethylstannylicuprate 8 [29], a new reagent developed for this transformation, to produce 3-trimethylstannylic2-cyclohexen-1-one 9 in excellent yield. This material was converted into the silyl enol ether 10 which underwent transmetalation [30] with methyllithium to produce the vinylithium species 11. The latter reagent, which is a β-acylvinyll anion equivalent (d^1 synthon), reacted with a number of electrophiles to afford dienes 12 which were hydrolyzed to the β-substituted enones 13. This new methodology was complementary to the earlier work involving nucleophilic additions to β-halo enones [8].

1.3 The problem

We were interested in determining whether similar methodology could be extended to other cyclic systems, especially five-membered ring analogues. Firstly, it was likely that protection of the carbonyl system of 14 as the silyl enol ether 15 would be futile, since treatment with base (e.g., alkyllithium) would probably lead to deprotonation to yield 16 (a "stable" cyclopentadienyl anion) instead of transmetalation (equation 4). One could envisage the formation of the dianion 17, upon treatment of 15 with two equivalents of base (e.g., alkyllithium) (equation 5). However if this were to be successful, the addition of electrophiles would lead to regiochemical ambiguity in the products, which was not desirable.
Hence it seemed likely that the dianion\(^{4}\) 17 would not serve as a useful d\(^3\) synthon. Therefore, the method of protection of the carbonyl system should not involve formation of the diene system within the molecule. Secondly, since the trialkyltin functionality is acid labile, any method chosen to protect the carbonyl group prior to transmetalation should not involve an acid catalyst.

The objective of the work described in this thesis was to investigate the possibility of extending the above methodology to the use of the \(\beta\)-trimethylstannyl enone 14 as a potential precursor of a synthetic equivalent of the d\(^3\) synthon 5. Presumably, this would involve protection of the carbonyl group of 14 under non-acidic conditions \(^{32}\) (Scheme 5, path A) to give 18 which after transmetalation\(^{7}\) \(^{30}\) would produce the desired d\(^3\) synthon 19.

Alternatively, it might be possible to reduce the carbonyl group and protect the resultant alcohol function to yield species 20. Transmetalation of 20 would produce the desired d\(^3\) synthon 21\(^{1}\) (Scheme 5, path B). Treatment of either 19 or 21 with electrophilic reagents would afford, after removal of the protecting group, the desired d\(^3\) synthon.

\(^{4}\) For successful manipulation of a related dianion towards the total synthesis of (\(\pm\))-coriolin, see reference 31.


\(^{1}\) For similar five membered d\(^3\) synthons, see species 49 (cf. reference 20b) and species 60 (cf. reference 21b) (\textit{vide infra}).
In addition to the reaction of 19 and/or 21 with electrophiles, we were also interested in the possibility of converting these reagents into the corresponding cuprates. If this were to be successful, one could investigate the Michael addition of the cuprates to enones and related compounds.

Clearly these proposed reactions (Scheme 5), if successful, coupled with our earlier studies [21a] would establish masked β-acylvinylltin compounds as a source of novel and synthetically viable β-acylvinyll anions (d^3 synthons).
1.4 Selected recent reports concerning cyclic $\beta$-acylvinyl anion equivalents

(Method B) *

(a) Using $\beta$-acylvinyl halo reagents:

Since the development of a general method for conversion of $\beta$-diketones into $\beta$-halo-$\alpha,\beta$-unsaturated ketones 2 [7], the latter have been employed by a number of groups [19a, 20a-b] for the preparation of cyclic $\beta$-acylvinyl anion synthons. Recently however, the conversion of these substances into the mixed vinylcuprate reagents 23, a process quite similar to the one which we wished to accomplish, has been reported (Scheme 6) [19a].

These vinylcuprate reagents 23 reacted smoothly with a variety of electrophilic reagents. For example, reduction of the cyclic $\beta$-iodo enones 24 with sodium borohydride, followed by protection of the resulting alcohols 25, using the procedure developed by Corey [33], gave the silyl ethers 26 (equation 6, Scheme 6). Lithium-iodine exchange of 26 was accomplished by treatment of the latter substances with two equivalents of $t$-butyllithium. Treatment of the resultant vinyllithium reagents 27 with 3-methoxy-3-methyl-1-butynylcopper resulted in the formation of the mixed cuprate reagents 28. Reaction of 28 with the benzoate 29 followed by treatment of the resultant mixtures with

* This brief account is not meant to be exhaustive, but is given only to provide the reader with some background in this area. The examples were chosen for their close relationship to the work discussed in this thesis. For other reports of related $\beta$-acylvinyl anion equivalents see references 19-21.
where $R = H$ or Me; $L = \text{--C}≡\text{C--C(Me)$_2$OMe}$

Scheme 6
tetra-\textit{n}-butylammonium fluoride gave the alcohols 30 in excellent yield [19a]. The conversion of 30 into the corresponding enones 31 was not attempted. However these transformations should pose no problem\textsuperscript{10}.

\[
\begin{align*}
\text{OSiR}_3 \\
\text{X} \\
\text{32 X = Br, I} \\
\text{33 X = Li} \\
\text{7} \\
\text{34} \\
\text{35}
\end{align*}
\]

Protection of the carbonyl group of \(\beta\)-halo enones 2 as the corresponding enol silyl ethers 32, followed by lithium-halogen exchange (e.g., alkyllithium) of the protected species 32 to produce 33, the synthetic equivalent of 5, has been envisaged [21a]. However, attempts to convert 3-iodo-2-cyclohexen-1-one 7 into the corresponding enol silyl ether 34, under variety of experimental conditions, failed to produce synthetically useful yields of the desired product 34. Furthermore, the product was contaminated with isomer 35, and these compounds proved to be quite unstable.

\[
\begin{align*}
\text{Br} & \quad \text{OH} \quad \text{OH} \\
\text{Benzene} \\
\text{TsOH (cat.)} & \quad \text{36} \\
& \quad \text{37 (68\%)} \\
& \quad \text{38 (17\%)}
\end{align*}
\]

\textsuperscript{10} For a number of related examples (of cuprates) involving the use of acyclic \(\beta\)-iodo enones as precursors to \(\beta\)-acylviny1 anion equivalents, see reference 19b.
Recently Swenton et al. reported that glycol ketals of β-bromo enones can be used as β-acylvinylic anion equivalents [20a]. However, the chemistry derived from these studies revealed a number of limitations. First, the ketalization step was found to produce substantial amounts of the bisketal (equation 7). For example, 3-bromo-2-cyclohexen-1-one 36 gave, under carefully controlled conditions, monoketal 37 (68%) and bisketal 38 (17%). Due to severe problems in the ketalization of β-bromo cyclopentenones, the chemistry does not serve to prepare functionalized cyclopentenones. Secondly, for the parent system, double-bond isomerization accompanied ketalization (equation 7) (cf. species 37)\(^{11}\). While this does not impose a serious limitation on its use as a β-acylvinylic anion equivalent, it cannot be used in a projected study in which double-bond migration is synthetically undesirable (cf. Scheme 8). Furthermore, the protected species 37 required two equivalents of alkyl lithium to effect lithium-halogen exchange (equation 8)\(^{12}\).

\[\text{BuLi (2 equiv.)} \rightarrow 37 \rightarrow 39 \rightarrow 13\]

\(^{11}\) The ketalization of C-2 substituted cyclohexenone compounds furnished ketals in good yields in which the double-bond isomerization did not occur.

Third, while in most cases, no rearrangements were noted under the mild acid hydrolysis conditions employed in the work, rearrangement was observed in the case of the product derived from use of cyclohexenone as an electrophile (equation 9).

![Chemical structure](image)

Protection of the carbonyl group via dithioketalization of β-bromo enones partially alleviated some of the problems mentioned above [20b]. Under the standard conditions, when β-bromo enones 36 and 41 were treated with one equivalent of ethanedithiol in the presence of boron trifluoride-etherate as a catalyst, the desired β-bromo enone dithioketals 42 and 43, respectively, were obtained in good yields, with bisdithioketals 44 and 45 as minor products (equation 10). Importantly, this process resulted in no double-bond isomerization
in the desired monoketals 44 and 45. As a result, the functionalization chemistry of the \( \beta \)-bromo enones dithioketals was carried out in the standard fashion: metal-halogen exchange at \(-78^\circ C\) with one equivalent of alkyllithium followed by addition of the electrophile. The reactions of these lithiated dithioketals with a standard set of electrophiles gave good yields of products for both five- and six-membered ring systems (Scheme 7).

\[
\text{\textbf{Scheme 7}}
\]

However, as in the case of acetal 37 (equation 9), the corresponding dithioketal 46 on hydrolysis with a mixture of mercuric chloride and mercuric oxide in acetonitrile/water yielded the rearranged product 40, which on oxidation gave the symmetrical product 47 (Scheme 7).
Paquette et al. have used this methodology for the rapid and efficient construction of the ophiobolin nucleus using the dithioketal 49 and the bicyclic ketone 48 [20d]. Metal-halogen exchange of the dithioketal 43 at −78°C [20b], followed by sequential addition of the epimerically pure 48 and methyl iodide furnished, via intermediate 50, the single crystalline ketone 51 in 71% yield (Scheme 8). The close relationship of 51 to sesterterpenes such as ophiobolin F 52 and albolic acid 53 is self apparent.
During the course of our work, other workers have used the methodology developed in our laboratories (cf. Scheme 4) for the preparation of 2-substituted 4-(tetrahydropyran-2-yloxy)-2-cyclopenten-1-ones 62, via a process quite similar to the one which we wished to accomplish (Scheme 5) [21b]. They described the preparation of (3S*,5R*)-1-lithio-5-(t-butyldimethylsiloxy)-3-(tetrahydropyran-2-yloxy)cyclopentene 60 from the chloro cyclopentenone 54 and the stannyl
cyclopentenediol derivative 59; this latent 3,5-dihydroxycyclopentenyl carbanion reacted efficiently with various electrophiles to form substituted cyclopentenediol derivatives 61, some of which were converted into their corresponding 2-substituted 4-(tetrahydropyran-2-yloxy)-2-cyclopenten-1-ones 62.

The addition of chloro cyclopentenone 54 (in tetrahydrofuran) to lithium bis(tri-n-butylstannyl)cuprate (1.1 equiv.) in tetrahydrofuran-dimethylsulfide at -25°C gave the stannyl cyclopentenone 58 in 84% yield. Stereoselective reduction\(^\text{14}\) of the carbonyl group in compound 58 followed by tetrahydropyranylation of the newly-formed hydroxy! group gave the (1R\(^*\),4S\(^*\))-stannyl cyclopentenediol derivative 59 in 94% overall yield from the stannyl enone 58. The transmetalation step was found to be troublesome. However, with n-butyllithium (2 equiv.) at -45°C this was accomplished within 0.75 h. The intermediate lithio cyclopentene 60, thus generated, reacted efficiently with a variety of electrophiles to yield the substituted cyclopentenediol derivatives 61.

