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The novel preparation of butenolides and 3,4-disubstituted furans: Approaches towards halenaquinone.

Jean-Louis Joseph. Bontront
University of Windsor

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THE NOVEL PREPARATION OF BUTENOLIDES

AND 3,4-DISUBSTITUTED FURANS:

APPROACHES TOWARDS HALENAQUINONE

by

Jean-Louis Joseph Bontron

A Thesis
submitted to the
Faculty of Graduate Studies and Research
through the Department of
Chemistry and Biochemistry in Partial Fulfillment
of the requirements for the Degree
of Master of Science at
the University of Windsor

Windsor, Ontario, Canada

1990
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ABSTRACT

Part 1: PALLADIUM CATALYZED CROSS-COUPLING REACTION

Many aryl bromides will undergo a palladium catalyzed cross-coupling reaction with 3-[(t-butyldimethylsilyl)oxymethyl]-4-(tri-n-butylstannyl)furan to form a new class of 3,4-disubstituted furans in excellent yields. The reaction is fast and easy to perform. It also represents an expansion of the scope of the cross-coupling reaction as it provides examples of rare aryl tin-aryl bromide couplings.

Part 2: LEAD TETRAACETATE OXIDATIONS OF 2-(TRIALKYSILYL)FURANS

The treatment of 2-(t-butyldimethylsilyl)furan with lead tetraacetate in warm (70°C) acetic acid provides 2-acetoxy-3-(t-butyldimethylsilyl)-Δ3-butenoledie and 4-acetoxy-4-(t-butyldimethylsilyl)-Δ2-butenoledie in a 2:1 ratio and 90% yield. The formation of the major product may involve a rare acid catalyzed 1,2-silyl migration. The reaction proceeds slower in refluxing chloroform providing the products in a 1:1 ratio and slightly lower yields. The altered ratio may be due to a much lower acid concentration. The reaction does not tolerate bulky or aryl groups on the silicon atom.

Part 3: SYNTHETIC APPROACHES TOWARDS HALENAQUINONE

Synthesis of the natural product Halenaquinone was attempted. Difficulties were encountered in the 6-membered ring closing step to form a tetrahydroisobenzofuran. The C-4 iodine on the furan ring resisted reaction to carbanion and carbon radical generating techniques.
To Mary
ACKNOWLEDGEMENTS

The author is grateful to his supervisor Dr. Brian A. Keay for his encouragement and guidance during the course of this work.

Thanks are also directed to members of the faculty and staff of the Department of Chemistry and Biochemistry, as well as fellow graduate students, in particular C. Rogers-Goulin, for their useful discussions, social interactions and patience.

The author would also like to thank M. Fuerth for his expertise in providing numerous spectral data.
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   4-(tri-n-butylstanny1)furan (60)
   3-[(t-Butylidimethylsilyl)oxymethyl]-4-(
   tri-n-butylstanny1)furan (67)
   2-(t-Butylidimethylsilyl)-3-(hydroxymethyl)-
   4-phenylfuran (68)
   2-(t-Butylidimethylsilyl)-3-(hydroxymethyl)-
   4-(2-pyridyl)furan (69)
   3-[(t-Butylidimethylsilyl)oxymethyl]-
   4-phenylfuran (71)
   3-[(t-Butylidimethylsilyl)oxymethyl]-
   4-(2,4,6-trimethylphenyl)furan (73)
   3-[(t-Butylidimethylsilyl)oxymethyl]-
   4-(2-tolyl)furan (74)
   3-[(t-Butylidimethylsilyl)oxymethyl]-
   4-(4-biphenyl)furan (75)
   3-[(t-Butylidimethylsilyl)oxymethyl]-4-
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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBN</td>
<td>azo bis(isobutryonitrile)</td>
</tr>
<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
</tr>
<tr>
<td>bp.</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium(IV) ammonium nitrate</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRS</td>
<td>hours</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LTA</td>
<td>lead tetraacetate</td>
</tr>
<tr>
<td>MCPBA</td>
<td><em>meta</em>-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>MMPP</td>
<td>magnesium monoperoxyphthalate</td>
</tr>
<tr>
<td>mp.</td>
<td>melting point</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>N.R.</td>
<td>no reaction</td>
</tr>
<tr>
<td>OAc</td>
<td>acetoxy</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBDMS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin later chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluene sulfonyl</td>
</tr>
<tr>
<td>TTPP</td>
<td>tetrakis(triphenylphosphine) palladium(0)</td>
</tr>
</tbody>
</table>
Palladium Catalyzed Cross-Coupling Reaction

1.1.0 Introduction

The synthesis of 3,4-disubstituted furans is not a trivial matter since furans tend to add electrophiles at the C-2 and/or C-5 positions. In addition, the increased acidity of the C-2 and C-5 protons relative to the C-3 and C-4 protons leads to deprotonation at the C-2 and/or C-5 positions with n-butyllithium.\(^1\) Therefore, the development of useful methods for the synthesis of 3,4-disubstituted furans becomes an interesting and important challenge. The following introduction will address this challenge in three parts; 1) a review of the palladium catalyzed cross-coupling reaction of organotin and organohalide compounds, 2) the presentation of previous methodology developed in our lab for the preparation of 3,4-disubstituted furans and 3) a proposed extension of the latter work involving the aforementioned palladium catalyzed cross-coupling reaction.

1.1.1 Existing Cross-Coupling Reactions

The palladium catalyzed cross-coupling of organotin reagents with organic halides, particularly bromides and iodides, provides a novel method for the generation of carbon-carbon bonds.\(^2\) The reaction is considerably versatile. The functional groups on the tin atom\(^3\) can be an allyl, aryl or vinyl group as well as a hydride or an enolate. Alkyl, aryl, acyl or allyl halides may be used in addition to diazonium salts or triflates.

The mechanism of this reaction is believed to occur in at least 5 distinct steps\(^2\) (scheme 1). The first step (step 1) must be the generation of the coordinatively unsaturated palladium(0) catalyst. The most common catalyst used\(^2\) is tetrakis(triphenylphosphine) palladium(0) (TTPP). The dissociation of two of its phosphine ligands generates the required catalyst. Step 2 is the oxidative insertion of the palladium catalyst into the carbon-halogen bond of the organic molecule. Following this (step 3) is the transmetallation of the organotin reagent with the palladium complex, generating a diorganopalladium species. The latter then undergoes (step 4) an isomerization which allows a reductive elimination (step 5) to occur producing the coupled organic compound with regeneration of the palladium (0) catalyst.

The literature is replete with aryltin-vinylhalide, vinyltin-arylhalide and vinyltin-vinylhalide coupling reactions and has recently been reviewed.\(^2\) The following
will present some representative examples.

Substituted vinyl halides react in good yields with vinyltin reagents. Stille has shown\(^2\) that vinyl iodides react readily at 25-40\(^\circ\)C whereas vinyl bromides require higher temperatures (100\(^\circ\)C) to undergo the palladium oxidative insertion. In addition, retention of configuration of the double-bond in the vinyl halide occurs (scheme 2).

Vinyltriflates can also be used in the coupling reaction, provided that lithium chloride is also present.\(^4\) It is believed that the vinyl palladium chloride complex must be formed since the corresponding palladium triflates will not participate in the transmetallation with the vinyltin partner (scheme 3). Note that these reactions demonstrate that vinylsilanes are not affected.

The furan ring has been shown to be a suitable functional group in these coupling reactions. A furan ring was present in the vinyltin partner used in the synthesis of pleraplysilin-1\(^4\) (scheme 4); the furan ring did not hinder the reaction nor was it adversely affected by the palladium catalyst.

Aryl halides will react with both allyl and vinyltin reagents\(^5,6,7\) (scheme 5).
Bis-coupling is also possible when the vinyltin reagent is doubly functionalized with two trialkyltin groups (scheme 5). When both a bromide and a chloride are present on the arylhalide, the coupling occurs exclusively at the carbon atom bearing the bromine atom(5) (scheme 5).

The use of an aryltin and an arylhalide in the same coupling reaction is rare. There are no reported examples in the literature prior to 1987; the following illustrate the few examples reported in the literature since 1988.

Majee et al(8) coupled a stannylated pyrimidine 23 with iodobenzene using
bistriphenylphosphine palladium dichloride in refluxing 1,2-dichloroethane (scheme 6), affording the coupled product 24 in good yield. Note that a chlorine atom is tolerated on the aryltin compound (scheme 6).

Echavarren and Stille\(^9\) have performed a variety of coupling reactions with aryltriflates and aryltin reagents (table 1). A number of aryl systems and functional groups are tolerated; yields are generally good to high.

The use of furyltin or thiényltin reagents in coupling reactions with arylhalides is practically nonexistent in the literature. The only example to be found is the coupling of 2-tributyristannylthiophene 33 (scheme 7) with a halopyrimidine 34 to afford the coupled product 35 in 73% yield.\(^{10}\)

The 5-stannylatedfuran 36 (scheme 8) has been coupled with vinyliodides to provide products 38 (scheme 8).\(^{11}\) The authors intend to use products such as 38 in the synthesis of lophotoxin, a potent neurotoxin.

A carbonylation-coupling reaction with 3-trimethylstannylfuran 39 (scheme 9) and vinylchlorides\(^{12}\) has been performed (scheme 9). The mechanism of this reaction is the same as that shown in scheme 1 except that a carbon monoxide insertion into the palladium complex occurs between steps 2 and 3.

A related reaction is the palladium catalyzed coupling of aryl and vinyltriflates with 2-furylzinc chloride 44 (scheme 10).\(^{13}\) It is supposed that this reaction proceeds by a transmetallation of 44 by the palladium complex formed from insertion of palladium (0) into the carbon-triflate bond.
Table 1

Aryltin and Aryl triflate Cross-Couplings

\[ \text{ArSnR}_3 + \text{Ar'OTf} \xrightarrow{\text{TTPP}, \text{LiCl}} \xrightarrow{\text{Dioxane}, \Delta} \text{Ar-Ar'} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryltin</th>
<th>Aryl triflate</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><img src="25" alt="Image" /></td>
<td><img src="26" alt="Image" /></td>
<td>68HRS</td>
<td>79%</td>
</tr>
<tr>
<td>B</td>
<td><img src="27" alt="Image" /></td>
<td><img src="28" alt="Image" /></td>
<td>23HRS</td>
<td>85%</td>
</tr>
<tr>
<td>C</td>
<td><img src="29" alt="Image" /></td>
<td><img src="30" alt="Image" /></td>
<td>36HRS</td>
<td>74%</td>
</tr>
<tr>
<td>D</td>
<td><img src="31" alt="Image" /></td>
<td><img src="28" alt="Image" /></td>
<td>82HRS</td>
<td>61%</td>
</tr>
<tr>
<td>E</td>
<td><img src="32" alt="Image" /></td>
<td><img src="30" alt="Image" /></td>
<td>92HRS</td>
<td>28%</td>
</tr>
</tbody>
</table>
Scheme 7

\[
\text{33} \quad \text{SnBu}_3 + \quad \begin{array}{c}
\text{34} \\
\text{MeS} \\
\text{Cl}
\end{array} \quad \xrightarrow{1,2\text{-dichloro-ethane}} \\
\begin{array}{c}
\text{35} \\
\text{MeS} \\
\text{Cl}
\end{array} \\
(\text{PPh}_3)_2\text{PdCl}_2 \\
82^\circ C \\
73\%
\]

Scheme 8

\[
\begin{array}{c}
\text{36} \\
\text{OTBDMS} \\
\text{SnMe}_3
\end{array} + \\
\begin{array}{c}
\text{37} \\
\text{R}
\end{array} \quad \xrightarrow{TTPP, \text{DMF}} \\
\begin{array}{c}
\text{38} \\
\text{OTBDMS} \\
\text{R}
\end{array}
\]
**Scheme 9**

\[
\text{Scheme 9} \\
\begin{align*}
\text{SnMe}_3 & \text{SnMe}_3 \\
\text{39} & \text{40} \\
& \text{[Pd]} \text{CO} \\
\text{39} & \text{40} \\
& \text{41} \\
& \text{42} \\
& \text{43}
\end{align*}
\]

**Scheme 10**

\[
\text{Scheme 10} \\
\begin{align*}
\text{ZnCl} & \text{ZnCl} \\
\text{44} & \text{45} \\
& \text{TTPP} \text{THF} \\
& 50^\circ \text{C} \text{95\%} \\
\text{44} & \text{47} \\
& \text{48}
\end{align*}
\]
1.1.2 **Existing Methodology Towards 3,4-Disubstituted Furans**

Bures and Keay\(^1\) have developed a facile method for preparing 3,4-disubstituted furans by C-4 carbon lithiation of furan 49 (table 2) followed by the addition of organic electrophiles; desilylation with fluoride ion provided 3,4-disubstituted furans in excellent yields. Unfortunately this methodology is limited to the use of electrophiles which are suitable for a nucleophilic displacement by carbanions. Further studies have shown that systems such as 56 and 57 (scheme 11) will undergo a 1,4 C→O silicon migration when treated with catalytic sodium hydride in DMF, providing the corresponding 3,4-disubstituted furans in excellent yields in which the hydroxymethyl group is protected with a silane (scheme 11).\(^{14}\)