\(^\text{13}\) For an alternative equivalent of this anion, see reference 25a. Appropriately protected lithio cyclopentenes of type 60 may also be regarded as latent 5-hydroxy-3-oxocyclopentenyl, a \(\beta\)-acylvinyl anion, or 3-hydroxy-5-oxocyclopentenyl carbanions.

\(^\text{14}\)For recent developments in this area, see reference 34.
These conversions leading to the 3,5-dihydroxycyclopentenyl carbanion equivalent 55 were complementary to the previously reported conversion of the chloro enone 54 into the corresponding alkyl substituted cyclopentenediol derivative 61 by a conjugate addition-elimination route [9]. In this process, the chloro cyclopentenone 54 was shown to be synthetically equivalent to the 3,5-dihydroxycyclopentenyl carbocation 56 which undergoes nucleophilic alkylation (Scheme 9).

Still et al. [21c] have prepared the four-membered ring analogue β-acylvinyl anion synthon, carbonyl protected β-acylvinyltin compound 65, from the known acetal 63, via a hitherto unknown route15 (Scheme 10). Low-temperature addition of tri-n-butylstannylmagnesium chloride (prepared from tri-n-butylstannyllithium

15 This route is an exception to methods by which all the other cyclic β-acylvinyl anion synthons [19a, 20a-b, 21b] are synthesized, via Method B, all of which have used methodology developed in this laboratory [7, 21a]. For previous use of similar methodology for alkylative 1,3-carbonyl transposition, see references 3a and 10.
[36] and magnesium chloride at -70°C) followed by in situ mesylation gave 64 in 68% yield. Elimination was accomplished with excess powdered potassium carbonate in dimethylsulfoxide at 100°C for 1 h and led to the desired cyclobuteryl tin compound 65 in 96% yield (Scheme 10). As expected, this compound 65 was found to be a suitable precursor of a synthetic equivalent of the β-acylvinyl anion (d3 synthon) 5, as demonstrated in the total synthesis of the cytotoxic germacranoide eucannabinolide 70 [21c].

![Scheme 11](image-url)
Coupling of 66 and 67 was accomplished via lithiation of 65 (1.3 equiv. of 65, 1.0 equiv. of n-butyllithium in tetrahydrofuran, -70°C, 30 min) [30] and addition of 1.0 equiv. of the enone 67. The adduct 68 (Scheme 11), was a single diastereomer and was isolated by flash chromatography in 82% yield (85% conversion). Oxy-Cope ring expansion was effected by using five equivalents of potassium hexamethyldisilazide in dimethoxymethane at 85°C and led to the formation of 69 in high yield. As expected, the cyclobutenyllithium 66 added trans to the bulky isoprenyl substituent in 67 and the Oxy-Cope rearrangement proceeded via a chairlike transition state from the intermediate 68, resulting in the adduct 69. Kinetic protonation under variety of conditions yielded a 1:1 mixture of diastereomers, 69a and 69b. However, when the mixture was stirred in dry methanol containing powdered potassium carbonate, a 15:1 ratio of isomers was produced. The major isomer was the desired cis-69a. The intermediate 69a was then transformed into the natural product eucannabinolide 70.

Although no detailed chemistry of the compound 65 was reported, the preceding transformations illustrated the masked β-acylvinylltin reagent 65 as a novel and viable source of the hitherto unknown vinylolithium species 66, a synthetically equivalent of a β-acylvinyll anion 5.

---

16 For use of cyclic β-acylvinyll anion equivalent 5 to effect the oxy-Cope ring expansion for synthesis of macrocycles, see Scheme 8 (cf. reference 20c).
DISCUSSION

2.1 Preparation of 3-trimethylstannyl-2-cyclopenten-1-one 14

Earlier work in our laboratory had found that the β-iodo enones 71 serve as excellent synthetic equivalents of β-acylvinyl cations 3 (summarized earlier in this thesis). It was found in our laboratories that these compounds could be converted efficiently into the corresponding β-trialkylstannyl derivatives 72 by reacting with various types of organocuprates\(^1\), like lithium (phenylthio)(trimethylstannyl)cuprate 8 [29], the trimethylstannylcopper reagent 73 [38] and lithium (cyano)(trimethylstannyl)cuprate 74 [39] (equation 10) [41].

\[
\text{71} \quad \xrightarrow{(\text{Me}_3\text{Sn})\text{L} \text{CuLi}} \quad \text{72}
\]

For example, reaction of 3-iodo-2-cyclopenten-1-one 75 with 1.1 equivalents of the cuprate reagent 8 in tetrahydrofuran (\(-20^\circ\text{C}, 15\) min; room temperature, 30 min) afforded the corresponding β-trimethylstannyl-\(\alpha,\beta\)-unsaturated ketone 14 in 83% yield (equation 12). Other cuprate reagents also gave the desired product 14 in excellent yields (Table I). However, our attempts to scale up the reaction gave unacceptable amounts of 3,3-bis(trimethylstannyl)cyclopentanone [38]. Although this problem was later circumvented by performing these reactions at lower

\(^1\) One of the fundamental contributions of organocopper chemistry to organic synthesis is the ability of Gilman reagents or modified Gilman reagents to deliver a variety of ligands in a 1,4 sense to \(\alpha,\beta\)-unsaturated ketones [40]. For recent insights into the reagent nature, see reference 37.
temperatures and with extended reaction times (vide infra), we were interested in exploring other methods to effect the desired transformation.

\[
\text{Me}_3\text{Sn(PhS)CuLi} \quad 8
\]

\[
\text{Me}_3\text{SnCu.SMe}_2\text{LiBr} \quad 73
\]

\[
\text{Me}_3\text{SnCu(CN)Li} \quad 74
\]

![Chemical structure](image)

Table I: Reaction of the $\beta$-iodo-$\alpha,\beta$-unsaturated ketone 75 with organotin cuprates.

<table>
<thead>
<tr>
<th>Cuprate</th>
<th>Reaction condition</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>$-20^\circ\text{C}$, 15 min; room temperature 30 min</td>
<td>83</td>
</tr>
<tr>
<td>73</td>
<td>$-48^\circ\text{C}$, 2 h; $-20^\circ\text{C}$, 1 h; room temperature 1 h</td>
<td>80</td>
</tr>
<tr>
<td>74</td>
<td>$-48^\circ\text{C}$, 90 min; $-20^\circ\text{C}$, 90 min</td>
<td>82</td>
</tr>
</tbody>
</table>
During the course of our work, Lipshutz and co-workers reported that higher order organocuprates of general formula $R_2Cu(CN)Li_2$ react rapidly with $\alpha,\beta$-unsaturated ketones at low temperatures to provide high yields of the conjugated addition products\(^2\) [42a]. From a practical standpoint, these reagents apparently did not require the use of additives such as dimethylsulfoxide [43], lithium bromide [44], and perhaps more commonly, phosphorous derivatives (e.g. hexamethylphosphoramide [45], triethylphosphite [46], tri-$\beta$-butylphosphine [47]) for stabilizing or solubilizing purposes, and, hence, the overall reaction, workup and isolation procedures were simplified. Moreover, cuprous cyanide, used to prepare these reagents, in addition to other inherent benefits (stability and expense [48]), is a readily available source of copper (I) which already possesses a non-transferable "dummy" ligand attached to copper.

Lipshutz and coworkers also reported that more highly mixed higher order organocuprates of the form $R_1R_2Cu(CN)Li_2$ [42] ($R_1 =$ a transferable ligand, $R_2 =$ a second "dummy" ligand = methyl), the tendency to transfer $R_1$ in preference to the methyl group was high\(^3\) (thereby saving the valuable $R_1$).

To use this new methodology towards our endeavour, i.e. to effect the desired transformation of iodo enone 2 into the trimethylstannyl enone 72, the following goals had to be achieved.

(a) Reagent of the form $(Me_3Sn)(Me)Cu(CN)Li_2$ had to be prepared.

\(^2\) The presence of boron trifluoride-etherate was shown to enhance reaction rates and/or product yield relative to those observed in the absence of this Lewis acid [42c].

\(^3\) Preferential release of one group from a copper center relies on several factors [42, 50], such as aggregation state, extent of back bonding between a ligand and copper, and stability of both 77 and the lower order cuprate resulting from the loss of $R_1$ in 77.
(b) More importantly, this reagent had to react with \(\beta\)-iodo enones in a conjugate sense and be able to deliver the trimethylstannyl group selectively in synthetically useful yields.

2.1.1 Preparation of the higher order cyanocuprate 78

Addition of one equivalent of solid cuprous cyanide to a cold (-78°C) solution of trimethylstannyllithium in tetrahydrofuran\(^4\) (-78°C, 5 min; -48°C, 15 min) resulted in a bright orange solution of lithium (cyano)(trimethylstannyl)cuprate 74 [49] (equation 12).

\[
\text{Me}_3\text{SnLi} + \text{CuCN} \rightarrow \text{Me}_3\text{SnCu(CN)Li}  \quad 74 \quad (12)
\]

Subsequent addition of one equivalent of methyllithium at -20°C (5 min) afforded a homogeneous tan solution of the higher order cyanocuprate 78 (equation 13).

\[
\text{Me}_3\text{SnCu(CN)Li} + \text{MeLi} \rightarrow \text{Me}_3\text{Sn(Me)Cu(CN)Li}  \quad 78 \quad (13)
\]

We were also pleased to find that, alternatively, the higher order cyanocuprate 78 can be prepared in a one-pot reaction by direct addition of two equivalents of methyllithium to a slurry of one equivalent of cuprous cyanide in tetrahydrofuran\(^5\) with one equivalent of hexamethylditin at -78°C (-78°C to -20°C, 15 min) to give immediately a bright yellow slurry\(^6\), which turned into a

\(^4\) This reagent can also be prepared in diethyl ether. However, for these reagents tetrahydrofuran is the preferred solvent since more highly mixed cuprates like \(\text{Me(\(\eta\)-Bu)Cu(CN)Li}\), in diethyl ether revealed free methyllithium at low temperatures, along with its lower order counterpart \(\text{MeCu(CN)Li}\) [57-59].

\(^5\) These reagents have markedly different reactivity depending on whether these reagents are prepared in tetrahydrofuran or diethyl ether [42b] (vide infra).

\(^6\) This occurred when approximately half the volume of methyllithium was added (=1 equiv.) to the reaction mixture. This could have been due to the formation of 74. This suspicion was later confirmed to be true. Thus, the lower order cuprate 74 formed via this method reacted with 3-iodo-2-cyclopenten-1-one (-48°C, 90 min, -20°C, 90 min) to give 79% of the corresponding tin enone 14 as the only product. There was no indication (glc analysis), that methyl transfer
homogeneous tan solution soon thereafter.

2.1.2 Reaction of the higher order cyanocuprate 78 with the β-iodo enone 75

We were extremely pleased to find that the reaction of 3-iodo-2-cyclopenten-1-one 75 with 1.2 equivalents of the higher order cyanocuprate reagent 78 in tetrahydrofuran (−78°C, 90 min; −48°C, 60 min; 0°C, 90 min) afforded the corresponding 3-trimethylstannyl-2-cyclopenten-1-one 14 in 83% yield (equation 14). This yield compared well with those obtained in the earlier studies (Table I).

\[
\begin{align*}
\text{K} & \quad \xrightarrow{\text{Me}_3\text{Sn(Me)Cu(CN)Li}_2} \\
\text{75} & \quad \rightarrow \\
\text{14} & 
\end{align*}
\]

None of the methyl transfer product could be detected (tlc and glc analyses showed the presence of only one component beside a small amount of hexamethylditin). The spectral properties of this material were identical with those reported earlier [38].

The structure of the tin enone 14 was confirmed by its spectral data. A strong absorption band at 1685 cm\(^{-1}\) in the ir spectrum of this compound

(cont'd) had occurred. Formation of this "one-pot tin cuprates" by addition of 1 equiv. of methyllithium in ether to a cold (usually −78°C) tetrahydrofuran solution of 1 equiv. of hexamethylditin and 1 equiv. of copper (I) source (phenylthiocopper or cuprous cyanide) gave reagents which behaved exactly the same as the cuprates 8, or 74 respectively. This method was employed for large scale (using phenylthiocuprate 8) preparation of the tin enone 14.

1 From practical stand point the second method was found to be more convenient.
indicated the presence of an \( \alpha, \beta \)-unsaturated ketone. The ir spectrum also showed a strong absorption band at 762 cm\(^{-1} \) which was attributed to the trimethylstannyl group [52]. The \(^1\)H nmr spectrum of this material exhibited a nine-proton singlet at \( \delta 0.25 \) (with satellite peaks due to tin coupling, \( J_{\text{Sn-H}} = 56 \) Hz) which was attributed to the stannyl methyl protons\(^8\). The olefinic proton of this compound gave rise to a one-proton triplet (\( J = 2.3 \) Hz) at \( \delta 6.37 \) (with satellite peaks, \( J_{\text{Sn-H}} = 33 \) Hz).

Reaction of 3-iodo-2-cyclopenten-1-one 75 with 1.2 equivalents of the higher order cyanocuprate 78 (prepared in diethyl ether instead of tetrahydrofuran, with similar reaction conditions) in diethyl ether (-78°C, 90 min; -20°C, 90 min, room temperature 15 min) afforded the corresponding 3-trimethylstannyl-2-cyclopenten-1-one 14 and 3-methyl-2-cyclopenten-1-one 79 in a ratio 4.5 : 1 (glc) with complete consumption of starting material. This indicated that in ether medium, although the trimethylstannyl group is transferred preferentially, transfer of a methyl group can also occur \(^9\) \(^10\) [42b]. Although further study in this area is required to establish the trimethylstannyl higher order cuprate 78 as a viable

---

\(^8\) The proton chemical shifts of the trimethylstannyl compounds are relative to CHCl\(_3\). There are three naturally occurring tin isotopes which have magnetic moments (\( I = 1/2 \)): \( ^{119}\text{Sn}, ^{117}\text{Sn}, \text{and} ^{119}\text{Sn} \). Due to their higher relative abundance, \( ^{119}\text{Sn} (7.67\%) \) and \( ^{119}\text{Sn} (8.68\%) \) are the important ones. As a general rule of the indirect tin proton couplings \( J(\text{Sn-C-H}) \) and \( J(\text{Sn-C-C-H}) \) are always slightly larger (\( \approx 5\%) \) for \( ^{119}\text{Sn} \) than for \( ^{117}\text{Sn} \) [53]. Throughout this thesis the magnitude of these coupling constants are given as \( J(119\text{Sn-H})/J(117\text{Sn-H}) \) where the coupling constants for the two isotopes are distinct and as an average of the two values where they are not distinct.

\(^9\) The 1,4 additions performed in tetrahydrofuran as solvent are notoriously sluggish [54-55]. The differences in aggregation state of 78, a function of solvent, might be responsible for this behaviour [50, 56, 57].

\(^10\) Reaction of 3-iodo-2-cyclohexen-1-one 7 with 1.2 equivalents of the higher order cyanocuprate in diethyl ether (-20°C, 30 min) gave 3-trimethylstannyl-2-cyclohexen-1-one 9 and 3-methyl-2-cyclohexen-1-one 80 in a ratio of 15.7:1 with complete consumption of 7, whereas reaction in tetrahydrofuran (-20°C, 45 min) gave the product 9 and starting material in the ratio 3.4:1 (These results confirm the fact that the higher order cyanocuprate is less reactive but more selective in tetrahydrofuran).
reagent for transferring a trimethylstannyl group, we were pleased to discover that it can transfer this group selectively and it could be used to alleviate our problems.

All large scale preparations of the β-trimethylstannyl enone 14 were carried out by methods described elsewhere [39], or with slight modifications to the reaction conditions. Thus, using the phenylthiocuprate 8 in tetrahydrofuran (−78°C, 3 h) there was obtained an 82% isolated yield of the β-trimethylstannyl enone 14 [21b].

2.2 Preparation of 3-trimethylstannyl-2-cyclopenten-1-ol 81

![Diagram](image)

During the early stages of our investigations, we considered two different routes to obtain the cyclopentenone d3 synthon. Our choice was (Path B, Scheme 5) via the cyclopentenol d3 synthon (equation 15). This route was attractive to us since the reagent corresponding to this synthon had not been synthesized before [21b] and since 3-substituted-2-cyclopenten-1-ol derivatives had recently gained importance in synthetic studies [60]. Moreover, from a practical standpoint, this pathway seemed simple to effect. More importantly, our efforts to effect the acetalization of 3-trimethylstannyl-2-cyclopenten-1-one 14 at −78°C via Noyori’s procedure [32] failed. Any attempt to raise the temperature (for example −20°C) led to blackening of the solution and led to partial recovery of the starting
material at the end of the experiment.

\[
\begin{array}{ccc}
\text{O} & \text{SnMe}_3 \\
\text{DIBAH} & \rightarrow & \text{OH} \\
14 & \rightarrow & 81 \\
\end{array}
\]

Reaction of 3-trimethylstannyl-2-cyclopenten-1-one 14 with 1.2 equivalents of diisobutylaluminium hydride (DIBAH)\(^{11}\) in dry hexane (0°C, 1.75 h) yielded 3-trimethylstannyl-2-cyclopenten-1-ol 81 in 98% yield (equation 16) [61]. The structure of this material was confirmed by its spectral data. A broad absorption band at 3290 cm\(^{-1}\) indicated the presence of a hydroxy functionality. The ir spectrum also showed absorption bands at 1690 cm\(^{-1}\) and 767 cm\(^{-1}\) indicating the presence of a double bond and a trimethylstannyl functionality, respectively. The \(^1\)H nmr spectrum of this material exhibited a nine-proton singlet at 6 0.16 (with satellite peaks due to tin coupling, \(J_{\text{Sn-H}} = 55\) Hz) which was attributed to the stannyl methyl protons. The proton of the hydroxy group gave rise to a broad singlet at 6 1.48 (exchanges with D\(_2\)O). The olefinic proton of this compound gave rise to a one-proton broad doublet (\(J = 2\) Hz) at 6 5.94 (with satellite peaks, \(J_{\text{Sn-H}} = 35/39\) Hz).

\(^{11}\) Okamura and co-workers have used sodium borohydride to effect a similar transformation (\textit{vide supra}) [19a]. While Luche's procedure gives excellent yields [62], for reduction of conjugated enones, DIBAH [61] is considered to be the reagent of choice. Besides, sodium borohydride was shown to yield saturated alcohols as well as Michael addition products in addition to the desired unsaturated alcohol, see M.R. Johnson, and B. Rickborn, \textit{J. Org. Chem.}, 35, 1041 (1970).
Silyl ether derivatives of alcohols have a number of useful properties. The volatility of trimethylsilyl [63] and dimethylsilyl [64] ethers make them suited for separation and structure elucidation by a combination of gas chromatography and mass spectrometry. On the other hand, the ease of hydrolysis of these derivatives limits their utility as protecting groups [65]. The stability of tert-butyldimethylsilyl [33, 66] ether derivatives to a wide range of reaction conditions, make them particularly effective protecting groups for the hydroxyl group. Their stability to strongly basic conditions (e.g. treatment with alkyl lithium reagents) results from the fact that these reactions proceed by nucleophilic attack at silicon, which is, therefore, sensitive to steric hindrance [67]. More importantly, because of its specific and mild removal by either fluoride ion [33] or aqueous acid [33], this protecting group was attractive to our endeavour.

Reaction of 3-trimethylstannyl-2-cyclopenten-1-ol 81 with 1.1 equivalents of tert-butyldimethylsilyl chloride in the presence of 5 equivalents of imidazole in dry dimethylformamide (room temperature, 90 min) gave 97% of 3-tert-butyldimethylsiloxyl-1-trimethylstannylcyclopentene 83 (equation 17).

\[ \text{OH} \quad \text{t-BuMe}_2\text{SiCl} \quad \text{imidazole, DMF} \quad \rightarrow \quad \text{OSi(Me)}_3\text{Bu}^+ \]

\( 81 \quad 83 \) (17)

\[ 83 \]

\[ 81 \]
The structure of this compound was confirmed by its spectral data. The IR spectrum showed absorptions at 1583, 1090 and 778 cm\(^{-1}\), indicating the presence of an isolated double bond, an ether (C=O stretching) and the trimethylstannyl group respectively. The \(^1\)H nmr spectrum exhibited a six-proton singlet (δ 0.097) due to the silyl methyl groups, while a nine-proton singlet due to the tert-butyl methyl groups appeared at δ 0.93. The trimethylstannyl methyls appeared at δ 0.15. A one-proton broad doublet (\(J = 2\) Hz) at δ 5.82 (with satellite peaks due to tin coupling, \(J_{\text{Sn-H}} = 36/40\) Hz) was attributed to the C-2 olefinic proton.

The \(^1\)H broad band decoupled \(^{13}\)C nmr showed nine signals. Seven of them were attributed to the saturated (sp\(^3\)) carbons (δ -10.83, -5.10, 17.98, 25.67, 34.09, 36.90 and 79.45) and the other two were attributed to the sp\(^3\) carbon centers (δ 143.95 and 148.22). These data confirmed the structure.

2.4 Preparation of 1-lithio-3-tert-butylidimethylsiloxycyclopentene 84 and its reaction with electrophiles

Gilman and co-workers [68] showed that tetra-n-butyltin can be prepared by reaction of tetraphenyltin with excess n-butyllithium (equation 18). This process, now commonly referred to as transmetalation [30], has been developed into a valuable tool in organic synthesis.