### Table 2

**Preparation of 3,4-Disubstituted Furans**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product (Yield)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>DOCH(_3)</td>
<td>50 R(_1)=D, R(_2)=H (92)</td>
</tr>
<tr>
<td>2</td>
<td>I(_2)</td>
<td>51 R(_1)=I, R(_2)=H (91)</td>
</tr>
<tr>
<td>3</td>
<td>ICH(_3)</td>
<td>52 R(_1)=CH(_3), R(_2)=H (90)</td>
</tr>
<tr>
<td>4</td>
<td>Cl(CH(_2))(_3)I</td>
<td>53 R(_1)=(CH(_2))(_3), R(_2)=H (60)</td>
</tr>
<tr>
<td>5</td>
<td>ClCON(Et)(_2)</td>
<td>54 R(_1)=R(_2)=CON(Et)(_2) (69)</td>
</tr>
<tr>
<td>6</td>
<td>CICOCH(_3)</td>
<td>55 R(_1)=R(_2)=COOCH(_3) (49)</td>
</tr>
</tbody>
</table>

![Image of chemical reaction]
1.1.3 Application of the Cross-Coupling Reaction

We envisioned expanding the scope of the above methodology, developed by Bures and Keay\textsuperscript{1}, to include electrophiles suitable for palladium (0) catalyzed cross-coupling reactions (scheme 12). Lithiation of compound 49 followed by the addition of tri-n-butyltin chloride should provide the stannylated furan 60 (scheme 12). The palladium catalyzed cross-coupling reaction between 60 and a variety of arylbromides should provide trisubstituted furans such as 61. The \( \text{t-butyl} \text{dimethylsilyl} \)
group (TBDMS) could then be either removed with fluoride ion to provide 3-aryl-4-hydroxymethylfurans 62 or migrated to the hydroxymethyl group to afford 3-aryl-4-[(t-butyldimethylsilyloxy)methyl]furans 63 (scheme 12). The preparation of this class of 3,4-disubstituted furans will accomplish three goals: 1) provide a synthetic pathway for a new class of 3,4-disubstituted furans, 2) expand the scope of the palladium catalyzed cross-coupling reaction with stannylfurans and 3) expand the general scope of aryl-aryl couplings. The next section describes our endeavours into this new area of chemistry.
1.2.0  \textit{Results and Discussion}

The synthesis of the beta-stannyl furan 60 was straightforward when accomplished by the method developed by Bures and Keay\textsuperscript{1} and is shown in scheme 13. The starting material, 3-furoic acid 64 was reduced to the alcohol 65 in quantitative yield with lithium aluminum hydride in diethyl ether. Compound 65 was then protected as the tert-butyldimethylsilyl (TBDMS) ether in 95% yield with the corresponding silyl chloride and imidazole in N,N-dimethylformamide (DMF) to provide furan 66. The 1,4-O→C silicon migration proceeded smoothly when furan 66 was treated with one equivalent each of n-butyllithium and hexamethylphosphoramide (HMPA) in THF; the 2,3-disubstituted furan 49 was obtained in 87% yield. Compound 49 was then lithiated at the C-4 position using two equivalents of n-butyllithium (the alcohol is also deprotonated) and the C-4 anion trapped selectively by adding one equivalent of tri-n-butyltin chloride, providing furan 60 in 89% yield.

The assignment of this structure was straightforward using the following spectral evidence: the furan beta-proton NMR signal at δ 6.46 of compound 49 had disappeared, indicating that substitution had occurred at the C-4 carbon of furan 60. The identification of this substituent as the tri-n-butylstannyl group was confirmed by the following spectra evidence. The presence of numerous proton NMR signals between δ 1.6 and 0.8 whose integral ratio was 18:9 respectively indicate a tri-n-butyl moiety. In addition, the carbon DEPT NMR spectrum indicated the presence of only
one tertiary furan carbon, whose chemical shift of δ151.53 was indicative of an alpha-furan carbon atom. The presence of the tin atom was confirmed by a mass spectrum which clearly showed mass patterns indicative of a tin atom. A low resolution mass spectrum did not indicate a molecular ion; however, a fragment due to the loss of the t-butyl group was evident at a m/e of 444.

The 1,4-C-O silicon migration, performed in DMF with a catalytic amount of sodium hydride, proceeded quantitatively to afford compound 67 (scheme 13). It was initially feared that the hydride anion might attack the tri-n-butylstanny1 group causing destannylation, regenerating compound 49. The absence of a beta-furan proton NMR signal at or about δ 6.5 indicated that this had not occurred. The confirmation of the silicon shift was easy to obtain from spectral analysis. In addition to the proton NMR signal at δ 7.44, a second one at δ 7.14 appeared, indicating that the silyl group was no longer on the furan ring. As well, there was no absorption above 2985 cm⁻¹ in the infrared spectrum, indicating the absence of any free hydroxyl group in the molecule; therefore, the TBDMS group had in fact migrated back to the oxygen, providing 67.

Compound 60 was then employed in two palladium catalyzed coupling reactions with bromobenzene and 2-bromopyridine. In each case, the method used was the one developed by Stille. This involved mixing the tin reagent, the aryl bromide and tetrakis(triphenylphosphine) palladium(0) (TTPP) (catalytic amount) in toluene and warming the mixture to reflux (scheme 14). The aryl bromide was used in slight excess

\[ \text{Scheme 14} \]

\[
\begin{align*}
\text{SnBu}_3 & \quad \text{OH} & \quad \text{ArBr} & \quad \text{TTTP} & \quad \Delta & \quad \text{PhCH}_3 \\
\text{60} & \quad \text{TBDMS} & \quad \text{OH} & \quad \text{Ar} & \quad \text{TBDMS} & \quad \text{Ar=C}_6\text{H}_5, 68 \\
& & & \quad \text{Ar=2-3H}_4\text{N}, 69
\end{align*}
\]

(1.1 equivalents). Surprisingly, both of these reactions required excessive amounts of time to consume both the aryl bromide and the stanny1 reagents. In the case of the bromobenzene reaction, only about half of the bromide had been consumed after five hours of stirring in refluxing toluene. A second addition of catalyst and six more hours were required to consume all the starting materials. The coupled product 68 was obtained in only 51% yield. An alarming 10% yield of the destanny1ated starting
material 49 was also produced. This is in contrast to typical coupling reactions using bromobenzene as the aryl bromide\textsuperscript{15,16} where the coupled product is formed in high yield and within one hour.

The reaction using 2-bromopyridine was even more disappointing. After a total of eighteen hours of stirring with extra additions of catalyst at the five and twelve hour marks, about 60\% of 2-bromopyridine and furan 60 were left intact. The coupled product 69 was obtained in 20\% yield. A significant 15\% yield of the destannylated starting material 49 was also produced. Clearly, compound 60 was not a suitable starting material for this kind of palladium catalyzed coupling reaction. The long reaction times, poor yields of coupled products and destannylation of starting material demonstrate this quite poignantly.

Since the production of the destannylated starting material was particularly surprising, a search for its source was undertaken. It was ultimately found that when compound 60 was refluxed in toluene with a catalytic amount of TTPP for 5 hours, compound 49 was formed in 10\% yield. In the absence of the palladium catalyst, compound 60 was left untouched. It was speculated that the free hydroxyl group of compound 60 may have been causing this side reaction by acting as a source of a hydrogen atom. However, this seems unlikely when one considers the following facts. This coupling reaction has been shown to possess radical character in its mechanism\textsuperscript{15}. This is underlined by its insensitivity to water\textsuperscript{15}, a poor source of hydrogen atoms, and its acceleration in the presence of molecular oxygen which exhibits radical character\textsuperscript{16}. It is also known that free hydroxyl groups are poor sources of hydrogen atoms\textsuperscript{17}. Therefore, one is forced to conclude that the hydroxyl group of compound 60 is most likely not the source of hydrogen atoms responsible for the production of 49.

Ultimately, the hydroxyl group of compound 60 was found to be interfering with the reaction. When compound 67, with the hydroxyl group protected by a TBDMS group, was refluxed in toluene with a catalytic amount of TTPP, the corresponding destannylated product 66 (Table 3) was not produced, even after 24 hours of reflux; only compound 67 was recovered in high yield.

The above result also provided evidence that compound 67 might be suitable for the palladium catalyzed coupling reaction. Using compound 67 instead of compound 60 in an otherwise identical coupling reaction with bromobenzene, the expected product 3-[(t-butyldimethylsilyl)oxy]methyl)-4-phenylfuran 71 was obtained in 90\% yield in less than one hour of stirring at reflux. Less than 1\% of compound 67 was destannylated to form 66. The fact that compound 71 was in fact the product was
easy to see from the NMR spectra. The proton NMR spectrum exhibited no resonances at or around δ 6.5, indicating the absence of any beta-furan protons. There were no resonances from any butyl groups, indicating that something other than hydrogen had replaced the tri-n-butylstannyl group at the C-4 position of the furan ring. The complex pattern of resonances between δ 7.6 and 7.3 integrating to seven protons suggested the presence of a mono-substituted phenyl ring and two alpha-furan protons. The eight 13C NMR resonances at δ 147.82, 141.73, 139.95, 132.38, 128.59, 127.89, 126.24 and 124.44, three of which were shown to be quaternary by a DEPT experiment, also supported this assignment. The mass spectrum also supported the NMR data; a molecular ion at m/e 288 was observed in the low resolution mass spectrum. It was thus concluded that the phenyl group from bromobenzene had replaced the tri-n-butylstannyl group of compound 67.

A number of other aryl bromides were used in this coupling reaction, expanding the scope of the reaction. These are summarized in table 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArBr</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Bromobenzene</td>
<td>45min</td>
<td>90%, 71</td>
</tr>
<tr>
<td>B</td>
<td>2-Bromopyridine</td>
<td>18HRS&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>&lt;5%, 72</td>
</tr>
<tr>
<td>C</td>
<td>2-bromomesitylene</td>
<td>6HRS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>55%, 73</td>
</tr>
<tr>
<td>D</td>
<td>2-methyl-1-bromobenzene</td>
<td>4HRS</td>
<td>80%, 74</td>
</tr>
<tr>
<td>E</td>
<td>4-bromobiphenyl</td>
<td>3HRS</td>
<td>70%, 75</td>
</tr>
<tr>
<td>F</td>
<td>2-methyl-1-bromoraphthalene</td>
<td>3HRS</td>
<td>82%, 76</td>
</tr>
<tr>
<td>G</td>
<td>4-chloro-1-bromobenzene</td>
<td>1HRS</td>
<td>88%, 77</td>
</tr>
<tr>
<td>H</td>
<td>2-methoxy-1-bromobenzene</td>
<td>18HRS&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>---</td>
</tr>
</tbody>
</table>

<sup>a</sup> added more catalyst at 6HR and 12HR marks; <sup>b</sup> recovered 80% of 67; <sup>c</sup> added more catalyst at 3HR mark; <sup>d</sup> recovered 20% of 67 and isolated 15% of 66
It can be seen that a great deal of aryl bromides can be used effectively in this reaction: phenyl, biphenyl and naphthyl bromides are tolerated quite nicely (entries A, E and F). Steric hindrance present in the aryl bromide has an effect on the speed and yield of the reaction as entries C and D demonstrate. The reaction using 2-mesityl bromide is slow and moderately yielding requiring repeated additions of catalyst to effect the complete consumption of the starting materials. When 2-methyl-1-bromobenzene is used, no additional catalyst is required, but a longer reaction time is needed to complete the reaction. Entry G demonstrated that palladium insertion occurs exclusively at the carbon-bromine bond in the presence of a carbon-chlorine bond. The reaction attempt using 2-methoxy-1-bromobenzene (entry H) failed to produce any coupled product. This is in agreement with reports that aryl bromides with electron donating substituents react sluggishly and require incremental additions of catalyst.\(^{15}\) The fact that no product was formed may be due to steric hindrance offered by the orthodisposition of the substituents on the benzene ring.

It is interesting to note that 2-bromopyridine (entry B) gave poor yields of the expected product. This was unexpected since other workers have used bromopyridines in similar reactions involving palladium catalysts.\(^{18}\)

These results clearly show that this methodology can be used to prepare a new class of 3,4-disubstituted furans. This reaction is easy to perform, requiring no special care to remove water or oxygen in order to obtain high yields. The products are easily purified by flash column chromatography. In addition, the presence of the silyl-protected hydroxymethyl group on the furan ring allows for easy manipulation for further functionalization. Studies are now under way to examine this methodology's application to natural product syntheses.
2.0.0 **Lead Tetraacetate Oxidations of 2-(Trialkylsilyl)furans**

2.1.0 **Introduction**

The use of lead tetraacetate (LTA) as an oxidant in organic synthesis has been known for quite some time.\(^{19}\) Our interest in this particular reagent lies in its reaction with 2-(trialkylsilyl)furans. The following introduction will be divided into three parts: 1) a discussion on the mechanism of LTA oxidations of carbon-carbon double bonds, 2) a review on the chemistry of LTA oxidations on furan systems and 3) a proposed application for the reaction of LTA on 2-(trialkylsilyl)furans.

2.1.1 **Mechanism of LTA Oxidations of Carbon-Carbon Double Bonds**

The mechanism of LTA oxidations of carbon-carbon double bonds and conjugated systems has been the subject of ongoing research and debate since the early 1950's\(^{20}\) and has been coined as 'solvent dependant'.\(^{21}\) However, some generalizations have been made. It is known that Pb(OAc)\(_3\) will form π-complexes with olefins\(^{20}\) and that Pb(OAc)\(_2\) is a good leaving group.\(^{22}\) Proof has also been provided that symmetrical intermediates are formed (when possible) in the course of such oxidations.\(^{23,24}\) With these facts in mind, a general mechanism of oxidation of carbon-carbon double bonds has been presented (scheme 15).