The synthetic utility of this reaction was demonstrated when Seyferth and co-workers published the preparation of vinylithium, a reagent hitherto unknown, by reaction of phenyllithium with tetravinyltin (equation 19) [69].

\[
\begin{align*}
\text{Ph}_4\text{Sn} + 4 \text{n-BuLi} & \rightarrow \text{n-Bu}_4\text{Sn} + 4 \text{PhLi} \\
(\text{CH}_3\text{=CH})_4\text{Sn} + 4 \text{PhLi} & \rightarrow 4 \text{CH}_3\text{=CHLi} + \text{Ph}_4\text{Sn}
\end{align*}
\]
Corey and Wollenberg [70], in one of the earliest reports of the use of a functionalized vinylstannane as a precursor of a $\beta$-acylvinyl anion synthon, showed that the functionalized vinylstannane 86 could be prepared via hydrostannation of the terminal acetylene 85. Transmetalation of 86 with n-butyllithium at low temperature (−78°C) resulted in the formation of the lithio species 87. Conversion of the resulting lithio species into the corresponding cuprate allowed for the ready conjugate addition of the protected (E)-3-hydroxypropenyl group to an $\alpha,\beta$-unsaturated ketone (scheme 12).

A similar approach has been used in a prostaglandin synthesis [30b] (scheme 13). Thus, the acetylene 89 was converted into the vinylstannane 90 via hydrostannation. Transmetalation of 90 yielded the corresponding $\beta$-acylvinyl
anion reagent 91. Formation of the cuprate reagent, reaction with the highly functionalized cyclopentenone 92, and hydrolysis, afforded (±)-prostaglandin E$_2$ 93 and (±)-15-epiprostaglandin E$_2$ 94.

The literature records an extensive survey of recent examples of vinyllithium reagents accessible via transmetalation of vinylstannanes [71, 30]. This process has become popular among synthetic organic chemists for the following reasons: (a) the reaction usually proceeds smoothly at low temperatures, (b) the reaction
is completely stereospecific, and (c) the by-product of the reaction is a coordinatively saturated tetraalkyltin which does not interfere with the reactions of the vinyllithium species.

With our preparation of the β-acylvinyl anion precursor (3-tert-butyldimethylsiloxycyclopentene 83) accomplished, the task at hand was to study the transmetalation of this substance. We were pleased to find that the transmetalation of 83 proceeded smoothly and cleanly at -78°C. Thus, when a tetrahydrofuran solution of 83 was treated with 1.2 equivalents of methyllithium at -78°C for 1 h, a pale yellow solution of 1-lithio-3-tert-butyldimethylsiloxycyclopentene 84 was obtained (equation 20).

![Chemical structure](image)

The intermediate 84 reacted smoothly with a variety of electrophilic reagents to produce the corresponding substituted allyl ethers. Some of the results are summarized in Table II.

A typical procedure is as follows [35]. To a cold (-78°C), stirred solution of 83 (0.27 mmol) in 3 mL of dry tetrahydrofuran, under an atmosphere of argon, was added dropwise a solution of methyllithium in ether (0.32 mmol) and the resultant pale yellow solution was stirred at -78°C for 1 h. Cyclohexanone
Table II: Reaction of 1-lithio-3-tert-butylidimethylsiloxydicyclopentene 84 with electrophiles.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile ($E^+$)</th>
<th>Product</th>
<th>$E$ in 95</th>
<th>% Yield$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$(CH$_2$)$_3$I</td>
<td>96</td>
<td>CH$_3$(CH$_2$)$^-$</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>R(CH$_2$)$_2$Br$^2$</td>
<td>97</td>
<td>R(CH$_2$)$_2$$^-$</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>cyclohexanone</td>
<td>98</td>
<td>1-hydroxy-cyclohexyl</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>cyclopentanone</td>
<td>99</td>
<td>1-hydroxy-cyclopentyl</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>RCH$_2$-CHO$^2$</td>
<td>100</td>
<td>RCH$_2$CH(OH)$^-$</td>
<td>61</td>
</tr>
</tbody>
</table>

$^1$ Yield of distilled purified product

$^2$ R = 2-cyclopentenyl

(0.35 mmol) was added (in 1 mL tetrahydrofuran) and the reaction mixture was stirred for an additional period of 1 h. After successive addition of saturated aqueous sodium bicarbonate and diethyl ether, the mixture was allowed to warm to room temperature. The ether solution was then washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation of
solvent, followed by distillation (air-bath) of the residual oil gave 52 mg (78\%) of pure 1-(1-hydroxycyclohexyl)-3-tert-butylidimethylsiloxy cyclopentene 98. The structure of 98 was confirmed by its spectral data. The $^1$H nmr spectrum of this compound exhibited a one-proton broad doublet ($J = 2$ Hz) at $\delta$ 5.55 which was attributed to C-2 olefinic proton. A broad unresolved signal at $\delta$ 1.27-2.71 was attributed to the cyclohexyl and cyclopentenyl methylene protons and the hydroxyl proton. The weak absorption band at 1618 cm$^{-1}$ in the ir spectrum indicated the presence of a double bond. There also appeared a broad absorption band at 3360 cm$^{-1}$ which was due to the hydroxyl function.

Similarly, the vinnyllithium intermediate 84 was allowed to react with a variety of other electrophilic reagents. The results are summarized in Table II. All of the products listed in Table II gave spectral data in full accord with the assigned structures. Each of these products also gave a satisfactory molecular weight determination (high resolution mass spectrometry).

![98]

In connection with the data summarized in Table II, the following points should be noted. Although, the reaction of the vinylithium reagent 84 with carbonyl compounds (entries 3-5, Table II) proceeded to completion at $-78^\circ$C (1 h), the alkylation reactions (entries 1-2, Table II) were carried out for 1 h at $-78^\circ$C and 1 h at room temperature. Ggc analysis of the crude reaction products showed that essentially only one product, contaminated with small amount of the
protonated species, was obtained from each reaction. In general the products could be purified by a simple distillation (air-bath), since the relatively volatile tetramethyltin could be separated very easily from the various reaction products 95.

2.5 Conjugate addition of cuprate and Grignard species derived from 1-lithio-3-tert-butyl(dimethyl)siloxy-cyclopentene 84 to enones

Organocopper reagents have played a pivotal role in the recent history of organic synthesis. The usefulness of these reagents can be attributed to their ability to form carbon-carbon bonds under relatively mild conditions (e.g., at or below room temperature) [72]. After having demonstrated the viability of 1-lithio-3-tert-butyl(dimethyl)siloxy-cyclopentene 84 as the equivalent of a d3 synthon, the important task at hand was to explore whether cuprate species could be generated from 84, and, if so, whether such reagents are viable to effect conjugate addition to enones and β-iodo enones.

\[ R(L)CuLi \quad 101 \]
\[ R_2CuLi \quad 102 \]

It was desirable to generate heterocuprates of the general structure 101 rather than bis-homocuprates 102, in order to save one equivalent of the valuable vinylethylithium reagent in the process. It was equally important to select a proper auxiliary ligand so as to enable us to perform conjugate addition reactions at low temperatures (at higher temperatures these vinylethylithium reagents tend to couple [73]). Both the phenylthio and the cyano groups proved to be excellent non-transferable ligands.
Addition of solid phenylthiocopper (1 equiv.) to a cold (-78°C) solution of 1-lithio-3-tert-butyldimethylsiloxy-cyclopentene 84 in tetrahydrofuran yielded a yellow slurry which was stirred at -78°C for 1 h to afford a yellow solution of the phenylthiocuprate 103. Similarly, the cyanocuprate 104 was prepared by adding cuprous cyanide (1 equiv) to a cold (-78°C) solution of 84 in tetrahydrofuran. The pale yellow slurry thus produced was allowed to stir at -78°C for 1 h to afford a yellow solution of 104. The corresponding Grignard reagent 105 was made by addition of 1 equiv. of dry magnesium bromide to the solution of 84 at -78°C for 1 h to yield the desired white solution of 105 (equation 21).

Importantly, reagents 103, 104 and 105 were sufficiently stable to allow for reaction with enones, to afford good to excellent yields of the corresponding conjugate addition products. Specifically, 2-cyclopenten-1-one, 2-cyclohexen-1-one, 3-iodo-2-cyclopenten-1-one and 3-iodo-2-cyclohexen-1-one were allowed to react with tetrahydrofuran solutions of 103 (-78°C, 3 h) or 104 (-78°C, 1 h; -48°C, 3 h) to produce the corresponding products 106 - 109. The results of these transformations are listed in the Table III. Similarly, compounds 106 and 107 could be produced by reaction of the Grignard reagent 105 with the appropriate enone in the presence of 0.5 equivalents of copper (I) bromide-dimethylsulfide complex.
A typical procedure is as follows. To a cold (−78°C), stirred solution of 84 (0.2 mmol) in 3 mL of dry tetrahydrofuran, under an atmosphere of argon, was added phenylthiocopper (0.27 mmol) as a solid (by rotation of a bent tube) and the resultant yellow slurry was stirred at −78°C for 1 h. A solution of 3-iodo-2-cyclopenten-1-one (0.33 mmol) in ≈1 mL of dry tetrahydrofuran was slowly added and the resultant yellow solution was stirred at −78°C for 3 h. After successive addition of methanol (0.5 mL) and petroleum ether (15 mL), the mixture was allowed to warm to room temperature. The resulting yellow slurry was filtered through a column of Florisil and the column was eluted with 50 mL of petroleum ether. The combined eluate was dried over magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography [76] of the residue on silica gel (8 g, elution with petroleum ether–ether, 3:1) and distillation (air-bath) of the oil thus obtained afforded 55.4 mg (74%) of pure 3-(3-tert-butyldimethylsiloxycyclopent-1-enyl)-2-cyclopenten-1-one 108.

The structure of 108 was confirmed by its spectral data. The 1H nmr spectrum of this compound exhibited a one-proton broad doublet (J = 2 Hz) at δ 6.19 which was attributed to the olefinic proton of the allylic ether. The other singlet at δ 5.99 was attributed to the olefinic proton of the cyclopentenone system. The series of multiplets from δ 1.75–2.88 was attributed to the cyclopentenyl and cyclopentenone methylene protons. The strong absorption at 1707 cm⁻¹ in the ir spectrum indicated the presence of unsaturated carbonyl system. The weak absorption bands at 1624 and 1640 cm⁻¹ were attributed to the two double bonds present in the molecule.

Similarly, the cuprate intermediate 103 was allowed to react with other enone systems. The other reagents 104 and 105 were similarly reacted with the enones. The data is summarized in Table III. All of the products cited in Table
III gave spectral data in full accord with the assigned structures. Each of these products also gave a satisfactory molecular weight determination (high resolution mass spectrometry).

In all cases studied, the reactions were quite efficient and experimentally straightforward. The phenylthiocuprate, the cyanocuprate and the Grignard reagent (103, 104 and 105 respectively) gave comparable yields in the conjugate addition process, involving enones. In each case, the crude product obtained after addition of the reagents 103, 104 and 105 to the enones, including iodoenones, consisted essentially of the conjugate addition product and a small amount of the enone. These materials were easily separated by column chromatography on silica gel (elution with petroleum ether–ether).
Table III: Reaction of the cuprates 103 and 104 and the Grignard reagent 105 with enones and β-iodo enones.

![Reaction diagram]

<table>
<thead>
<tr>
<th>X</th>
<th>Electrophile (E')</th>
<th>Product</th>
<th>E in 95</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>X = [CuSPh]Li</td>
<td></td>
<td>2-cyclopent-1-one</td>
<td>106</td>
<td>72</td>
</tr>
<tr>
<td>X = [CuCN]Li</td>
<td></td>
<td>3-oxocyclopently</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>X = MgBr</td>
<td></td>
<td></td>
<td></td>
<td>69</td>
</tr>
<tr>
<td>X = [CuSPh]Li</td>
<td></td>
<td>2-cyclohexen-1-one</td>
<td>107</td>
<td>91</td>
</tr>
<tr>
<td>X = [CuCN]Li</td>
<td></td>
<td>3-oxocyclohexyl</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>X = MgBr</td>
<td></td>
<td></td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>X = [CuSPh]Li</td>
<td></td>
<td>3-iodo-2-cyclopent-1-one</td>
<td>108</td>
<td>74</td>
</tr>
<tr>
<td>X = [CuCN]Li</td>
<td></td>
<td>3-oxocyclopent-1-enyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X = MgBr</td>
<td></td>
<td></td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>X = [CuSPh]Li</td>
<td></td>
<td>3-iodo-2-cyclohex-1-one</td>
<td>109</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-oxocyclohex-1-enyl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Isolated yield with respect to the enones
2 Catalyzed by CuBr.SMe₂
3 Via "one-pot" cuprate formation
Our success at the "one-pot cuprate" formation led us to explore whether the 1-trimethylstannyl-3-tert-butyldimethyldiethoxycyclopentene 83 could be transmetalated and made to form the cuprate in a similar fashion. Success was at hand when we added 1 equiv. of methyllithium to a cold (-78°C) stirred solution of 1 equiv. of cuprous cyanide and 1 equiv. of the stannyl ether 83 in tetrahydrofuran (-78°C, 15 min; -20°C, 30 min) (equation 22). A pale yellow suspension was produced, which behaved exactly in the same manner as the cyanocuprate 104 described earlier. Hence, 0.9 equiv. of 3-iodo-2-cyclopenten-1-one in tetrahydrofuran (1 mL) (-78°C, 1 h; -48°C, 3 h) was transformed into the desired product 108 in 72% yield. Although further research is required to generalize these findings, we were pleased to find that these practical and simple "one-pot" procedures could be applied to our endeavours.
3.1 General information

Boiling points are uncorrected and those indicated as air-bath temperatures refer to short path (Kugelrohr) distillations. Infrared (ir) spectra were obtained on liquid films (neat) using a Perkin-Elmer model 710B spectrophotometer and were calibrated using the 1601 cm$^{-1}$ band of polystyrene film. Proton and carbon-13 nuclear magnetic resonance (nmr) spectra were run as deuterochloroform solution using Varian Associates models T-60, EM-360, XA-100 or XL-100 spectrometers or Bruker models WP-80 or WH-400 spectrometers. The 270 MHz spectra were recorded on a unit comprised of an Oxford Instruments 63.4 KG superconducting magnet and a Nicolet 16K computer attached to a Bruker TT-23 console. All $^1$H nmr spectra were 80 MHz spectra unless stated otherwise. Signal positions are given in $\delta$ units, with tetramethylsilane (TMS) as internal standard. In the case of compounds with trimethylstannyl and/or tert-butyldimethylsilyl groups the resonance positions were determined relative to the chloroform signal ($\delta$ 7.25 [74]) unless stated otherwise. The multiplicity, number of protons, coupling constants (wherever possible) and assignments are indicated in parentheses. The tin-proton coupling constants $J$(Sn-H) are given as $J^{119}$Sn-H)/ $J^{119}$Sn-H) where the coupling constants for the two isotopes are distinct and as an average of the two values where they are not distinct. Low resolution mass spectra were recorded with a Varian/MAT CH4B mass spectrometer while high resolution mass spectra were recorded with a Kratos/AEI MS 50 or MS 902 mass spectrometer. In the case of compounds with trimethylstannyl groups the molecular weight determinations (high resolution mass spectrometry) were based on $^{120}$Sn and were usually made on the (M$^+$ - alkyl) peak [75].
Analytical gas-liquid chromatography (glc) was performed on a Hewlett-Packard model 5832A gas chromatograph using a 6 ft x 0.125 in. stainless steel column packed with 3–5% OV-17 on 80–100 mesh Chromosorb W(HP) (column A) and a thermal conductivity detector, or on a Hewlett-Packard model 5880 gas chromatograph using a 25 mm x 0.21 mm fused silica column coated with cross-linked SE-54 (column B) and a flame ionization detector.

Thin-layer chromatography (tlc) was carried out on commercial plastic-backed silica gel plates (Eastman Chromatogram Sheet Type 13181) or on aluminum-backed plates (E. Merck, Type 5554). Preparative tlc was accomplished on 20 x 20 cm glass plates coated with 0.7 mm of silica gel (E. Merck, Silica Gel 60). Conventional column chromatography was done on 70–230 mesh silica gel (E. Merck, Silica Gel 60) or Florisil (J.T. Baker Chemical Co., 100–200 mesh). Flash chromatography [76] was done on 230–400 mesh silica gel (E. Merck, Silica Gel 60).

Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon using either dry or carefully flame-dried glassware.

Cold temperatures were maintained by use of the following baths [77]: aqueous calcium chloride/ CO₂ (−20°C) [78], acetonitrile/ CO₂ (−48°C), acetone/ CO₂ (−78°C).

All compounds which were characterized by high resolution mass measurements were homogeneous by glc and tlc analyses.
3.2 Solvents and reagents

Solvents and reagents were purified and dried using established procedures [79-80] and are summarized in Table IV. All solvents were distilled before use. Petroleum ether refers to the fraction boiling between 30-60°C.

Hexamethylditin was obtained from the Alfa Division of the Ventron Corporation or from Organometallics, Inc.

Solutions of methyllithium–lithium bromide complex in ether were obtained from Aldrich Chemical Co., Inc. and were standardized using the double-titration procedure of Gilman [81]. Diisobutylaluminum hydride (DIBAH) as a 1.0 M solution in hexane was also obtained from Aldrich.

1,3-Cyclopentanedione was obtained from Aldrich Chemical Co., Inc. and was recrystallized from methylene chloride/petroleum ether, or was synthesized according to Schank et al. [82]. Triphenylphosphine diiodide was prepared by a procedure slightly modified from that reported [7]. To a stirred suspension of azeotropically dried [84] iodine in dry acetonitrile under an atmosphere of argon was added triphenylphosphine¹ (recrystallized from ethyl acetate/methanol) and the mixture was stirred at room temperature for 15 min [83c-d].

3-Iodo-2-cyclopenten-1-one was prepared by refluxing (4 h) 1,3-cyclopentanedione with triphenylphosphine diiodide (prepared as outlined above) in dry acetonitrile in the presence of freshly distilled triethylamine under an atmosphere of dry argon [83].

¹ This order of addition was found to be important and led to increase in yield of the β-iodo enone (sometimes greater than reported yield of 85%).
Table IV: Purification of solvents and reagents

<table>
<thead>
<tr>
<th>Material</th>
<th>Drying Agent</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>P₂O₅</td>
<td>80a</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>P₂O₅</td>
<td>79</td>
</tr>
<tr>
<td>N,N-Dimethylformamide¹</td>
<td>CaH₂</td>
<td>80b</td>
</tr>
<tr>
<td>Dimethyl sulfoxide²</td>
<td>CaH₂</td>
<td>80b</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>Na/ Ph₂CO</td>
<td>80a</td>
</tr>
<tr>
<td>Hexamethylphosphoramide²</td>
<td>CaH₂</td>
<td>80b</td>
</tr>
<tr>
<td>Hexane</td>
<td>CaH₂</td>
<td>79</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>Na/ Ph₂CO</td>
<td>80a</td>
</tr>
<tr>
<td>Triethylamine</td>
<td>LiAlH₄</td>
<td>80c</td>
</tr>
</tbody>
</table>

¹ Distilled under reduced pressure (12 Torr)
² Distilled under reduced pressure (0.2 Torr)

Phenylthiocopper [85] was prepared by refluxing a mixture of cuprous oxide (36 g, 0.25 mmol) and thiophenol (63 g, 0.57 mmol) in absolute ethanol (1000 ml) for seven days. The resultant yellow slurry was filtered, the collected material was washed thoroughly with ethanol, and dried for several days under high vacuum. The product was stored under argon in the absence of light.

Copper (I) bromide-dimethylsulfide complex [86] was prepared by the method of House [86a], after washing commercial cuprous bromide with methanol [86b].
Cuprous cyanide was purchased from J.T. Baker Co. and was used without further purification [87].

Magnesium bromide was prepared by addition of freshly distilled 1,2-dibromoethane (from Aldrich Chemical Co. Inc.) to a cold (0°C) suspension of magnesium in dry ether. Ether was removed under high vacuum and the resultant white powder was stored under argon in a dry box.

1-Bromo-2-(2-cyclopentenyl)ethane was prepared by treatment of 2-(2-cyclopentenyl)ethanol [88] (prepared by lithium aluminum hydride reduction of 2-(2-cyclopentenyl)acetic acid) with triphenylphosphine dibromide [89] in acetonitrile with triethylamine at 0°C.

2-(2-Cyclopentenyl)ethanal [90] was prepared by treating 2-(2-cyclopentenyl)-ethanol with stirred suspension of pyridinium chlorochromate in anhydrous dichloromethane, under an atmosphere of argon at 0°C.

Saturated basic ammonium chloride (pH 8) was prepared by the addition of \( \approx 50 \text{ mL} \) of aqueous ammonium hydroxide (58%) to 1 L of saturated aqueous ammonium chloride.

3.3 Typical procedures for the preparation of trimethylstannyl reagents

3.3.1 Preparation of trimethylstannyllithium

To a cold (0°C) stirred solution of hexamethylditin in dry tetrahydrofuran (\( \approx 10 \text{ mL per mmol of hexamethylditin} \)) was added a solution of methyllithium in ether (1.0 equiv.). The resulting solution was stirred at \(-20^\circ\text{C}\) for 15 min to afford a pale yellow solution of trimethylstannyllithium [36].
3.3.2 Preparation of lithium (phenylthio)(trimethylstannyl)cuprate 8

\[ \text{[Me}_3\text{SnCuSPh]Li} \]

To a cold \((-20^\circ C)\), stirred solution of trimethylstannyl lithium (0.39 mmol, prepared as outlined above) in 5 mL of dry tetrahydrofuran was added in one portion solid phenylthiocopper (67.3 mg, 0.39 mmol). The resulting yellow slurry was stirred at \(-20^\circ C\) for 15 min to afford a dark red solution of lithium (phenylthio)(trimethylstannyl)cuprate 8 [29].