The addition of LTA to cyclohexene 78 to provide the symmetrical intermediate 79 is reversible. One of two alkyl plumbates can then be formed, 80 or 83. The alkyl plumbate 80 forms by the loss of a proton. The loss of the plumbate anion from compound 80 occurs very quickly to afford the allyl cation 81. The liberated plumbate anion then quickly disproportionnates to acetate anion and lead diacetate. The trapping of the intermediate 81 by acetate anion then affords the allyl acetate 82. Alternatively, the plumbate 79 can be attacked by acetate in an S\(_{N2}\) manner to provide compound 83. Both the cis and trans diacetate 84 are formed from the loss of the lead triacetate anion and quenching of the so-formed carbocation by acetate anion. The trans acetate is most probably formed via anchimeric assistance\(^{25}\) from the acetate already present on compound 83 whereas the cis diacetate is formed by simple S\(_{N2}\) displacement of the lead triacetate by acetate anion. There is still a question of whether the mechanism
follows an ionic or free radical pathway\textsuperscript{26}, it appears it is dependent on the conditions of the reactions and on the substrate used in the oxidation.

2.1.2 \textit{Existing LTA Oxidations of Furan Systems}

It is known that LTA will oxidize furan to 2,5-diacetoxy-2,5-dihydrofuran \textsuperscript{86}\textsuperscript{27} (scheme 16). Extensive studies have been made\textsuperscript{28} with 2,5-diarylfurans \textsuperscript{87} (scheme 17). Depending on the solvent used, one of two possible products is formed. In chloroform, the LTA adds and eliminates lead triacetate anion to form a \textit{beta}-carbonium ion (89). Attack of acetate anion on compound \textsuperscript{90} provides the diketone \textsuperscript{91}. Conversely, in acetic acid, the initial LTA addition occurs in the opposite sense leaving the carbonium ion in the \textit{alpha}-position (92) which then loses a proton to generate the acetoxylated furan \textsuperscript{93}. A second addition of LTA then provides compound \textsuperscript{94} which, following acetate anion attack, provides \textsuperscript{95}.

Japanese workers\textsuperscript{29} have shown that the 2-stannylated furans \textsuperscript{96} and \textsuperscript{97} (scheme
18) undergo an oxidative substitution reaction with LTA to supposedly provide the furan acetates 98 and 99 as intermediates. These acetoxyfurans are then further oxidized by LTA\textsuperscript{30} to the butenolides 100 and 101.

Scheme 18

The effect of LTA on various 2-(trialkylsilyloxy)furans has also been studied\textsuperscript{31} (Scheme 19). The mechanism is consistent with that proposed for the oxidation of 2,5-diarylfurans (Scheme 17).
2.1.3 *An Approach to the Synthesis of 3-Halogenated Butenolides*

The chloro- and bromobeckereelides 112 and 113\(^{32a}\) (figure 1) and the hydroxy- and acetoxyfimbrolides 114 and 115\(^{32b}\) (figure 1) have been isolated from the red marine algae *Beckerella subcostatum* and *Delisea fimбриata* respectively and exhibit potent antifungal and antimicrobial properties. Only bromobeckerelide 113 has been successfully synthesized\(^{32c}\) (scheme 20).

![Figure 1](image)

112; X=Cl
113; X=Br
114; R=X=H; Y=Cl,Br,I
115; R=Ac, X=Y=Br

Other syntheses of di- and tri-substituted butenolides having a halogen in the C-3 position have involved the preparation of complicated epoxide precursors followed by acid-catalyzed rearrangements to produce the required butenolides in low yields.\(^{33}\) We propose to prepare 4-halogenated-3-substituted-2-(t-butyldimethylsilyl)furans and convert these regiospecifically into butenolides by the action of LTA (scheme 21).

Since the methodology developed by Bures and Keay\(^1\) provides 3,4-disubstituted furans which only contain a t-butyldimethylsilyl moiety in the C-2 position of the furan, Kuwajima’s method of converting 2-(trimethylsilyl)furans into butenolides with m-chloroperoxybenzoic acid cannot be used.\(^{34}\) Therefore a new method for the conversion of 2-(t-butyldimethylsilyl)furans into butenolides must be developed.

We have envisioned that furans containing a C-2 t-butyldimethylsilyl group may be converted into butenolides regioselectively by the action of LTA on suitable precursors (scheme 21). Compound 122 is readily available by previously established methodology (table 2). The preparation of furan 123 is straightforward by oxidation of
the hydroxyl group of 122 via a Swern oxidation and attack of the so-formed aldehyde by propylmagnesium bromide. The secondary alcohol would then be protected by a suitable protecting group. The oxidation of furan 123 by LTA should lead to the key intermediate 124 (cf. scheme 16) which, upon treatment with fluoride ion should result in the acetoxyalted furan 125. Treatment of the latter with methyllithium should liberate the C-5 anion which, after trapping with an electrophile, will provide the highly substituted C-4 brominated butenolide 125a. Further elaboration of 125a will then afford the natural products 112-115 (figure 1).

The following section will present a model investigation into the reaction of
LTA on various 2-(trialkylsilyl)furans to determine its suitability for the proposed application to butenolide syntheses.
2.2.0 **Results and Discussion**

Treatment of 2-(t-butyldimethylsilyl)furan 126 with LTA in warm (70°C) acetic acid for four hours required 2 equivalents of LTA to consume furan 126. Two compounds were isolated in a ratio of 2:1 after silica gel chromatography in 90% yield. The $^1$H and $^{13}$C NMR spectra of the major and minor products can be found in figures 2 and 3 respectively.

The FAB (fast atom bombardment) mass spectrum of the major isomer indicated a m/e of 257, indicating a molecular weight of 256 g/mole. The EI (electron impact) mass spectrum showed no peak at a m/e of 256; however, a base peak at a m/e of 199 is consistent with a molecular ion at a m/e of 256 losing a t-butyl group. The EI mass spectrum of the minor isomer also exhibited a strong peak at a m/e of 199; the Cl (chemical ionization) mass spectrum showed a m/e of 257 indicative of a molecular weight of 256 g/mole.

The proposed molecular formulae for both products is C$_{12}$H$_{20}$O$_4$Si. This is consistent with not only the mass spectra but also the elemental analyses (EA). The theoretical carbon and hydrogen content are calculated at C=56.25% and H=7.81%. These are consistent with the observed elemental analysis of C=56.40% and H=7.89% for the major isomer and C=56.12%, H=7.82% for the minor isomer.

Infrared absorptions at 1769 cm$^{-1}$ for both products indicate the presence of a lactone moiety. This value is consistent with known 5-membered ring lactones; 5,5-dihydro-(2H)-2-furanone exhibits an infrared absorption at 1770 cm$^{-1}$.$^{35}$ In both spectra, the carbonyl absorptions were broad with small shoulders at longer wavenumbers suggesting that more than one carbonyl group may be present. The IR spectra of both products indicated an absence of hydroxy groups and carbon-carbon triple bonds. Surprisingly, there were no absorptions between 1700 and 1550 cm$^{-1}$; this region usually indicates the presence of carbon-carbon double bonds.

An acetoxy moiety is proposed to be the source of the additional carbonyl in both products. The $^1$H NMR spectra of the major and minor products indicate a three hydrogen singlet at δ 2.1 and 2.0 respectively.

The molecular formulae indicate a degree of hydrogen deficiency of four (4). Assuming a lactone ring and an additional carbonyl group one more unsaturation must be present. Although the IR does not support the presence of a carbon-carbon double bond, the $^1$H and $^{13}$C NMR spectra (vide infra) and the Ultraviolet (UV) spectra provide evidence for a carbon-carbon double bond.
Figure 2

$^1$H and $^{13}$C NMR spectra of major product.

DEPT NMR

$^{13}$C NMR

$^1$H NMR
Figure 3

$^1$H and $^{13}$C NMR spectra of minor product.
A carbon-carbon double bond can be placed either in or out of conjugation with the carbonyl of the lactone. The ultraviolet spectra of the two products provide evidence for the placement of the carbon-carbon double bond. The UV spectrum of the major product exhibited an absorption maximum at $\lambda_{\text{max}} = 220$ nm with a molar absorptivity of $\epsilon = 130 \text{ Lmol}^{-1}\text{cm}^{-1}$; the minor product indicated a $\lambda_{\text{max}} = 218$ nm and a $\epsilon = 17200 \text{ Lmol}^{-1}\text{cm}^{-1}$. The larger molar absorptivity of the minor isomer indicates that the double bond is in conjugation with the carbonyl of the lactone, while the major product, with a smaller molar absorptivity, indicates an unconjugated carbon-carbon double bond.

The $^{13}\text{C}$ NMR spectra of the major and minor isomers exhibit singlets at $\delta = 172.6$ and 169.1 for the major product and $\delta = 170.6$ and 169.2 for the minor product. This is consistent with the presence of two carbonyl functionalities in both compounds (i.e. a lactone and acetate carbonyl).

The $^1\text{H}$ NMR spectrum of the major isomer shows two doublets at $\delta = 7.33$ and 6.86, each with a coupling constant of 1 Hz. Although the chemical shifts are consistent with the presence of two vinyl protons, the very small coupling constant does not support the presence of a cis-double bond. In addition, the compound exhibits a $^{13}\text{C}$ NMR signal at $\delta = 93.79$ ($3^\circ$ carbon atom), indicating that one of the two hydrogen bearing carbon atoms does not form part of the double bond. The signal at $\delta = 158.23$ ($3^\circ$ carbon) and signal at $\delta = 137.91$ ($4^\circ$ carbon) indicate a trisubstituted double bond; the former signal is indicative of a vinyl C-H geminal to an oxygen atom.

The $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of the minor isomer so support the presence of a disubstituted double bond. The $^{13}\text{C}$ NMR signals at $\delta = 155.03$ and 120.68 (both $3^\circ$ carbons), along with $^1\text{H}$ NMR doublets at $\delta = 7.60$ and 6.11 with a coupling constant of 5.6 Hz are consistent with this assignment. A $^{13}\text{C}$ NMR signal at $\delta = 107.49$ ($4^\circ$ carbon) is consistent with a carbon atom attached to the lactone oxygen and bearing both an acetoxy and silyl group.

Both the $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of both products indicated the presence of a t-butyldimethylsilyl group.

Figure 4 illustrates the proposed structures for the major (127) and minor (128) products along with important NMR spectral data assignments. The values in parentheses represent the estimated chemical shifts based on data from chemical shift additivity charts.36

As can be seen, the agreement between observed and estimated chemical shifts is within reason. In both cases, the placement of the acetoxy group elsewhere would
provide estimated $^{13}$C chemical shifts not consistent with the observed values or multiplicities.

For compound 128, the placement of the silyl group was unambiguous. If the silyl group were placed at either the C-2 or C-3 positions then the two vinyl C-H signals would not appear in the $^1$H NMR spectrum.

In the case of compound 127, further proof was sought for the placement of the acetoxy group. When the acetate moiety of 127 was removed (MeOH, K$_2$CO$_3$), the $^1$H NMR doublet at $\delta$ 6.86 experienced an upfield shift to $\delta$ 6.12. This clearly indicates that the doublet at $\delta$ 7.33 is the signal for the vinyl hydrogen.
The placement of the silyl moiety in compound 127 required a more careful study. It was clear that the TBDMS group could not be placed at the C-2 position; the $^{13}$C NMR signal at $\delta$ 93.79 (3° carbon) could not be accounted for. There are, therefore, only two possibilities: either the silyl group is attached to the C-3 position as postulated, or at the C-4 position. In figure 5, the C-4 placement of the silyl group is considered. It is clear that this cannot be the structure of compound 127 since the estimated chemical shifts of carbon-3 and its vinyl hydrogen do not correspond to the observed values. Therefore, the proposed structure of compound 127 is as shown in figure 4.

Compound 127 crystallized and although we have suitable crystals for an x-ray crystal structure, we have been unable at this time to get an x-ray structure solved.

Since these results were unexpected, the reaction of LTA on furan was repeated to verify the validity of the literature report. A mixture of the cis- and trans-2,5-diacetoxy-2,5-dihydrofurans were in fact isolated after treating furan with one equivalent of LTA in warm (70°) acetic acid.

The $^1$H NMR spectrum showed singlets at $\delta$ 6.93, 6.71, 6.20 and 6.18, indicating the presence of the vinyl and acetal hydrogens of both isomers. The presence of the acetoxy moieties was indicated by the singlets at $\delta$ 2.06 and 2.04. The $^{13}$C NMR spectrum was also consistent with the structures of the two isomers.

Since the reaction of LTA on furan is reproducible, then the presence of the
silyl group on the furan ring must be in some way responsible for the formation of the two unexpected compounds (figure 4) when 2-silylated furans are treated with LTA in warm acetic acid.

A proposed mechanism for the formation of these two products is shown in scheme 22. Step 1 is the addition of the lead triacetate cation to the furan double bond remote from the bulky silyl group to form the C-5 carbonium ion. It has been shown\(^{37}\) (scheme 23) that the presence of a silyl group at the C-2 position of furan destabilizes the C-4 carbonium ion with respect to the C-5 carbonium ion. The C-5 carbonium ion (scheme 22) is quickly trapped with acetic acid (step 2) followed by the loss of lead triacetate anion (step 3) to form intermediate 130. The reaction can then follow one of two possible routes.

Furan 130 can undergo another LTA addition (step 4) on the least hindered double bond and form the stabilized C-5 carbonium ion. Acetic acid then attacks the C-5 acetate (step 6) to form the carbonyl. Displacement of the labile lead triacetate group (step 7) by an $S_N2'$ reaction with acetic acid affords the minor product 128.

Alternatively, furan 130 can undergo a reversible acid catalyzed 1,2-silicon migration (steps 5, 8 and 9) to provide furan 131. Similar acid catalyzed 1,2-silicon rearrangements have been observed on 1,2-((trimethylsilyl)benzene\(^{38}\) and various 1-naphthysilanes.\(^{39}\) They occur at low to moderate temperatures and in trace amounts of acids; the initial driving force is believed to be the relief of steric compression.