Alternatively, to a cold \((-78^\circ C)\), stirred solution of hexamethylditin (0.39 mmol) and phenylthiocopper (67 mg, 0.39 mmol) in 5 mL of dry tetrahydrofuran, was slowly added 1 equiv. of methylolithium (295 \(\mu\)l, 1.32 M, 0.39 mmol) over a period of 2 min. The resulting mixture was stirred at \(-20^\circ C\) for 30 min to afford a red solution of the phenylthiocuprate 8.

3.3.4 Preparation of lithium (cyano)(trimethylstannyl)cuprate 74

\[ \text{[Me}_3\text{SnCuCN]Li} \]

To a cold \((-78^\circ C)\), stirred solution of trimethylstannyl lithium (0.39 mmol, prepared as outlined above) in 5 mL of dry tetrahydrofuran was added in one portion solid cuprous cyanide (34.9 mg, 0.39 mmol). The resulting mixture was stirred at \(-78^\circ C\) for 5 min and then at \(-48^\circ C\) for 15 min to afford a bright yellow solution of the cyanocuprate 74 (0.39 mmol) [49].

Alternatively, to a cold \(-78^\circ C\), stirred solution of hexamethylditin (0.39 mmol) and azeotropically dried (toluene) cuprous cyanide (0.39 mmol) in 5 mL of
dry tetrahydrofuran, was slowly added 1 equiv. of methyllithium (277 μl, 1.41 M, 0.39 mmol) over a period of 2 min. The resultant flocculent yellow suspension was stirred at -48°C for 30 min to give the cyanocuprate 74.

3.3.5 Preparation of dilithium (cyano)(methyl)(trimethylstannyl)cuprate 78

\[ [\text{Me}_3\text{Sn(Me)CuCN}]\text{Li}_2 \]

78

To a cold (-78°C), stirred solution of lithium (cyano)(trimethylstannyl)cuprate 80 (0.39 mmol, prepared as outlined above) in 5 mL of dry tetrahydrofuran was added a solution of methyllithium in ether (0.39 mmol). The resulting mixture was stirred at -20° for 15 min to afford a homogeneous tan solution of the higher order cyanocuprate 78 (0.39 mmol).

Alternatively, to a cold (-78°C), stirred solution of hexamethylditin (0.39 mmol) and cuprous cyanide (34.9 mg, 0.39 mmol), previously azeotropically dried with toluene [87], in 5 mL of dry tetrahydrofuran, was slowly added 2 equiv. of methyllithium. The resulting mixture was stirred at -20°C for 30 min to afford a homogeneous tan solution of higher order cuprate 78 (0.39 mmol).

3.4 Preparation of 3-trimethylstannyl-2-cyclopenten-1-one 14

3.4.1 Using the higher order cyanocuprate 78
To a cold (-78°C), stirred solution of the higher order cuprate 78 (0.39 mmol, prepared as outlined above) in 5 mL of dry tetrahydrofuran, under an atmosphere of argon, was added a solution (THF, 1 mL) of 3-iodo-2-cyclopenten-1-one (69 mg, 0.33 mmol). The resulting dark tan solution was stirred at -78°C for 90 min, at -48°C for 60 min, and at 0°C for 60 min. Saturated aqueous basic (pH 8) ammonium chloride (2 mL) and ether (10 mL) were added, and the resulting mixture was stirred (in the fumehood) vigorously at room temperature for several minutes. The ether layer was washed with saturated aqueous basic (pH 8) ammonium chloride, and dried over anhydrous magnesium sulfate. Removal of the solvent afforded a pale yellow oil which on glc analysis showed only desired product accompanied by some hexamethylditin. Flash chromatography [76] (3 g silica gel, eluting with petroleum ether–ether, 4:1), concentration of the appropriate fractions and distillation (air-bath temperature 61-72°C/ 0.02 Torr) of the reduced material afforded 67 mg (83%) of the β-trimethylstannylenone 14 [29]. Tlc and glc analysis (silica gel and column B, respectively) showed the presence of one component. The spectral properties of this material were identical with those reported earlier [38].

3.5 Large scale preparation of 3-trimethylstannylenone 14

3.5.1 Using the phenylthiocuprate 8

To a cold (-78°C), stirred solution of lithium (phenylthio)(trimethylstannyl)cuprate 8 (4.0 mmol, prepared as outlined above) in 50 mL of dry tetrahydrofuran, under an atmosphere of argon, was added a solution (THF, 5 mL) of 3-iodo-2-cyclopenten-1-one 75 (728 mg, 3.5 mmol). The resulting mixture was stirred at -78°C for 3 h. Methanol (≈2 mL) and petroleum ether (200 mL) were added, and the mixture was stirred at room temperature for several minutes. The
resultant yellow slurry was filtered through a short column of Florisil (20 g, 100–200 mesh). The column was eluted with a further 3 x 100 mL of petroleum ether followed by 100 mL of ether and the eluate was combined. Removal of the solvent afforded a yellow oil which, on the basis of glc analysis (column B), consisted of one product, accompanied by hexamethylditin. Subjection of this oil to flash chromatography (30 g silica gel, elution with petroleum ether–ether, 4:1) gave after concentration of the appropriate fractions and distillation (air–bath) of the residual material, 703 mg (82%) of the trimethylstannyl enone 14. The spectral properties of this material were identical with those reported earlier [38].

3.6 Preparation of 3–trimethylstannyl–2–cyclopenten–1–ol 81

\[
\text{OH} \quad \text{SnMe}_3
\]

3.6.1 Small scale

To a cold (0°C), vigorously stirred mixture of 3–trimethylstannyl–2–cyclopenten–1–one 14 (78 mg, 0.32 mmol) in 5 mL of dry hexane, under an atmosphere of argon, was added dropwise a solution of diisobutylaluminum hydride in hexane (0.38 mmol). The resulting mixture was stirred at 0°C for 1.75 h [61]. Sodium sulphate decahydrate (powdered) was added carefully and the mixture was vigorously stirred for several minutes until a white precipitate had formed. The inorganic salts were removed by filtration and were washed with several portions of hot ether. The combined filtrate was concentrated under
reduced pressure (aspirator). Distillation (air-bath temperature 42–52°C/ 0.02 Torr) of the residual oil afforded 78 mg (98%) of 3-trimethylstannyl-2-cyclopenten-1-ol 81. Tlc and glc analysis (silica gel and column B, respectively) showed the presence of one component. This material exhibited ir (film): 3290, 2880, 1690, 767 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.16 (s, 9 H, stannyl methyls, J₈Sn-H = 55 Hz), 1.48 (br. s, 1 H, -OH, exchanges with D₂O), 1.61–1.71 (m, 1 H), 2.19–2.29 (m, 1 H), 2.34–2.44 (m, 1 H), 2.56–2.67 (m, 1 H), 4.88 (br. m, 1 H), 5.94 (br. d, 1 H, J = 2 Hz, J₈Sn-H = 35/39 Hz). Exact Mass calcd. for C₉H₁₆O Sn: 248.0223; found: 248.0233.

3.6.2 Large scale

To a cold (-78°C), vigorously stirred solution of 3-trimethylstannyl-2-cyclopenten-1-one 14 (788 mg, 3.22 mmol) in 30 mL of dry diethyl ether under argon, was added dropwise over a period of 5 min a solution of diisobutylaluminum hydride in hexane (4.0 mL, 4.0 mmol). The resulting mixture was stirred at 0°C for 2 h. Saturated aqueous ammonium chloride (1 mL) and ether (60 mL) were carefully added and the mixture was stirred until a white precipitate was formed. Anhydrous magnesium sulphate was added and the resultant mixture was filtered through a pad of celite under suction (water aspirator). The collected material was washed with several portions of hot ether (10 x 10 mL). The combined filtrate was concentrated under reduced pressure. Distillation (air-bath) of the residual oil afforded 755 mg (95%) of 3-trimethylstannyl-2-cyclopenten-1-ol 81. The spectral properties of this material (ir, ¹H nmr) were identical with those described above.
3.7 Preparation of 3-tert-butyldimethysiloxy-1-trimethylstannylcyclopentene 83

To a stirred solution of 3-trimethylstannyl-2-cyclopenten-1-ol 81 (76.5 mg, 0.31 mmol) in 1 mL of dry N,N-dimethylformamide, under an atmosphere of argon, was added, successively, imidazole (0.11 g, 1.6 mmol) and freshly sublimed tert-butylidimethylsilyl chloride (49 mg, 0.32 mmol). After the reaction mixture had been stirred at room temperature for 90 min, it was diluted with 5% (W/V) aqueous sodium bicarbonate and thoroughly extracted with ether. The combined extract was washed with 5% (W/V) aqueous sodium bicarbonate and dried over anhydrous magnesium sulphate. Removal of the solvent, followed by flash chromatography (4 g, silica gel, elution with petroleum ether–ether, 9:1) gave after concentration of all the fractions containing the desired product, a colorless oil. Fractional distillation of the crude product to remove tert-butylidimethylsilanol (air-bath temperature ≈60°C/12 Torr) and distillation (air-bath temperature 58–60°C/0.2 Torr) provided 110 mg (97%) of 3-tert-butylidimethysiloxy-1-tri-methylstannylcyclopentene 83 as a colorless liquid. Glc analysis (column A) showed the presence of one compound. This material exhibited ir (film): 2893, 1583, 1090, 778 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.097 (s, 6 H, silyl methyls), 0.15 (s, 9 H, stannyl methyls, J_{Sn-H} = 56 Hz), 0.93 (s, 9 H, silyl tert-butyl), 1.56–1.67 (m, 1 H), 2.16–2.26 (m, 1 H), 2.26–2.38 (m, 1 H), 2.55–2.66 (m, 1 H),
4.95 (m, 1 H), 5.82 (br. d, 1 H, J = 2 Hz, J<sub>Sn-H</sub> = 36/40 Hz). <sup>13</sup>C nmr (20.15 MHz, CDCl<sub>3</sub>, <sup>1</sup>H broad band decoupled) δ: -10.83 (stannyl methyls), -5.10 (silyl methyls), 17.98 (quaternary carbon), 25.67 (tert-butyl methyls), 34.09, 36.90 (methylene carbons), 79.45 (−CH(OSiR<sub>3</sub>)−), 143.95 (−C(SnMe<sub>3</sub>)−), 148.22 (−CH−).