This 1,2-silyl rearrangement should occur faster than the LTA addition (step 4) as the proton is much smaller than the bulky lead moiety. Furan 131 then undergoes a reversible LTA addition on the least hindered double bond to form the C-3 carbonium ion (step 10). This carbonium ion is more stable than that produced from step 4 as it is stabilized by silicon in both of its resonance forms through the carbon-carbon double bond. The carbonium ion is then trapped by acetic acid (step 11). Finally, the lead triacetate group is removed via acetic acid attack on the acetate $\text{alpha}$ to the lead group (step 12) to afford the major isomer 127.

The 2:1 ratio of butenolides 127:128 indicates that the acid catalyzed 1,2-silicon rearrangement (step 5 and 8) is faster than the LTA addition to compound 130 (step 4). The driving force for the silyl migration may be due to the greater stability of the carbonium ion formed from compound 131 (step 10) over that formed from furan 130 (step 5).

A variety of solvents, known to be inert towards LTA\(^{40}\), were used to investigate their effect on the reaction and the ratio of the products (table 4). The first
Scheme 22

126

T=TBDMSS

X=Pb(OAc)₃

HOAc

1

2

3

4

5

6

7

8

9

10

11

12

130

131

127

128
four solvents employed (entries A through D) did not provide any of the butenolides 127 and 128 even after long reaction times; over 80% of the starting material 126 was recovered in each case. This is most likely due to the insolubility of LTA in these solvents. Dichloromethane (entries E and F) did dissolve the LTA, even at room temperature; however, the starting material 126 was unaffected after 24 hours of stirring at room temperature. Refluxing the dichloromethane mixture (entry F) did produce a small amount of the expected products in the same 2:1 ratio, but only after 24 hours. Longer reaction times had no effect on the yield of the products. These results indicated higher temperatures were necessary.

Dimethylformamide (entry G) and toluene (entry H) were also tried at elevated temperatures, but failed to provide any products. When refluxing benzene was used for the reaction (entry I), the products 127 and 128 were afforded in good yields. Six hours were required to consume all of the LTA; the remainder of the starting material was recovered.

The most interesting result was obtained in refluxing chloroform (entry J). The two butenolides 127 and 128 were produced in an 80% yield and in a 1:1 ratio after 10 hours. The different ratio is not surprising as it is consistent with the proposed mechanism (scheme 22). Since the proton (H⁺) concentration in chloroform would be several orders of magnitude less than in glacial acetic acid, it is reasonable to deduce that the acid catalyzed 1,2-silicon rearrangement would occur much less frequently in chloroform than in acetic acid. Therefore, more of the conjugated butenolide 128,
Table 4

Solvent Effects On LTA Oxidation Of Furan 126

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp(°C)</th>
<th>Time(HRS)</th>
<th>127(% Yield)</th>
<th>128(% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>THF</td>
<td>r.t.</td>
<td>40</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>B</td>
<td>DME</td>
<td>r.t.</td>
<td>48</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>C</td>
<td>Et₂O</td>
<td>r.t.</td>
<td>72</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>D</td>
<td>Pyridine</td>
<td>r.t.</td>
<td>48</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>E</td>
<td>CH₂Cl₂</td>
<td>r.t.</td>
<td>24</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>F</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>24</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>G</td>
<td>DMF</td>
<td>75</td>
<td>24</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>H</td>
<td>Toluene</td>
<td>111</td>
<td>24</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>I</td>
<td>C₆H₆</td>
<td>80</td>
<td>6</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>J</td>
<td>CHCl₃</td>
<td>61</td>
<td>10</td>
<td>40</td>
<td>---</td>
</tr>
</tbody>
</table>

a) time required to consume 2eq. of LTA; b) LTA dissolved in solvent

which is formed prior to any silyl group shift, would be produced.

It was thought that the placement of an additional substituent at the C-3 position of the silyl furan might increase the amount of conjugated butenolide formed. The 1,2-silyl shift, from the C-2 to the C-3 position, would be hindered by the presence of the additional group, inhibiting the production of the unconjugated butenolide. Furan 49 was acetylated using DMAP and acetic anhydride in dichloromethane to provide the 2,3-disubstituted furan 134 (scheme 24). Unfortunately, compound 134 did not react with LTA in warm (70°C) acetic acid, even after 48 hours. The starting material was recovered almost quantitatively and the ¹H NMR showed no signals other than that from the starting material. Since the bulky lead moiety must add at carbon-4, it is
reasonable to conclude that the substituent at the C-3 position is preventing this addition from occurring.

Since it was possible to form the butenolides 127 and 128 in different ratios and in high yields, an investigation was undertaken to find out what type of groups could be tolerated on the silicon atom as well as what effect they might have on the ratio of the products.

Seven other 2-silyl substituted furans were prepared by lithiating furan with n-butyllithium (in THF) and trapping the anion with an appropriate silyl chloride (table 5). All of the products provided spectral data consistent with 2-substituted silylfurans. For instance, the $^1$H NMR spectrum of 2-(triethylsilyl)furan 135 exhibited two doublets at $\delta$ 7.63 and 6.62 and a doublet of doublets at $\delta$ 6.38, all integrating for one proton. This indicated a furan ring was substituted at the C-2 position. The $^{13}$C NMR spectrum contained a signal at $\delta$ 158.19 (4° carbon) and three peaks at $\delta$ 146.55, 120.48 and 109.10 (all 3° carbons), which also indicated a C-2 substitution of the furan ring had occurred.

The 2-silylated furans 135 through 141 were exposed to LTA in either acetic acid or chloroform (table 6). All but compound 141 were exposed to LTA in acetic acid (entries A through F). It was feared that the trimethylsilyl group of compound 141 would prove to be too labile in glacial acetic acid. Of the other six 2-silylfurans, only three produced any of the expected butenolides (entries A, E and F).

2-(Triethylsilyl)furan 135 (entry A) and 2-(tributylsilyl)furan 139 (entry E) both produced only the unconjugated butenolides 142 and 143 respectively in 5% yield. Some desilylation had occurred in these two reactions since 2,5-diacetoxyl-2,5-dihydrofuran 86 was detected in the crude $^1$H NMR spectrum and later isolated. This product arises from the reaction of LTA on furan (cf. scheme 16).

The lack of any conjugated butenolide may be due to the nature of the
Table 5

Preparation of 2-Silyl Substituted Furans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product (%Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>135, R'=R''=Et, (92)</td>
</tr>
<tr>
<td>B</td>
<td>136, R'=Me, R''=Ph, (89)</td>
</tr>
<tr>
<td>C</td>
<td>137, R'=Ph, R''=Me, (96)</td>
</tr>
<tr>
<td>D</td>
<td>138, R'=Ph, R''=t-Bu, (90)</td>
</tr>
<tr>
<td>E</td>
<td>139, R'=R''=Bu, (96)</td>
</tr>
<tr>
<td>F</td>
<td>140, R'=R''=i-Pr, (94)</td>
</tr>
<tr>
<td>G</td>
<td>141, R'=R''=Me, (96)</td>
</tr>
</tbody>
</table>

trialkylsilyl groups on the furan ring. The triethylsilyl group is known to be more labile than the TBDMS group. The complexity of the crude $^1$H NMR spectrum, as well as the evidence of desilylation, reflect this. In the case of the tributylsilyl group, the problem may be one of steric hindrance. Referring back to the mechanism (scheme 22), the acetic acid may be hindered from attacking the carbon alpha to the bulky silyl group (step 7). Decomposition of the organolead compound could then be occurring over time at the elevated temperature. The low yield of the unconjugated butenolide can also be rationalized using steric arguments. In step 10 (scheme 22), the lead triacetate must add at carbon-3 which is flanked by an acetoxy group and the bulky silyl group. Compound 131 could then be decomposing over time.

The 2-(triisopropylsilyl)furan 140 (entry F) provided a 1.5:1 ratio of the unconjugated:conjugated products 144 and 145 in poor yield. Any attempts at improving the yield met with failure. The fact that some conjugated butenolide was isolated may be due to the greater stability of the triisopropylsilyl group as opposed to the triethyl- and tributyl- analogues. The overall low yield may be due to the large
Table 6

LTA Oxidations of Various 2-Silylfurans

\[
\begin{align*}
\text{Furan} & \quad \text{Solvent} & \quad \% \text{Yield} & \quad \% \text{Yield} \\
A & 135 & \text{HOAc}^{a,b} & 5\% & 142 & --- \\
B & 136 & \text{HOAc}^{a,b,c} & --- & --- & --- \\
C & 137 & \text{HOAc}^{a,b,c} & --- & --- & --- \\
D & 138 & \text{HOAc} & --- & --- & --- \\
E & 139 & \text{HOAc}^{a,b} & 5\% & 143 & --- \\
F & 140 & \text{HOAc} & 15\% & 144 & 10\% & 145 \\
G & 135 & \text{CHCl}_3 & --- & --- & --- \\
H & 139 & \text{CHCl}_3 & --- & --- & --- \\
I & 140 & \text{CHCl}_3 & --- & --- & --- \\
J & 141 & \text{CHCl}_3^{a,b} & 10\% & 146 & --- \\
\end{align*}
\]

a) desilylation had occurred; b) complex mixtures obtained

c) 6 eq. LTA were used

size of the triisopropylsilyl moiety.

Phenyl groups on the silicon atom were found to be unsuitable for this reaction (entries B, C, and D). Not only did these starting materials fail to produce the expected butenolides, but an excess of LTA was required to consume the furan rings. It is possible that the phenyl rings were reacting with the LTA.

Kalman et al. have shown\textsuperscript{42} that substituted trimethylsilylbenzenes react with lead tetrakis(trifluoroacetate) to provide the corresponding trifluoroacetoxybenzene compounds in which the trimethylsilyl group has been replaced with the trifluoroacetoxy group. The large number of \textsuperscript{1}H NMR signals between \( \delta \) 5.0 and 7.0 ppm in the crude \textsuperscript{1}H NMR spectra indicate that the LTA may have reacted with the arylsilanes to provide some \textit{ipsos} acetoxylated by-products.
Only the three silylfurans which had provided some results in acetic acid were exposed to LTA in chloroform (entries G, H and I); however, none of the butenolide products were formed. In fact, very little reaction occurred; in all cases, over 75% of the starting material was recovered. Only 2-(trimethylsilyl)furan 141 (entry J) provided the unconjugated butenolide 146 in 10% yield; 50% of the starting material was recovered, the rest having suffered desilylation.

Although this reaction does not appear useful for the preparation of the halogenated butenolides 112 through 115, it has proved very interesting. The reaction appears to work best with 2-(t-butyldimethylsilyl)furan 126 and does not tolerate bulky groups on the silicon atom nor phenyl substituted silanes. The reaction does seem to involve a rare 1,2-silyl shift.

As an extension of this work, further studies should be undertaken to uncover the mechanism of this reaction, particularly the validity of the proposed 1,2-silicon rearrangement. In addition an x-ray crystal structure of the major product 127 should be obtained.

As shown in scheme 25, it should be possible to synthesize the compound 130,
3.0.0 Synthetic Approaches Towards Halenaquinone

3.1.0 Introduction

This chapter will present our efforts towards the synthesis of halenaquinone. The following introduction will be presented in three parts: 1) the isolation and characterization of halenaquinone, 2) a brief presentation of the only total synthesis of halenaquinone and 3) our retrosynthetic analysis of this natural product.

3.1.1 Isolation and Characterization of Halenaquinone

Halenaquinone 149 (figure 6) was first isolated in 1983\textsuperscript{43a} from the marine sponge \textit{Xestospongia exigua}\textsuperscript{43b} in Palau, Western Caroline Islands as a pale yellow solid which decomposed above 250\textdegree{}C. Its name is derived from the Hawaiian word 'halena' which means pale yellow. It was found to be optically active with the optical rotation constant $[\alpha]_D^{25}$ of +22.2\textdegree{}. Its composition of C\textsubscript{20}H\textsubscript{12}O\textsubscript{5} was determined by high resolution mass spectrometry with a mass to charge ratio of 332.06847. A 2,3-unsubstituted-1,4-naphthoquinone ring structure was suggested by successive losses of CO and C\textsubscript{2}H\textsubscript{2} from the molecular ion, an IR band at 1680 cm\textsuperscript{-1}, a two proton singlet at $\delta$ 7.13 in the proton NMR spectrum and the following signals in the $^{13}$C NMR spectrum: $\delta$ 183.8(s), 183.3(s), 138.8(d), 138.7(d). Crystals suitable for X-ray crystal structure analysis were obtained from a solvent mixture of benzene/ethyl acetate (2:1) and a vapour diffusion of hexane. No absolute stereochemistry could be determined from the crystallographic data. Biological studies have shown that halenaquinone demonstrates in vitro antibiotic activity against \textit{Staphylococcus aureus} and \textit{Bacillus subtilis.}\textsuperscript{43a}

Structural analogues of halenaquinone have been isolated from other marine sponges, some of which also exhibit biological activity. The pentacyclic compounds 151 and 152 (figure 6) have been isolated from a sponge \textit{Adocia sp.} from Tnik Lagoon\textsuperscript{44} along with halenaquinone 149 and xestoquinone 150. Two other analogs, halenaquinol 153 and halenaquinol sulfate 154, also shown in figure 6, have been isolated from the Okinawan sponge \textit{Xestospongia sapra.}\textsuperscript{45} Compound 153 can be oxidized by either heating in the air at 40\textdegree{}C or by UV-radiation to afford halenaquinone 149.\textsuperscript{46}

The absolute stereochemistry at carbon 12\textsubscript{b} of halenaquinol was first
determined from theoretical calculations of circular dichroism spectra of compound 155 (cf. figure 6); configuration at carbon 12b was assigned as $S$.\textsuperscript{45,47} The authors inferred that the 12b carbon of halenaquinone 149 was also $S$.\textsuperscript{45,47}
3.1.2 Previous Synthesis of Halenaquinone

The first synthesis\textsuperscript{48} of halenaquinone confirmed the absolute stereochemistry. This synthesis is outlined in schemes 26, 27 and 28\textsuperscript{48} and begins with the optically pure (8aR)-(−)-Wieland-Miescher ketone 156.

**Scheme 26**

\begin{align*}
\text{156} & \xrightarrow{\text{a}} \text{157} & \text{b} \xrightarrow{} \text{158} \\
\text{160} & \xrightarrow{\text{e}} \text{161} & \xrightarrow{\text{f}} \text{162} \\
\text{163} & \xrightarrow{\text{g}} \text{164} \\
\end{align*}

- a) 2-ethyl-2-methyl-1,3-dioxolane, p-TsOH; 
- b) Li, NH\textsubscript{3}, THF then TMSCl, Et\textsubscript{3}N;
- c) MeLi, THF then CH\textsubscript{2}O, 82%;
- d) LiBu\textsubscript{3}BH, THF, 92%;
- e) H\textsubscript{2}O, p-TsOH, 98%;
- f) p-toluenesulfonylhydrazide, EtOH, quant.;
- g) MeLi, THF, quant.;
- h) acetone, p-TsOH, quant.;
- i) Cr\textsubscript{2}O, 3,5-dimethylpyrazole, CH\textsubscript{2}Cl\textsubscript{2}, 63%
Since halenaquinone exhibits antibiotic activity against the aforementioned bacteria and possesses a unique pentacyclic ring structure incorporating a furan ring, we undertook the challenge to synthesize it from readily available material. Our initial attempts preceded Harada et al's synthesis by approximately one year. Since Harada et al's is a long synthesis, an additional challenge was recognized in developing a short synthesis of halenaquinone.
Scheme 28

\[
\text{164} + \text{169} \xrightarrow{a} \text{170} \\
\text{OMe} \quad \text{OMe} \\
\text{OMe 171} \\
\text{OMe 172} \\
\text{OMe 173} \\
\text{OMe 174} \\
\text{149}
\]

a) Benzene, 210°C, 33%; b) DDQ, benzene, 89%; c) Potassium tert-butoxide, Bu'OH, O₂, 90%; d) 60% HOAc(aq); e) DMSO, DCC, benzene, TFA, pyridine; f) Ce(NH₄)₂(NO₃)₆, MeOH(aq), 44%
3.1.3  
**Retroynthetic Analysis of Halenaquinone**

Our retrosynthetic analysis is shown in scheme 29. Step 1 could be achieved by forming a radical at the aryl carbon bearing the iodine which should add to the endocyclic double bond in a 6-exo-trig manner forming the six-membered ring C. Step 2 is a simple oxidation of the alcohol to a ketone by a Swern oxidation\(^1\) formed in step 3 from attack of the C-5 anion of 177 on the aldehyde of 178. Step 4 is the acid catalyzed aromatization of the six-membered oxo-bridged ring\(^5\) of 179 formed by the Diels-Alder reaction of furan 180 with 1,4-quinone (step 5). Furan 180 is readily
available through synthetic methodology developed in our research labs. Step 6 involves the complete reduction of the carbonyl of 182 to a methylene group by forming the 1,3-dithiolane of the carbonyl and catalytically hydrogenating it with Raney Nickel. Step 7 is an intramolecular palladium catalyzed Heck reaction with the furylic iodine. The choice of the Heck reaction was sparked by the successful reaction of 4-iodo-3-(methoxymethyl)furan 187 with methyl acrylate by a Heck reaction forming the coupled product 189 in 60% yield (scheme 30). It was thought that the intramolecular nature of the proposed reaction would proceed in a similar or improved yield. Step 8 is the addition of the anion of the trimethylsilyl protected cyanohydrin 184 to crotonaldehyde followed by the oxidation of the secondary allylic alcohol. The protected cyanohydrin can be easily formed by treating the parent aldehyde 186 with trimethylsilyl cyanide and zinc iodide (step 9). Compound 186 is a direct precursor of compound 180 and is therefore readily available.

This synthetic analysis differs from the total synthesis previously described in many ways. Firstly, it does not require the use of an expensive chiral starting material. The fact that the optically active material was used at the beginning of the synthesis raises its overall effective cost when one considers some of the low yielding steps towards the final compound. Although our analysis will provide a racemic product, asymmetric induction reactions could be introduced along the synthetic pathway. Secondly, this analysis represents a convergent synthesis where compounds 177 and 178 are prepared from very similar starting materials 186 and 180 which are both easily accessible. Thirdly, there are potentially fewer steps in the overall synthesis, all based on well established methodologies. The work presented in this part of the thesis concentrates on the synthesis of the intermediate product 182.
3.2.0 **Results and Discussion**

A model study was first undertaken to investigate the feasibility of using the cyanohydrin as the anion source for any alkylations. It was decided to remove the C-2 silane on the furan ring for fear of it impeding the formation of the cyanohydrin from the aldehyde or the subsequent alkylation.

The synthesis of the alcohol precursor 49 was accomplished by the method developed by Keay\(^1\) (scheme 31). Treatment of compound 49 with 2 equivalents of \(n\)-butyllithium in DME followed by iodine (freshly sublimed) dissolved in DME provided 190 in 95% yield.\(^1\) Removal of the silane by treating compound 190 with tetra-\(n\)-butylammonium fluoride in THF afforded 191 in 94% yield. The \(^1\)H NMR spectra of compound 191 indicated absorptions at \(\delta\) 7.36 and 7.32, both indicative of protons at the alpha positions of the furan ring. The methylene group protons appeared at \(\delta\) 4.37.

Swern oxidation of furan 191 provided the corresponding aldehyde 180 (scheme 32); the disappearance of the methylene signal in the \(^1\)H NMR spectrum and the appearance of aldehyde signals at \(\delta\) 9.85 and 184.84 in the \(^1\)H and \(^{13}\)C NMR spectra respectively confirmed the structure. In addition, one of the furan proton signals shifted downfield to \(\delta\) 7.99 relative to that in compound 191 alluding to the presence of the aldehyde carbonyl. The absence of an alcohol O-H stretch in the IR spectrum and
the appearance of a strong absorption at 1690 cm\(^{-1}\) for a carbonyl stretch indicated an oxidation had occurred. A strong molecular ion peak at a m/e of 222 in the mass spectrum confirmed the presence of the iodine and, ultimately, the assigned structure.

Treatment of aldehyde 180 with trimethylsilyl cyanide in the presence of catalytic zinc iodide afforded cyanohydrin 192 in 95% yield (scheme 32). The disappearance of the aldehyde signal in both the \(^1\)H and \(^{13}\)C NMR spectra coupled with the appearance of the trimethylsilyl cyanide hydrogen signal at \(\delta 5.30\) and a molecular ion peak at a m/e of 321 in the mass spectrum, attested to the success of the reaction.

Since the reaction of trimethylsilyl cyanohydrin anions with carbonyl compounds can often lead to silicon scrambling with the newly formed alcohol\(^{54}\), the trimethylsilyl group was exchanged for an ethoxyethyl protecting group. This was accomplished by treating compound 192 with a crystal of p-toluensulfonic acid in wet THF followed by ethyl vinyl ether (scheme 32). The disappearance of the trimethylsilyl peaks in the \(^1\)H NMR spectrum, coupled with the appearance of multiplets indicative of an ethoxy ethyl group and a molecular ion peak at a m/e of 321 in the mass spectrum confirmed the exchange of the alcohol protecting groups. The doubling of the signals in the \(^1\)H NMR spectrum was attributed to the presence of two asymmetric centres in the molecule resulting in diastereomers.

The formation of the anion of cyanohydrin 193 with LDA followed by its reaction with crotonaldehyde provided 194 in 59% yield; the low yield is possibly due
to steric hindrance from the ethoxyethyl protecting group on the incoming electrophile (scheme 33). Since this compound decomposed upon distillation or storage at 0°C, it was immediately subjected to a Swern oxidation to afford compound 195 in 85% yield. The \( ^1H \) NMR spectrum of compound 195 displayed no cyanohydrin proton near \( \delta \) 5.3. Multiplets at \( \delta \) 6.55 and 7.2, each integrating to one proton, indicated the presence of the double bond originally from crotonaldehyde. The presence of the ketone was indicated by an absorption at \( \delta \) 187.18 in the \( ^{13}C \) NMR spectrum and a strong IR absorption at 1706.2 cm\(^{-1}\), finally proving the structure of compound 195 as assigned (scheme 33). Unlike its alcohol precursor, it was stable to storage at room temperature

\[
\text{Scheme 33}
\]

and survived a distillation.

Compound 195 was then subjected to palladium catalyzed Heck reaction conditions: the furan 195 was dissolved in acetonitrile with 5 equivalents of triethylamine and 1 mol% of palladium (II) acetate. Unfortunately, this did not succeed in forming the expected six-membered ring. In fact, the \( ^1H \) NMR spectrum indicated that the major product was deiodized starting material. This was indicated by a singlet at \( \delta \) 6.5. Approximately 20% of the starting material 195 was recovered. The proton absorptions between \( \delta \) 1.5 and 0.5 dwarfed the remainder of the spectrum, suggesting that some decomposition or destruction of the starting material or product(s) had occurred. Since nitrile groups and oxygen containing solvents\(^{55}\) have the effect of coordinating to and solvating palladium, perhaps the use of the cyanohydrin and ethoxyethyl protecting group prevented the ring closure from occurring by affecting the catalyst's behaviour.

Despite these results, the cyanohydrin route was repeated with the TBDMS group attached to the C-2 position of the furan ring. The reason for doing this was twofold. First, the presence of the silyl group at that particular site of the furan ring was required for the future alkylation at the other alpha-site. Second, the excess steric bulk offered by the silyl group may help to guide the olefin arm closer to the remote
beta-site of the furan ring where the palladium catalyzed ring closure was to occur.

The synthesis of the trimethylsilyl protected cyanohydrin 184 from the parent aldehyde 186 proceeded smoothly in 96% yield (scheme 34). Unfortunately, exchange of the TMS group with an ethoxyethyl group could not be effected. Although the TMS group could be easily removed, the reaction of the free hydroxyl group with ethyl vinyl ether did not proceed at all. This is most likely due to the added steric bulk of the silyl group on the furan ring.

Attempts were then made at replacing the ethoxyethyl group of compound 195 (scheme 33) with a t-butyldimethylsilyl group. Treating compound 195 with p-toluenesulfonic acid in methanol had no effect on removing the ethoxyethyl group; however, it could be removed from the unalkylated cyanohydrin 193 to produce the unprotected cyanohydrin 197 (scheme 35). This compound was extremely unstable and reverted back to the aldehyde 180 (scheme 32) on contact with air. Furan 197 was therefore silylated immediately to provide compound 198 in 70% yield (scheme 35). Attempts at alkylating compound 198 with crotonaldehyde were unsuccessful. It is likely that the cyanohydrin anion of compound 198 did not even form since it could not be deuterated. This is due to the added steric bulk of the silyl group. At this point the use of the cyanohydrin route was abandoned.

Attention was then given to employing either the dithiane or dithiolane
protecting group for the furan aldehyde, as they can serve as acyl anion equivalents. The 1,3-dithiolane of aldehyde 180 was synthesized in 83% yield using the procedure developed by Ong and Chan56 (scheme 36). The disappearance of the aldehyde signal in the $^1$H NMR spectrum as well as the appearance of a singlet at $\delta$ 5.36 (dithiolane hydrogen) and a multiplet at $\delta$ 3.30 indicated the success of the reaction. The furan proton absorptions moved upfield to $\delta$ 7.45 and 7.41 relative to those of compound 180, indicating the absence of the aldehyde carbonyl.

Unfortunately, LDA did not abstract the dithiolane proton of 200.56 Clearly, n-butyllithium could not be used as it has been found that halogen-metal exchange with
the iodine of the furan ring would occur.\textsuperscript{52} No other bases were employed in this reaction.

Since the anion of compound 200 could not be formed, it was thought that it might be useful to reverse the sense of the reaction; that is, prepare the 1,3-dithiane of crotonaldehyde, form the carbanion and add it to compounds 180 (scheme 36) or 186 (scheme 34). Attempts at synthesizing the 1,3-dithiane of acrolein (to use it in a model study) were unsuccessful; polymerization of the acrolein was instantaneous. Similar results were obtained with crotonaldehyde. Although the 1,3-dithiane of crotonaldehyde has been reported in the literature, we were unsuccessful in repeating their work.\textsuperscript{57}

The use of trimethylsilyl cyanide was reconsidered because of its speed and simplicity in reacting with carbonyls. This time, however, it would be used only temporarily and removed before the anticipated palladium catalyzed ring closure. Again, a model study was undertaken using 3-thiophenecarboxaldehyde 203 as the source of the aromatic aldehyde (it was readily available at the time) (scheme 37). The trimethylsilyl cyanide adduct of acrolein was generated in situ and used without isolation in the alkylation to follow; attempts at its isolation caused it to revert back to acrolein and trimethylsilyl cyanide. The addition of thiophene 203 to the anion
generated from the acrolein cyanohydrin with LDA produced a mixture of compounds which were unstable to silica gel chromatography. (A large amount of thiophene 203, not present in the crude reaction $^1$H NMR spectrum, was recovered from these columns). The large number of trimethylsilyl peaks in the $^1$H NMR spectrum indicated that 'silicon scrambling' between the two available hydroxyl groups had occurred. Converting the cyanohydrin back to the carbonyl generated a large amount of the starting material 203. Clearly, this approach towards a ring closure precursor was not the method of choice.