**Exact Mass** calcd. for C<sub>10</sub>H<sub>21</sub>OSiSn (M+ − Bu<sup>t</sup>): 305.0384; found: 305.0384.

### 3.8 General procedure A

**Preparation of 1-lithio-3-tert-butyl(dimethyl)siloxy)cyclopentene 84 and its reaction with electrophiles**

![Chemical Structure](image)

**84**

To a cold (−78°C), stirred solution of 3-tert-butyl(dimethyl)siloxy-1-trimethylstannyl)cyclopentene 83 (98 mg, 0.27 mmol) in 3 mL of dry tetrahydrofuran, under an atmosphere of argon, was added, dropwise, a solution of methyllithium in ether (220 μL, 1.47 M, 0.32 mmol). The resulting mixture was stirred at −78°C for a period of 1 h. A colorless solution of the vinylolithium intermediate 84 resulted.

A solution of the appropriate electrophile (1.3 equivalents) in dry tetrahydrofuran (0.5 mL) was added. When the electrophile was an alkyl halide, the reaction mixture was stirred at −78°C for 1 h, warmed to room temperature
over a period of 1 h, and then quenched with saturated aqueous sodium bicarbonate (0.3 mL). With carbonyl electrophiles, the reaction mixture was stirred at -78°C for 1 h, and treated at this temperature with saturated aqueous sodium bicarbonate (0.3 mL). The resulting mixtures were immediately diluted with ether, washed with saturated aqueous sodium bicarbonate, and dried over anhydrous magnesium sulfate. Removal of the solvent afforded a pale yellow oil. The reaction product was purified by simple distillation (air-bath).

3.9 Preparation of 1-n-butyl-3-tert-butyl(dimethyl)siloxy[1]cyclopentene 96

Following the general procedure A outlined above, 0.27 mmol of the vinylolithium reagent 84 (prepared from the reaction of 83 with methyllithium) was allowed to react with 1-bromobutane (40 μL, 0.35 mmol) in tetrahydrofuran (3 mL) at -78°C for 1 h, and at room temperature for 1 h. Normal workup, followed by distillation (air-bath temperature 55-60°C/ 0.5 Torr) of the residual oil afforded 54 mg (60%) of compound 96. A glc analysis (column B) showed the presence of one compound. This material exhibited IR (film): 2910, 1650, 1263, 1069 cm⁻¹; ¹H nmr (400 MHz, CDCl₃, external TMS as standard) δ: 0.08 (s, 6 H, silyl methyls), 0.90 (s, 9 H, tert-butyl methyls), 0.88-0.92 (m, 3 H, terminal methyl), 1.25-1.37 (m, 2 H, -CH₂-CH₃), 1.39-1.48 (m, 2 H, -CH₂-CH₂-CH₃), 1.62-1.72
(m, 1 H), 2.32–2.41 (m, 1 H), 4.88 (br. m, 1 H), 5.34 (d, 1 H, vinyl proton, $J = 1$ Hz). 

Exact Mass calcd. for $C_{11}H_{21}OSi$ (M$^+$ – Bu$^+$): 197.1361; found: 197.1358.

3.10 Preparation of 1-[2-(2-cyclopentenyl)ethyl]-3-tert-butyldimethylsiloxycyclopentene

Following the general procedure A outlined above, 0.27 mmol of the vinyl lithium reagent (prepared as outlined above) was allowed to react with 1-bromo-2-(2-cyclopentenyl)ethane (61 mg, 0.35 mmol), in the presence of dry hexamethylphosphoramide (61 µL, 0.35 mmol) in tetrahydrofuran at -78°C for 1 h, and room temperature for 4 h. Saturated aqueous sodium bicarbonate (1 mL) was added and the resultant mixture was thoroughly extracted with ether (2 x 10 mL). The combined extract was washed with saturated aqueous copper sulfate (10 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure, followed by distillation (air-bath temperature 71–75°C/ 0.2 Torr) of the residual oil afforded 57 mg (72%) of the ether. A glc analysis (column B) showed the presence of one component. This material exhibited IR (film): 2903, 1636, 1250, 1030 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.08 (s, 6 H, silyl methyls), 0.90 (s, 9 H, tert-butyl methyls), 1.35–1.73 (series of m, 4 H), 2.00–2.43 (series of m, 8 H), 2.64 (br. m, 1 H, allylic tertiary proton), 4.88 (br. m, 1 H), 5.30 (m, 1 H, vinylic –CH(OSiR$_3$)–CH=CR–), 6.50–6.70 (m, 2 H, cyclopentenyl olefinic protons). 

Exact Mass calcd. for $C_{19}H_{32}OSi$: 292.2222; found: 292.2218.
3.11 Preparation of 1-(1-hydroxycyclohexyl)-3-tert-butyldimethylsiloxy-cyclopentene

Following the general procedure A above, 0.27 mmol of the vinyllithium reagent 84 (prepared by reaction of 83 with methyllithium) was allowed to react with cyclohexanone (37 µL, 0.35 mmol) in tetrahydrofuran at -78°C for 1 h. Normal workup, followed by distillation (air-bath temperature 90-95°C/0.1 Torr) of the residual oil afforded 52 mg (78%) of the silyl ether 98. A glc analysis (column B) showed the presence of one component. This material exhibited ir (film): 3360, 2905, 1618, 1227, 1039 cm⁻¹; ¹H nmr (CDCl₃) δ: 0.07 (s, 6 H, silyl methyls), 1.27 (s, 9 H, tert-butyl methyls), 1.27-2.71 (broad unresolved signal, 15 H), 2.02-2.71 (m, 3 H), 4.89 (m, 1 H, -CH(OSiR₃)-), 5.55 (br. d, 1 H, -CH=CR-, J = 2 Hz). Exact Mass calcd. for C₁₇H₂₉O₂Si (M⁺ - CH₃): 293.1934; found: 293.1937.

3.12 Preparation of 1-(1-hydroxycyclopentyl)-3-tert-butyldimethylsiloxy-cyclopentene

58
Following the general procedure A outlined above, 0.27 mmol of vinyllithium reagent 84 (prepared by reaction of 83 with methyllithium) was allowed to react with cyclopentanone (31 µL, 0.35 mmol) in tetrahydrofuran at -78°C for 1 h. Normal workup, followed by distillation (air-bath temperature 84-87°C/0.1 Torr) of the residual oil, gave 60 mg (77%) of the silyl ether 99. A glc analysis (column B) showed the presence of one component. This material exhibited ir (film): 3330, 2930, 1619, 1227, 1037 cm⁻¹; ¹H nmr (CDCl₃) δ: 0.11 (s, 6 H, silyl methyls), 0.93 (s, 9 H, tert-butyl methyls), 1.32-2.10 (broad unresolved signal, 10 H), 2.10-2.67 (br. m, 3 H), 4.90 (br. m, 1 H, -CH(OSiR₃)-), 5.59 (br. d, 1 H, -CH=CR-, J = 2 Hz). Exact Mass calcd. for C₁₆H₂₇O₂Si (M⁺ - CH₃): 267.1780; found: 267.1781.

3.13 Preparation of 1-[(1-hydroxy-2-(2-cyclopentenyl)ethyl]-3-tert-butyldimethylsiloxy-cyclopentene 100

Following the general procedure A outlined above, 0.27 mmol of the vinyllithium reagent 84 (prepared by reaction of 83 with methyllithium) was allowed to react with 2-(2-cyclopentenyl)ethanal (37 mg, 0.35 mmol) in tetrahydrofuran (3 mL) at -78°C for 1 h. Normal workup, followed by distillation (air-bath temperature 138-145°C/0.2 Torr) of the residual oil afforded 51 mg
(61%) of the hydroxy silyl ether 100. A gic analysis (column B) showed the presence of two major components in a ratio of 4 : 5.5. This material exhibited

ir (film): 3375, 2930, 1629, 1605, 1225, 1028 cm⁻¹; ¹H nmr (CDCl₃) δ: 0.11 (s, 6 H, silyl methyls), 0.88 (s, 9 H, tert-butyl methyls), 1.12-3.0 (broad unresolved signal, 11 H), 2.02 (s, 1 H, -OH, exchanges with D₂O), 4.46 (br. t, 1 H, -CHOH, J = 6 Hz), 4.87 (m, 1H, -CH(OSiR₃⁻)), 5.50-5.88 (m, 3 H, vinylic protons). Exact Mass calcd. for C₁₇H₂₅O₂Si (M⁺ - CH₃): 293.1936; found: 293.1930.

3.14 General procedure B

Preparation of the phenylthiocuprate 103 and its reaction with αβ-unsaturated ketones and β-iodo-α,β-unsaturated ketones

To a cold (-78°C), stirred solution of 1-lithio-3-tert-butyldimethylsiloxy-cyclopentene 84 (0.27 mmol, prepared as outlined in general procedure A) in 3 mL of dry tetrahydrofuran was added in one portion, solid phenylthiocopper (46.6 mg, 0.27 mmol). The resulting yellow slurry was stirred at -78°C for 1 h to afford a yellow solution of lithium (3-tert-butyldimethylsiloxo-1-cyclopentenyl)-(phenylthio)cuprate 103.

A solution of the appropriate enone (0.25 mmol) in dry tetrahydrofuran (≈1 mL) was added and the mixture was stirred for 3 h at -78°C. Methanol (≈0.5
mL) and petroleum ether (15 mL) were added and the mixture was allowed to warm to room temperature. The resulting yellow slurry was filtered through a column of Florisil (5 g, elution with petroleum ether). The combined eluate was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Column chromatography of the residue on silica gel (8 g, elution with petroleum ether–ether, 3:1) and distillation of the oil thus obtained afforded pure product.

3.15 General procedure C

Preparation of the cyanocuprate 104 and its reaction with enones and β-iodo enones

To a cold (–78°C), stirred solution of 1-lithio-3-tert-butyldimethylsiloxy cyclopentene 84 (0.27 mmol, prepared as outlined in general procedure A) in 3 mL of dry tetrahydrofuran was added in one portion, solid cuprous cyanide [87] (24 mg, 0.27 mmol). The resulting mixture was stirred at –78°C for 1 h to afford a pale yellow solution of lithium (3-tert-butyldimethylsiloxy-1-cyclopentenyl)(cyano)cuprate 104.

Alternatively, to a cold (–78°C), stirred solution of 1-trimethylstanny1-3-tert-butyldimethylsiloxy cyclopentene 83 (0.27 mmol) and cuprous cyanide (24 mg, 0.27 mmol) in dry tetrahydrofuran (3 mL), was added methyllithium in ether
(489 μl, 1.32 M, 0.27 mmol). The resulting solution was stirred at -78°C for 15 min and at -20°C for 30 min to yield the desired cuprate 104.

A solution of the appropriate enone (0.25 mmol) in dry tetrahydrofuran (1 mL) was added and the resulting solution was stirred at -78°C for 1 h, warmed to -48°C, and stirred at this temperature for 3 h. Saturated aqueous ammonium chloride (pH 8) and ether (15 mL) were added and the mixture was allowed to warm to room temperature. The resulting solution was washed twice with saturated aqueous ammonium chloride (pH 8) and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by column chromatography and distillation of the material obtained from the appropriate fractions afforded pure product.