The unforeseen difficulty in synthesizing a ring closure precursor suitable for Heck reaction conditions resulted in a search for alternative methods for closing the required ring. One of these stemmed from the knowledge that epoxides can be subjected to nucleophilic attack, causing the opening of the epoxide. Presumably, an anion at the 4-position of the furan, which can be made from the corresponding iodo furan, would attack an epoxide in such a way as to form the required six-membered ring. The prerequisite furan is shown in figure 7. The potential of forming a

![Figure 7](image)

seven-membered ring was not considered to be a threat based on the fact that a 6-exo-tet ring closure is favoured over a 7-endo-tet ring closure. 58

In 1970, Cornforth and Green 59 developed a facile method of forming epoxides from iodohydins which in turn are prepared from olefins. Epoxides are formed by treating the iodohydrid with base. 59 The procedure involves treating the olefin with iodine and potassium iodate in a mixture of water, 1,4-dioxane and a small amount of acetic acid. There was concern that the furan ring may not survive the action of the oxidants present in the reaction; therefore, a model study was undertaken (scheme 38). The Grignard reagent, prepared from 4-bromo-1-butene and magnesium metal, was added to a THF solution of 3-furaldehyde 207 to form the alcohol 208 in 89% yield. The oxidation of alcohol 208 to the ketone 209 by a Swern oxidation proceeded
smoothly in 84% yield. Multiplet signals at δ 5.8 and 5.0 in the $^1$H NMR spectrum, integrating for one and two protons respectively, indicated the presence of the mono-substituted olefin. An IR absorption of 1690 cm$^{-1}$ confirmed the presence of the ketone carbonyl.

The iodohydridin 210 was formed in 30 seconds and in 96% yield upon treating compound 209 with iodine and potassium iodate. The regiochemistry of the iodohydridin was determined unambiguously by the combination of the $^{13}$C NMR spectrum and the DEPT experiment. These two spectra can be found in figure 8.

The absorption at δ 70.11, shown to be a tertiary carbon atom (by DEPT), is indicative of an aliphatic carbon atom bearing a hydroxyl or ether oxygen. The high field shift at δ 14.95, shown to be a secondary carbon atom, bears the iodine atom which, although electronegative, has the ability of shielding adjacent atoms with its own high electron density.

It was clear from this reaction that the furan ring would survive the reagents used to synthesize the iodohydridin.
Figure 8

$^{13}C$ spectra of compound 210
The same synthetic route illustrated in scheme 38 was followed using iodoform 180 (scheme 32) as the starting material. This provided iodoform 211 in 85% overall yield. The reaction to produce the corresponding iodohydrin failed; a complex mixture was obtained which included olefinic signals in the $^1$H NMR spectrum. In addition, the integration of proton absorptions between $\delta$ 8.00 and 7.00 was dwarfed by the remainder of the absorptions, suggesting that the furan ring in the starting material was destroyed. It is speculated that the iodine atom is increasing the electron density in the $\pi$-system of the furan ring, thereby rendering it more susceptible to oxidation by iodine and iodate anion.

Despite this unfortunate result, compound 212 (figure 9) was prepared by silylating the corresponding alcohol, prepared by the reaction of the Grignard of 4-bromo-1-butene on compound 180 (scheme 32), with t-butyldimethylsilyl chloride andimidazole in DMF. Unfortunately, compound 212 provided complex mixtures upon treatment with the iodohydrin forming reaction conditions. There were no signals in the $^1$H NMR spectrum resembling those provided from the same reaction performed on compound 211 (scheme 38).

Furan 211 was treated with MCPBA/NaHCO$_3$ in the hopes of obtaining the epoxide directly from the olefin. Although there was evidence in the $^1$H NMR spectrum that a small amount (<1%) of the epoxide formed, it was evident that the furan ring was being destroyed by the oxidizing agent. Clearly, another method had to be found to close the six membered ring onto the furan.

A completely new synthetic route was investigated. This was based on the fact that vinyl and aryl iodides can be induced to form radicals$^{60}$ which can in turn react with a variety of unsaturated compounds. Carbon radicals have been shown to form rings with alkynes forming an exocyclic double bond$^{61}$ (scheme 39). This reaction is potentially useful since the exocyclic double bond formed could be modified to allow
the formation of ring C in halenaquinone (cf. scheme 29). A model study was undertaken to find a method of attaching a suitable 'alkyne arm' on the furan ring.

The source of the alkyne was 1-iodo-3-butyne 219 which was synthesized from the commercially available 3-butyn-1-ol 217 (scheme 40). Treating the latter with p-toluene sulfonyl chloride and DMAP in methylene chloride afforded the tosylate 218 which when refluxed with NaI/acetone afforded compound 219 (scheme 40). When 1,4-dilithio-1-butyne 220, prepared from compound 219 with 3 equivalents of t-butyllithium, was added to 3-furaldehyde, a mixture of compounds was produced including 3-hydroxymethylfuran 221 and the two possible addition products 222 and 223 of the dilithio alkyne 220 to the carbonyl (figure 10). Since the dianion of alkyne 219 provided both 222 and 223, protection of the acetylene was necessary.

The trimethylsilyl protected analog of alkyne 219 was synthesized by the method developed by Negishi et al62 (scheme 41). The protected acetylene 228 was synthesized in a 78% overall yield.

The first reaction tried involved the synthesis of the Grignard reagent of 228 with magnesium metal in THF and adding this to 3-furaldehyde. The 1H NMR spectrum revealed that the iodide 228 was consumed but that 96% of 3-furaldehyde
was recovered. The Grignard reagent probably participated in a Wurtz coupling with unreacted iodide, effectively consuming both the starting material 228 and its Grignard reagent.

The use of the alkyne iodide 228 was therefore abandoned in favour of its corresponding bromide in the hopes that it would perform more usefully as a Grignard reagent. The alkyne 229 was synthesized in the same way as alkyne 228 except that lithium bromide was substituted for lithium iodide. Compound 229 was thus prepared in 96% overall yield (scheme 41).
The Grignard reagent of 229, prepared by treating it with magnesium metal in THF, reacted with 3-furaldehyde to produce the expected alcohol in 85% yield (scheme 42). When the same Grignard reagent was reacted with the furyl aldehyde 186, the expected alcohol was not obtained. Instead, the alcohol 190 was formed in 20% yield; the remainder of the starting material was recovered. It is well known that Grignard attack at hindered aldehydes may provide the corresponding alcohol via a hydride transfer from the Grignard reagent to the aldehyde. This result indicates that the aldehyde group of compound 186 is shielded from nucleophilic attack by presumably both the adjacent TBDMS group and the iodine atom. This is substantiated by the fact that the expected alcohol 231 was obtained in 96% yield when furan 180 is treated with the same Grignard reagent (scheme 42). The IR spectrum of 231 possessed no absorption near 1700 cm\(^{-1}\) indicating the disappearance of the aldehyde group. There was a broad absorption at 3384 cm\(^{-1}\), indicating an alcohol, and a sharp absorption at 2172 cm\(^{-1}\), which was assigned to the triple bond. The \(^1\)H NMR spectrum exhibited a trimethylsilyl singlet at \(\delta\) 0.12, two multiplets at \(\delta\) 1.8 and 2.35, each integrating to two protons and two sharp singlets at \(\delta\) 7.35 and 7.4. The ten absorptions in the \(^13\)C NMR spectrum were also unambiguously consistent with the assigned structure. Compound 231 was then subjected to carbon radical forming conditions.
Tri-n-butyltin hydride was chosen as the radical generator for two reasons. First, the tin-hydrogen bond can be homolytically cleaved in one of two ways, by irradiation with ultra-violet radiation generated by a mercury vapour lamp, or by treatment with azo bis(isobutyronitrile) (AIBN) which generated radicals at 60°C. Secondly, it has the ability to participate in radical chain reactions such as the one shown in scheme 43. The radical initiating procedure chosen for compound 231 was heating with AIBN since it is known that alkynes tend to produce polymeric material on irradiation with ultra-violet light.64

The reactions were carried out in refluxing benzene and at dilute starting material concentrations. Two different reactions were carried out, one in which the mixture of tin hydride and AIBN were slowly added by syringe pump over two hours and the other in which the required amount of tin hydride and AIBN were added in three batches over three hours. In both cases, the desired ring closed product was not obtained. Rather, a complex mixture of compounds, none of which were identified, were evident by ¹H NMR. It was clear from the ¹H NMR spectrum that the alkyne arm of compound 231 had been modified in several ways giving rise to the large amount of products. It was also clear that the iodine on the furan ring was unscathed. This was totally unexpected as it was believed that the carbon-iodine bond was the most...
susceptible to homolytic cleavage. It is known that tri-\(\alpha\)-butyltin hydride can add across triple bonds. This may have occurred in preference to the homolytic cleavage of the carbon-iodine bond. Therefore, a new ring closure precursor devoid of any carbon-carbon triple bond was prepared.

The furan 211 which was synthesized earlier (scheme 38) in the attempts to prepare iodothydrins and epoxides was ideally suited for this task. It is similar to compound 231 except that it possesses a double bond instead of a triple bond, has no trimethylsilyl group and has a ketone instead of a secondary alcohol. In addition, this compound could, in principle, be subjected to both the thermal and ultra-violet irradiation methods for radical generation. The reaction conditions under which furan 211 was subjected to can be found in table 7. In every entry one equivalent of tri-\(\alpha\)-butyltin hydride was used. In all of the reactions tried, the \(^1\)H NMR spectra suggested that the iodine on the furan ring was left intact. This is because there were no absorptions at or around \(\delta 6.5\), which would indicate the presence of a \(\beta\)-furan proton. There was some question about the possibility that benzophenone, which is often used as a radical scavenger, was contaminating the benzene obtained from the still used to dry it. Entry C (Table 7) used benzene from a stock bottle which had been
degassed with a stream of argon. Since no reaction occurred, that potential problem was ruled out.

At this point, the radical reaction approach to closing the six-membered ring was abandoned. There was no doubt that the carbon-iodine bond in these furan compounds was uncharacteristically unreactive to radical generating techniques. When this is added to the knowledge gained in the failure of the iodohydrin and epoxide reactions attempted earlier, the apparent abnormalities of the furan-iodine bond become even more intriguing. It may be possible that a back donation of electron density into the furan ring by the iodine atom may be strengthening that bond, causing the observed unreactivity towards free radical species. Further study will be required, however, to uncover the true nature of this unusual bond.

In view of the fact that sophisticated techniques involving palladium catalysis or carbon radical generation were unsuccessful in forming the elusive six-membered ring, a more 'direct' approach was investigated. It was thought that an anion could be generated on the furan carbon bearing the iodine via a halogen-metal exchange. This carbanion in turn may attack an aldehyde properly situated on the arm attached to the
other beta-site of the furan ring to close the desired six-membered ring (scheme 44).

![Scheme 44]

The alcohol formed could then be manipulated to allow for the subsequent steps towards halenaquinone.

The desired aldehyde was prepared as illustrated in scheme 45. The synthesis of the aldehyde resembles that used to obtain the olefin precursor for the radical reactions. It is interesting to note that the alcohol of compound 235 could not be silylated using the standard procedure, even upon heating. Presumably, the hydroxyl group is too sterically hindered to allow its protection by the bulky silyl group. The alcohol could be protected by a 1,4-C—O silicon migration with catalytic sodium hydride using DMF as the solvent. Subsequent hydroboration oxidation of compound 237 proceeded in 90% yield with 10% of the product being the secondary alcohol regioisomer of compound 238. This 9:1 ratio of regioisomers is what is to be expected from the reaction of borane with terminal olefins.

Compound 238 could not be distilled as it decomposed at 72°C at a reduced pressure of 1.3 X 10^-2 torr. It was used without further purification in the Swern oxidation providing compound 239 in high yield. The ¹H NMR absorption at δ 9.85 indicated the presence of an aldehyde moiety. The IR absorption at 1720 cm⁻¹ also indicated the presence of the aldehyde. The absence of any broad absorption above 3000 cm⁻¹ in the IR spectrum, coupled with the ¹H NMR absorptions at δ 0.90 (9 protons) and 0.20 (6 protons) indicated that the TBDMS group was attached to the hydroxyl group. Multiplets at δ 2.40 (2 protons) and 2.05 (2 protons) indicated the presence of an ethylene group with one of its carbon atoms adjacent to the aldehyde. The triplet at δ 4.65 (1 proton) indicated that the other ethylene group carbon atom was next to the carbon atom bearing the hydroxyl group.

Compound 239 was then subjected to a variety of reaction conditions known to couple vinyl iodides with aldehydes. These reactions are summarized in table 8.
There are several points of interest to highlight from these reactions. Absolutely no reaction occurred in entry A even in the presence of 30 equivalents of magnesium or after a small amount of 1,2-dibromoethane had been added. When warmed to reflux (entry B), the magnesium did react with the furyl iodide, albeit very slowly. One hour was necessary to consume 1.5 mg of compound 239. The appearance of a $^1$H NMR absorption at $\delta$ 6.35 indicated that the iodide had been replaced with a proton; therefore, the ring did not form. n-Butyllithium was then used to attempt the exchange of the iodine for a lithium (entry C). The cold temperature was
Table 8

Ring Closure Attempts on Compound 239

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>C- Generator</th>
<th>Temp</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>THF</td>
<td>Mg(^0)</td>
<td>r.t.</td>
</tr>
<tr>
<td>B</td>
<td>THF</td>
<td>Mg(^0)</td>
<td>67°C</td>
</tr>
<tr>
<td>C</td>
<td>Et(_2)O</td>
<td>Bu(^n)Li</td>
<td>-100°C</td>
</tr>
<tr>
<td>D</td>
<td>THF</td>
<td>Li wire</td>
<td>-78°C</td>
</tr>
<tr>
<td>E</td>
<td>THF</td>
<td>Li wire</td>
<td>0°C</td>
</tr>
<tr>
<td>F</td>
<td>THF</td>
<td>Li rod</td>
<td>-78°C</td>
</tr>
<tr>
<td>G</td>
<td>THF</td>
<td>Li rod</td>
<td>0°C</td>
</tr>
<tr>
<td>H</td>
<td>THF</td>
<td>Li ribbon</td>
<td>0°C</td>
</tr>
<tr>
<td>I</td>
<td>THF/HMPA</td>
<td>Li ribbon</td>
<td>0°C</td>
</tr>
</tbody>
</table>

intended to discourage the alkyllithium from reacting with the aldehyde of compound 239, but failed to do so. The presence of absorptions in the \(^1\)H NMR spectrum indicative of a butyl group suggested that this in fact had occurred. There was no evidence in the \(^1\)H NMR spectrum, such as a singlet near δ 6.5, suggesting that any of the iodine had been removed from the furan ring.

Entries D through H attempted lithium halogen exchanges with different sources of elemental lithium. In all cases, the lithium was cut and scraped of its oxide coating under an argon atmosphere preventing any destruction of the fresh metal surface by nitrogen or oxygen. In all cases, these reactions failed in producing a ring closed product. Although there were small amounts of deiodized material produced at the higher temperatures (entries E,G,H), only an average of 30% of the starting material had been converted to a gummy mix of unknown presumably polymeric material. It is known that beta-lithio species of both furan and thiophene can undergo ring opening, depending on the reaction conditions and the stability of the lithio species\(^{68,69}\) (scheme 46). If the beta-lithio species of compound 239 was in fact being formed, the furan ring
may have opened and ultimately lead to the polymeric material (scheme 46). It is also possible that the beta-lithio species may not have been forming at all. It is known that 3-iodofuran will not react with magnesium metal or lithium metal to form the corresponding anion.70

One final attempt at closing the six-membered ring was launched on a compound which possessed no iodine on the furan ring. This study was sparked by an unexpected discovery made in our lab where, upon heating or treatment with aqueous acid, compound 246 underwent a Friedal-Craft alkylation to form furan 247 in high yield37 (scheme 47). It was hoped that a Prins71 reaction, on compound 252 (scheme
48) may produce furan 253. The synthetic route to compound 252 is shown in scheme 48 and is very similar to that used to synthesize compound 239. There is, however, one major difference. The silylation of 249 using the standard procedure proceeded very well unlike the complete failure of the same reaction when tried with an iodine at the C-4 site of the
furan ring (scheme 45). It is now obvious the iodine was offering some steric interference to the protection of the alcohol.

Compound 251 decomposed during an attempted distillation and therefore was immediately oxidized to the aldehyde 252 via a Swern oxidation. The 1H NMR absorption at δ 9.75, the 13C NMR absorption at δ 202.33 and the IR absorption at 1725 cm⁻¹ indicated the presence of the aldehyde. There was no broad absorption above 3000 cm⁻¹ in the IR spectrum, indicating that the alcohol was protected. Two sharp singlets at δ 0.90 and 0.83 in the 1H NMR spectrum, each integrating for nine protons, indicated the presence of two TBDMS groups. The multiplets at δ 2.5 and 1.9, each integrating for two protons, indicated the presence of the ethylene group.

With aldehyde 252 in hand, we now turned our attention to the Prins reaction. Alkyl aluminum chlorides, particularly the dimethyl, ethyl and diethyl, have been shown to be useful catalysts in both the Prins and ene reactions.⁷¹ When using aluminum catalysts, methylene chloride as the solvent usually provides the best results.⁷² Dimethyl aluminum chloride was not initially used since the addition of a methyl group to the aldehyde is often the major reaction that occurs except when strongly nucleophilic olefins are used.⁷² Diethyl aluminum chloride has also been shown to cause problems; not only does it tend to add ethyl groups to aldehydes, but it can also reduce them over long reaction times.⁷³ With these facts in mind, the reactions tabulated in table 9 were carried out.

When ethyl aluminum dichloride was used (entries A,B), the starting material was completely consumed within 5 minutes. No sign of the ring-closed product was found. The 1H NMR spectra indicated that the furan ring had been destroyed. This was not totally unexpected since furan rings are susceptible to ring openings from some Lewis acids.⁷⁴ The same was true with diethyl aluminum chloride (entries C,D,E), even at very low temperatures where the problem of ethyl group transfer from the catalyst is minimized.⁷³ Aluminum trichloride was also used (entry F) but also produced similar disappointing results. The aluminum catalysts were then abandoned in favor of mineral and organic acids (entries G through L). Acetic acid and p-TsOH were not destructive to the furan ring at moderate temperatures; however, no ring was formed. At higher temperatures and long reaction times (greater than 12 hours), acetic acid succeeded in destroying the furan ring (entries K,L). Hydrochloric acid (entry J), even in catalytic amounts, was found to be too harsh on the furan ring. A final attempt was made using boron trifluoride etherate. Unproductive at low temperatures (entry M), it too destroyed the furan ring at 0°C (entry N).
### Table 9

**Attempted Prins Reactions on Compound 252**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>EtAlCl₂</td>
<td>CH₂Cl₂</td>
<td>0°C</td>
<td>?</td>
</tr>
<tr>
<td>B</td>
<td>EtAlCl₂</td>
<td>CH₂Cl₂</td>
<td>-20°C</td>
<td>?</td>
</tr>
<tr>
<td>C</td>
<td>Et₂AlCl</td>
<td>THF</td>
<td>-78°C</td>
<td>?</td>
</tr>
<tr>
<td>D</td>
<td>Et₂AlCl</td>
<td>THF</td>
<td>0°C</td>
<td>?</td>
</tr>
<tr>
<td>E</td>
<td>Et₂AlCl</td>
<td>THF</td>
<td>r.t.</td>
<td>?</td>
</tr>
<tr>
<td>F</td>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>-78°C</td>
<td>?</td>
</tr>
<tr>
<td>G</td>
<td>-----</td>
<td>PhCH₃</td>
<td>111°C</td>
<td>N.R.</td>
</tr>
<tr>
<td>H</td>
<td>-----</td>
<td>PhCH₃/HOAC</td>
<td>111°C</td>
<td>N.R.</td>
</tr>
<tr>
<td>I</td>
<td>pTsOH</td>
<td>THF</td>
<td>70°C</td>
<td>N.R.</td>
</tr>
<tr>
<td>J</td>
<td>HCl</td>
<td>THF</td>
<td>r.t.</td>
<td>?</td>
</tr>
<tr>
<td>K</td>
<td>-----</td>
<td>HOAc</td>
<td>r.t.</td>
<td>N.R.</td>
</tr>
<tr>
<td>L</td>
<td>-----</td>
<td>HOAc</td>
<td>85°C</td>
<td>?</td>
</tr>
<tr>
<td>M</td>
<td>BF₃·Et₂O</td>
<td>Et₂O</td>
<td>-100°C</td>
<td>N.R.</td>
</tr>
<tr>
<td>N</td>
<td>BF₃·Et₂O</td>
<td>Et₂O</td>
<td>0°C</td>
<td>?</td>
</tr>
</tbody>
</table>

The synthesis of a tetrahydroisobenzofuran suitable as a precursor for the synthesis of halenaquinone has not been accomplished. A great deal of difficulty was encountered in using the C-4 furan iodine in ring forming reactions. The results presented in chapter 1, which were carried out after this work was stopped, suggests an alternative route to such a precursor. In chapter 1, a C-4 furan tri-tributylstannyl group has proved to be useful in a Stille reaction with aryl bromides. Stille has also shown that aryl and vinyl triflates can be used in such coupling reactions instead of aryl
bromides. With this in mind, compound 258 should ring close under similar reaction conditions to provide the tetrahydroisobenzofuran 259 (scheme 49). Future extensions of this work may involve a synthesis of furan 258 as illustrated in scheme 49 to test out this hypothesis.

Scheme 49

\[
\begin{array}{c}
\text{a,b} & \text{254} & \text{a,b} & \text{OTBDMS} & \text{c,d,e,f} & \text{OTI} & \text{Br} \\
\text{SnBu}_3 & \text{CHO} & \text{255} & \text{257} & \text{256} \\
\text{SnBu}_3 & \text{OTBDMS} & \text{d,b} & \text{258} & \text{67} & \text{SnBu}_3 & \text{OTBDMS} \\
\text{SnBu}_3 & \text{OTBDMS} & \text{259} & \text{i} & \\
\end{array}
\]

a) NaH, THF, TBDMS; b) Swern [O]; c) LDA, -78°C, TiCl; d) n-Bu₄NF, THF; e) TsCl, DMAP, CH₂Cl₂; f) LiBr, acetone; g) Mg, THF; h) TBDMSO, imidazole, DMF; i) TTPP, LiCl, PhCH₃, 110°C
4.0.0 *Experimental*

4.1.0 *General Procedures*

Nuclear magnetic resonance spectra were obtained using a Bruker AC300 spectrometer using deuterochloroform as solvent (and internal standard) unless otherwise stated. All $^1$H NMR spectra listed in this section were obtained at 300MHz unless otherwise stated and will have the following format: chemical shift (in ppm), (multiplicity, number of protons, coupling constants, assignment). All $^{13}$C NMR spectra were obtained at 75 MHz and will have the following format: chemical shift (in ppm), (proton multiplicity [as determined by DEPT experiment]). Infrared spectra were obtained with a Nicolet 5DK-FTIR spectrometer. Solid samples were run as KBr pellets while oils were run neat between NaCl plates. Mass spectra were obtained with a Varian CH5 spectrometer. Ultraviolet spectra were obtained with a Shimadzu UV-160 spectrometer.

Thin layer chromatography plates were purchased from the Merck Frosst Company (catalog #M5735). The plates were developed in the following manner: 1) The plate was coated with a solution consisting of (NH$_4$)$_6$Mo$_7$O$_{24}$.4H$_2$O (118.4g), conc. H$_2$SO$_4$ (200ml) and water (2L) and then 2) heated to over 100°C with a hot air gun. Where column chromatography was necessary E. Merck silica gel (230-400 mesh A.S.T.M.) and the method developed by Still$^{45}$ were used.

Diethyl ether, THF, benzene and DME were dried (Na/benzophenone) and distilled immediately prior to use. Methylene chloride, HMPA and DMF were dried over calcium hydride and distilled prior to use.

Syringes and glassware were oven-dried at 120°C for 4 hours or longer and either cooled in a desiccator or with a flow of dry argon. All reactions which were sensitive to moisture or atmospheric conditions were conducted under argon.

Cooling baths were prepared using the following solvent/coolant systems: -60°C, chloroform/dry ice; -78°C, acetone/dry ice; -100°C, diethyl ether/liquid nitrogen. All temperatures are given in degrees Celsius. All boiling points were obtained using a Kugelrohr air bath apparatus while melting points were determined using a Thomas-Hoover capillary apparatus.
4.2.0  **Experimental Procedures**

4.3.0  **Palladium Catalyzed Cross-Coupling Reaction**

3-(Hydroxymethyl)furan (65)

![Chemical Structure of 3-(Hydroxymethyl)furan (65)]

3-Furoic acid (20g, 179mmol) was added to a solution of lithium aluminum hydride (7g, 171mmol) in dry diethyl ether (150ml) at 0°C. The mixture was stirred for 2 hours at 25°C and then cooled to 0°C. The mixture was then treated with water (7ml), 15% sodium hydroxide (7ml) and water (21ml) which produced an off-white slurry. The slurry was filtered through celite and the solvent removed *in vacuo* to yield after distillation a clear colourless oil 65 (>99%). bp 98-100°C/20mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 2.80(bs, 1H, OH), 4.45(s, 2H, H-6), 6.37(s, 1H, H-4), 7.34(d, 2H, J=1.1Hz, H-2 and H-5); \(^13\)C NMR (CDCl\(_3\), 75MHz) \(\delta\) 56.21(t), 109.72(d), 125.01(s), 139.76(d), 143.28(d); IR(neat) cm\(^{-1}\) 3390 (OH); mass spectrum 98(M\(^+\)).

3-l((t-Butyldimethylsilyl)oxy)methyl)furan (66)

![Chemical Structure of 3-l((t-Butyldimethylsilyl)oxy)methyl)furan (66)]

70
**General Silylation Procedure 1**

To a solution of t-butyldimethylsilyl chloride (6.1g, 40mmol) in DMF (20ml) at 0°C was added imidazole (5.7g, 84mmol) and alcohol 65 (3.56g, 36.7mmol). After 12 hours at 25°C, diethyl ether and aqueous sodium chloride were added. The organic layer was washed 6 times with saturated aqueous sodium chloride, dried (Na₂SO₄) and the solvent removed in vacuo to afford after distillation a clear colourless oil 66 (95%). bp 106-109°C/20mm; ¹H NMR(CDCl₃, 300MHz) δ -0.04(s, 6H, -Si-Me), 0.81(s, 9H, -Si-t-Bu), 4.54(s, 2H, H-6), 6.42(s, 1H, H-4), 7.51(d, 2H, J=6.1Hz, H-2 and H-5); ¹³C NMR(CDCl₃, 75MHz) δ -2.85(q), 18.21(d), 25.80(q), 57.52(t), 109.66(d), 125.85(s), 139.38(d), 143.14(d); IR(neat) cm⁻¹ 1063 (C-O); mass spectrum 212(M⁺).