3.16 General procedure D

Preparation of the Grignard reagent 105 from 84 and its copper (I) catalyzed conjugate addition to enones

To a cold (-78°C), stirred solution of 1-lithio-3-tert-butyldimethylsiloxycyclopentene 84 (0.27 mmol, prepared as outlined above in general procedure A) in 3 mL of dry tetrahydrofuran under an atmosphere of argon, was added anhydrous magnesium bromide (53 mg, 0.29 mmol). The resulting white slurry was
stirred at $-78^\circ$C for 1 h to afford the Grignard reagent, 3-\(\text{tert}\)-butyldimethylsiloxy-1-cyclopentenylmagnesium bromide, 105.

Copper (I) bromide-dimethylsulfide complex (30 mg, 0.15 mmol) was added ($-78^\circ$C, 30 min), followed by a solution of appropriate enone (0.25 mmol in 1 mL of tetrahydrofuran). The yellow-red solution thus obtained was stirred at $-78^\circ$C for 3 h. Saturated basic (pH 8) aqueous ammonium chloride (5 mL) and ether (15 mL) were added and the resulting mixture was allowed to warm to room temperature. Vigorous stirring was maintained until the aqueous phase became pale blue. The organic layer was separated, washed with saturated basic (pH 8) aqueous ammonium chloride, and dried over anhydrous magnesium sulfate. Evaporation of the solvent followed by distillation of the residual oil afforded pure product.

3.17 Preparation of 3-(3-\(\text{tert}\)-butyldimethylsiloxy-1-cyclopentenyl)cyclopentanone

![Chemical Structure](attachment:image.png)

106
3.17.1 Using the phenylthiocuprate 103

Following the general procedure B outlined above, 2-cyclopenten-1-one (27 mg, 0.33 mmol) was converted into the keto ether 106. Normal workup followed by column chromatography of the crude product on silica gel (8 g, elution with petroleum ether: ether, 3:1) and distillation (air-bath temperature, 185°-190°C/ 0.4 Torr) yielded 54.4 mg (72%) of 106 as a clear colorless oil. Glc analysis showed the presence of one component and the tic analysis (developing solvent, petroleum ether: ether, 3:1) gave one spot. This material exhibited ir (film): 2830, 1715, 1544, 1225, 1045 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.07 (s, 6 H, silyl methyls), 0.89 (s, 9 H, tert-butyl methyls), 1.60-1.88 (broad unresolved m, 2 H), 2.05-2.50 (broad unresolved signal, 8 H), 2.88 (m, 1 H), 4.93 (br. m, 1 H, -CH(OSiR₃)=), 5.41-5.40 (m, 1 H). Exact Mass calcd. for C₁₂H₁₇O₂Si (M⁺ - Bu⁺): 221.0998; found: 221.1000.

3.17.2 Using the cyanocuprate 104

Following the general procedure C outlined above, there was obtained 49 mg (65%) of the keto ether 106 from 27 mg (0.33 mmol) of 2-cyclopenten-1-one. The ¹H nmr and ir spectra were identical with those of the material described above.

3.17.3 Using the Grignard reagent 105

Following the general procedure D outlined above, 52 mg (69%) of the desired keto ether 106 was obtained from 27 mg (0.33 mmol) of 2-cyclopenten-1-one. The ir and ¹H nmr spectra were identical with those of the material described above.
3.18 Preparation of 3-(3-tert-butyl(dimethyl)siloxy-1-cyclopentenyl)cyclohexanone

3.18.1 Using the phenylthiocuprate

Following the general procedure B outlined above, 2-cyclohexen-1-one (33 mg, 0.33 mmol) was converted into the keto ether 107. Normal workup followed by column chromatography of the crude product on silica gel (8 g, elution with petroleum ether–ether, 3:1) and distillation (air-bath temperature 78–81°C/0.15 Torr) of the material thus obtained gave 72 mg (91%) of ether 107 as a clear, colorless oil. Glc analysis (column B) of this oil showed that it consisted of two components in the ratio 2.6:1, which on tlc analysis (developing solvent, petroleum ether–ether, 3:1) gave one spot. This material exhibited ir (film): 2920, 1703, 1620, 1250, 1038 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.50 (s, 6 H, silyl methyls), 0.88 (s, 9 H, tert-butyl methyls), 1.53–1.74 (m, 2 H), 1.91–2.50 (broad unresolved signal, 10 H), 4.88 (br. m, 1 H, –CH(OSiR₃)–), 5.43 (br. m, 1 H, olefinic proton). Exact Mass calcd. for C₁₃H₂₁O₂Si (M⁺ – Bu⁺): 237.1311; found: 237.1305.
3.18.2 Using the cyanocuprate

Following the general procedure C above, there was obtained 63 mg (80%) of the keto ether 107 from 33 mg (0.33 mmol) of 2-cyclohexen-1-one. The ir and $^1$H nmr spectra of this material were identical with those described above.

3.18.3 Using the Grignard reagent

Following the general procedure D outlined above, 67 mg (85%) of the desired keto ether 107 was obtained from 33 mg (0.33 mmol) of 2-cyclohexen-1-one. The ir and $^1$H nmr spectra obtained were identical with those of the material described above.

3.19 Preparation of 3-(3-tert-butylidimethylsiloxy-1-cyclopentenyl)-2-cyclopenten-1-one

![Chemical structure](image)

66
Following the general procedure B outlined above, 3-iodo-2-cyclopenten-1-one 75 (68.6 mg, 0.33 mmol) was converted into the enone ether 108. Normal workup followed by column chromatography of the crude product on silica gel (8 g, elution with petroleum ether–ether, 3:1) and distillation (air-bath temperature 88–93°C/0.01 Torr) yielded 55.4 mg (74%) of 108 as a clear colorless oil. Glc analysis (column B) showed the presence of one component and the tlc analysis (developing solvent, petroleum ether–ether, 3:1) gave one spot. This material exhibited ir (film): 2946, 1707, 1624, 1640, 1260, 1076 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.09 (s, 6 H, silyl methyls), 0.90 (s, 9 H, tert-butyl methyls), 1.75–1.85 (m, 1 H), 2.30–2.48 (m, 4 H), 2.65–2.88 (m, 3 H), 5.00 (br. m, 1 H, -CH(OSiBu¹Me₂)⁻), 5.99 (s, 1 H, vinyl proton of enone), 6.19 (br. d, 1 H, J = 2 Hz, vinyl proton of allyl ether). Exact Mass calcd. for C₁₆H₂₆O₂Si : 278.1702; found: 278.1703

Following the alternative procedure in general procedure C above, there was obtained 54 mg (72%) of enone ether 108 from 68.6 mg (0.33 mmol) of the iodo enone 75. The ir, ¹H nmr spectra were identical with those described above.

3.20 Preparation of 3-(3-tert-butyldimethylsiloxy-1-cyclopentenyl)-2-cyclohex-en-1-one 109
Following the general procedure B outlined above, 3-iodo-2-cyclohexen-1-one 7 (73.3 mg, 0.33 mmol) was converted into the enone ether 109. Normal workup followed by column chromatography of the crude product on silica gel (8 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 98–107°C/ 0.01 Torr) gave 71.1 mg (89%) of a clear, colorless oil. Glc analysis (column B) of this oil showed that it consisted of one component, which on tlc analysis (developing solvent, petroleum ether-ether, 3:1) gave one spot. This material exhibited ir (film): 2930, 1668, 1608, 1598, 1255 cm⁻¹; ¹H nmr (400 MHz, CDCl₃, δ: 0.08 (s, 6 H, silyl methyls), 0.89 (s, 9 H, tert-butyl methyls), 1.70–1.81 (m, 1 H), 2.01 (m, 2 H), 2.26–2.37 (m, 2 H), 2.37–2.42 (m, 2 H), 2.44–2.69 (m, 3 H), 4.96 (br. m, 1 H), 5.93 (s, 1 H, vinyl proton of enone), 6.09 (br. d, 1 H, J = 2 Hz). **Exact Mass** calcd. for C₁₇H₂₁O₂Si : 292.1859; found 292.1860.
REFERENCES


2. (a) E. Bernary, *Chem. Ber.*, 64, 2543 (1931)

   (b) For an interesting variation, see S. Cacchi, A. Caputo, and D. Misiti, *Indian J. Chem.*, 12, 325 (1974); see also reference 6a


11. For reviews and different types of classifications, see


16. (i) Phenylthio group as electron-withdrawing group:

(ii) Alkylthio group as electron-withdrawing group (acyclic):


(b) For the use of \(\gamma\)-oxygenated vinyl sulfones as precursors, see J.C. Sadler and P.L. Fuchs, *J. Am. Chem. Soc.*, 103, 2112 (1981) and references cited therein.

(c) For the use of cyclopropyl sulfones as precursors, see M. Pohmakotr and P. Pisutjaroenpong, *Tetrahedron Lett.*, 26, 3613 (1985); see also reference 11b for other related studies.


19. Ethers as latent carbonyl function:


20. Acetals or thioacetals as latent carbonyl function:


22. Propargylic ethers as precursors of \( \text{d}^1 \) synthon:


(b) As alkynyllithium species, see G. Stork and M. Isobe, *Ibid.*, 97, 4747 (1975)


27. For a closely related study, see K. Hirai and Y. Kishida, *Tetrahedron Lett.*, 2743 (1972) 
30. The formation of vinyllithium reagent via transmetalation of trialkylstannanes with an alkylolithium is well known. For some recent reports, along with references cited therein, see 
(a) reference 21a–e 


41. For the earliest report on the addition of trimethylstannyllithium in the presence of cuprous iodide to \(\alpha,\beta\)-unsaturated ketones, see J. Hudec, *J. Chem. Soc., Perkin Trans. 1*, 1020 (1975)


44. For example, see P. Vermeer, H. Westmijze, H. Kleijn, and L.A. van Dijck, *Recl. Trav. Chim.*, 56, 56 (1978)


53. Reference 52, p. 220


57. For other studies on effects of solvents on the reactivity of higher order cyanocuprates, see B.H. Lipshutz, *Tetrahedron Lett.* 24, 127 (1983)


73. V. Karunaratne, Ph.D. thesis, The University of British Columbia, Canada, 1985


83. (a) See reference 7
(b) See also references 19a, 20b


(c) For an alternative preparation of pure copper (I) bromide–dimethylsulfide complex, see A.B. Theis and C.A. Townsend, Ibid., 11, 157 (1981)


(b) See also reference 50; B.H. Lipshutz and R.S. Wilhelm, J. Am. Chem. Soc., 103, 7672 (1981)


(b) For recent modification, see M.S. Alnajjar and H.G. Kuivila, Ibid., 107, 416 (1985); see also references 49, 83c