**2-(t-Butyldimethylsilyl)-3-(hydroxymethyl)furan (49)**

\[ 
\begin{array}{c}
\text{TBDMS} \\
\text{4} \\
\text{5} \\
\text{6} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{OH}
\end{array} 
\]

To a mixture of furan 66 (0.69g, 3.3mmol) and HMPA (0.62ml, 3.6mmol) dissolved in THF (10ml) and cooled to -78°C was added n-butyllithium (1.43ml, 2.5M in hexane, 3.6mmol). After stirring for 1 hour at 0°C saturated ammonium chloride was added and the solution extracted with diethyl ether. The organic layer was washed 3 times with saturated copper sulfate, dried (Na₂SO₄) and the solvent removed in vacuo to afford after distillation a white crystalline product 49 (87%). bp 75-78°C/0.02mm; ¹H NMR(CDCl₃, 300MHz) δ 0.01(s, 6H, -Si-Me), 0.89(s, 9H, -Si-t-Bu), 1.5(bs, 1H, OH), 4.57(s, 2H, H-6), 6.46(d, 1H, J=1.8Hz, H-4), 7.57(d, 1H, J=1.8Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -5.73(q), 18.12(s), 25.69(q), 57.10(t), 110.52(d), 135.87(s), 146.69(d), 154.96(s); IR(KBr pellet) cm⁻¹ 3319(OH), 1070(C-O); mass spectrum 212 (0.1, M⁺).
2-(t-Butyldimethylsilyl)-3-(hydroxymethyl)-4-(tri-n-butyl stannyl)furan (60)

\[
\text{SnBu}_3\quad 6 \quad 3 \quad \text{OH} \\
\text{TBDMS}
\]

General Lithiation Procedure 2

To a solution of furan 49 (1.47g, 6.9mmol) in dry DME (20ml) at -78\(^0\)C was added n-butyllithium (7.6ml, 2.0M in hexane, 15.2mmol). After 15 minutes at 0\(^0\)C, tri-n-butyltin chloride (1.88ml, 6.9mmol) was added and the solution stirred for 1 hour. Saturated ammonium chloride was added, the solution extracted with ethyl acetate and the solvent removed \textit{in vacuo} to afford after silica gel column (petroleum ether:ethyl acetate (20:1)) and distillation the stannylated furan 60 (89%) as a clear colourless oil. bp. 148-150\(^0\)C/0.12mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 0.27 (s, 6H, -Si-Me), 0.81(s, 9H, -Si-t-Bu), 0.88(t, 9H, J=4.1Hz, -CH\(_2_\)-CH\(_3\)), 0.94(t, 6H, J=3.7Hz, -Sn-CH\(_2\)), 1.24(m, 6H, CH\(_3_\)-CH\(_2\)), 1.45(m, 6H, -CH\(_2_\)-CH\(_2\)), 2.05(s, 1H, OH), 4.50(s, 2H, H-6), 7.35(s, 1H, H-5); \(^1^3\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) -5.22(q), 9.95(t), 13.65(q), 17.33(s), 26.37(q), 27.29(t), 29.18(t), 58.30(t), 115.75(s), 141.02(s), 151.53(d), 154.78(s); IR(neat) cm\(^{-1}\) 3425(OH), 1252(C-O); mass spectrum 444(M\(^+\)-t-Bu).

3-[(t-Butyldimethylsilyl)oxymethyl]-4-(tri-n-butylstannyl) furan (67)

\[
\text{SnBu}_3\quad 4 \quad 3 \quad \text{OTBDMS} \\
\text{C}
\]

72
General Migration Procedure 3

To a solution of stannylfuran 60 (0.315g, 0.628mmol) in dry DMF (1ml) was added sodium hydride (0.75mg, 0.037mmol). After 5 minutes at 25°C diethyl ether and saturated sodium chloride was added. The mixture was washed six times with saturated sodium chloride dried (Na₂SO₄) and the solvent removed in vacuo to afford after distillation compound 67 (98%) as a clear colourless oil. bp 138°C/0.21mm; ¹H NMR(CDCl₃, 300MHz) δ 0.185(s, 6H, -Si-Me), 0.672(s, 9H, -Si-t-Bu), 0.864(t, 9H, J=7.0Hz, -CH₂-CH₃), 1.03(t, 6H, J=5.1Hz, -Sn-CH₂), 1.33(m, 6H, CH₃-CH₂), 1.51(m, 6H, -CH₂-CH₂), 4.54(s, 2H, H-6), 7.14(s, 1H, H-5), 7.45(s, 1H, H-2); ¹³C NMR(CDCl₃, 75MHz) δ -5.25(q), 9.71(t), 13.65(q), 18.48(s), 27.32(t), 29.14(t), 59.11(t), 114.14(s), 130.77(s), 139.63(d), 147.82(d); IR(neat) cm⁻¹ 1073(C-O); mass spectrum 444(M⁺-t-Bu).

2-(t-Butyldimethylsilyl)-3-(hydroxymethyl)-4-phenylfuran (68)

General Tin Coupling Procedure 4

To a solution of furan 60 (82mg, 0.16mmol) in dry toluene (1.5ml) was added bromobenzene (0.019ml, 0.176mmol), tetrakis(triphenylphosphine)palladium (0) (2mol%) and one crystal of butylated hydroxytoluene. After 6 hours at 110°C, another 2mol% of palladium catalyst was added and stirring was continued for an additional 6 hours. The solution was cooled to room temperature, water (1ml) was added and the mixture was filtered through celite. The mixture was extracted with diethyl ether, dried (Na₂SO₄) and the solvent removed in vacuo to yield after silica gel column (petroleum
ether:ethyl acetate (50:1)) and distillation compound 68(51%). bp 105°C/0.3mm; 

1H NMR(CDC\textsubscript{3}, 300MHz) δ 0.33(s, 6H, -Si-Me), 0.93(s, 9H, Si-t-Bu), 1.6(bs, 1H, OH), 4.60(s, 2H, H-6), 7.27(m, 1H, Ph), 7.36(m, 2H, Ph), 7.52(m, 2H, Ph); 13C NMR(CDC\textsubscript{3}, 75MHz) δ -5.55(q), 17.51(s), 26.41(q), 55.13(t), 127.11(d), 128.27(d), 128.72(d), 132.29(s), 133.93(s), 144.00(d), 158.09(s); IR(neat) cm\textsuperscript{-1} 3540(OH), 1099(C-O).

2-(t-Butyldimethylsilyl)-3-(hydroxymethyl)-4-(2-pyridyl) furan (69)

General tin coupling procedure 4 was used with furan 60 (74mg, 0.14mmol) and 2-bromopyridyl (0.16ml, 0.015mmol) with a total of 18 hours stirring with additional catalyst at the 5 and 12 hour marks to afford compound 69(20%). bp 125°C/0.32mm; 1H NMR(CDC\textsubscript{3}, 300MHz) δ 0.33(s, 6H, -Si-Me), 0.92(s, 9H, -Si-t-Bu), 1.34(bs, 1H, OH), 4.58(s, 2H, H-6), 7.18(m, 1H, Py), 7.52(m, 1H, Py), 7.70(m, 1H, Py), 8.00(s, 1H, H-5), 8.55(m, 1H, Py); 13C NMR(CDC\textsubscript{3}, 75MHz) δ-5.58(q), 13.58(s), 26.30(q), 55.26(t), 121.48(d), 121.67(d), 126.91(s), 129.76(s), 135.39(s), 137.34(d), 146.05(d), 148.50(d), 152.31(s); IR(neat) cm\textsuperscript{-1} 3450(OH), 1091(C-O); mass spectrum 289(M\textsuperscript{+}), 232(M\textsuperscript{+})-t-Bu.

3-[(t-Butyldimethylsilyl)oxymethyl]-4-phenylfuran (71)
General tin coupling procedure 4 was used on compound 67 (82mg, 0.16mmol) with bromobenzene (0.019ml, 0.18mmol) and a total stirring time of 50 minutes to afford furan 71 (90%). bp. 89°C/0.03mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 0.08(s,6H, -Si-Me), 0.93(s, 9H, -Si-t-Bu), 4.68(s, 2H, H-6), 7.33(m, 2H, Ph), 7.35(s, 1H, H-2), 7.41(s, 1H, H-5), 7.42(m, 3H, Ph); \(^{13}\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) -5.29(q), 18.21(s), 25.86(q), 56.53(t), 124.42(s), 126.32(s), 127.01(d), 127.89(d), 128.59(d), 132.38(s), 139.95(d), 141.73(d); IR(neat) cm\(^{-1}\) 1468(C=C), 1074(C-O); mass spectrum 288(M\(^+\), 231(M\(^+-t\)-Bu).

3-[(t-Butyldimethylsilyl)oxymethyl]-4-(2,4,6-trimethylphenyl) furan (73)

![Chemical Structure](image)

General tin coupling procedure 4 was used on compound 67 (78.5mg, 0.16mmol) with 2-bromomesitylene (0.020ml, 0.18mmol) with a total stirring time of 6 hours and additional catalyst at the 3 hour mark to yield furan 73 (55%). bp. 90°C/0.073mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 0.1(s, 6H, -Si-Me), 0.83(s, 9H, -Si-t-Bu), 2.05(s, 6H, H-13 and H-15), 2.29(s, 3H, H-14), 4.29(s, 2H, H-6), 6.89(s, 2H, H-9 and H-11), 7.17(s, 1H, H-2), 7.48(s, 1H, H-5); \(^{13}\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) -5.74(q), 19.4(s), 20.58(q), 21.01(q), 25.84(q), 56.94(q), 123.00(s), 125.64(s), 127.85(d), 128.08(s), 137.07(s), 137.76(s), 139.79(d), 140.66(d); IR(neat) cm\(^{-1}\) 1553(C=C), 1078.2(C-O); mass spectrum 330(M\(^+\), 273(M\(^+-t\)-Bu).
3-[(t-Butyldimethylsilyl)oxymethyl]-4-(2-tolyl)furan (74)

General tin coupling procedure 4 was used on compound 67 (81.9mg, 0.16mmol) with 2-bromotoluene (0.027ml, 0.18mmol) and a total stirring time of 4 hours to yield compound 74 (80%). bp. 85°C/0.1mm; ¹H NMR(CDCl₃, 300MHz) δ -0.06(s, 6H, -Si-Me), 0.84(s, 9H, -Si-t-Bu), 2.23(s, 3H, H-13), 4.42(s, 2H, H-6), 7.22(m, 4H, H-9 through H-12), 7.30(d, 1H, J=1.3Hz, H-2), 7.45(d, 1H, J=1.3Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -5.59(q), 17.51(s), 20.33(q), 25.83(q), 56.65(t), 124.59(s), 125.46(d), 125.69(s), 127.56(d), 129.98(d), 130.60(d), 131.60(s), 137.01(s), 140.38(d), 140.57(d); IR(neat) cm⁻¹ 1550(C=C), 1082.3(C-O); mass spectrum 245(M⁺-t-Bu).

3-[(t-butyldimethylsilyl)oxymethyl]-4-(4-biphenyl)furan (75)
General tin coupling procedure 4 was used on compound 67 (88.7mg, 0.180mmol) with 4-bromobiphenyl (41.2mg, 0.20mmol) and a total stirring time of 3 hours to yield furan 75 (70%). bp. 95°C/0.13mm; ¹H NMR(DCl₃, 300MHz) δ 0.11(s, 6H, -Si-Me), 0.92(s, 9H, -Si-t-Bu), 4.71(s, 2H, H-6), 7.41(m, 9H, biphenyl), 7.53(s, 1H, H-2 or H-5), 7.54(s, H-5 or H-2); ¹³C NMR(DCl₃, 75MHz) δ -5.30(q), 18.25(s), 25.83(q), 56.49(t), 124.40(s), 125.91(s), 126.99(d), 127.27(d), 128.21(d), 128.55(d), 128.76(d), 139.83(s), 140.02(d), 140.76(s), 141.18(s), 141.83(d); IR(neat) cm⁻¹ 1478.8(C=C), 1075.9(C-O); mass spectrum 364(M⁺), 307(M⁺-t-Bu).

3-[(t-butyldimethylsilyl)oxymethyl]-4-(2-methylnapthyl)furan (76)

![Diagram of 3-[(t-butyldimethylsilyl)oxymethyl]-4-(2-methylnapthyl)furan (76)]

General tin coupling procedure 4 was used on compound 67 (80.9mg, 0.16mmol) and 2-methyl-1-bromonaphthalene (0.028ml, 0.18mmol) and a total stirring time of 3 hours to provide furan 76 (82%). bp. 103°C/0.085mm; ¹H NMR(DCl₃, 300MHz) δ -0.26(s, 3H, -Si-Me), -0.16(s, 3H, -Si-Me), 0.74(s, 9H, -Si-t-Bu), 2.32(s, 3H, H-15), 4.25(s, 2H, H-6), 7.35(m, 5H, H-2 and naphthyl), 7.60(s, 1H, H-5), 7.79(m, 2H, naphthyl); ¹³C NMR(DCl₃, 75MHz) δ -5.90(q), 18.22(s), 20.78(q), 25.76(q), 56.87(t), 121.87(s), 124.81(d), 125.79(d), 126.00(d), 126.59(s), 127.71(d), 128.40(d), 131.89(s), 133.65(s), 135.20(s), 140.74(d), 140.99(d); IR(neat) cm⁻¹ 1470(C=C), 1084.8(C-O); mass spectrum 352(M⁺), 295(M⁺-t-Bu).
3-[(t-Butyldimethylsilyl)oxymethyl]-4-(4-chlorophenyl) furan (77)

General tin coupling procedure 4 was used on compound 67 (95mg, 0.19mmol) and 1-bromo-4-chlorobenzene (40mg, 0.21mmol) with a total stirring time of 1 hour to yield furan 77 (88%). bp. 95°C/0.1mm; $^1$H NMR(CDCl$_3$, 300MHz) $\delta$ 0.08(s, 6H, -Si-Me), 0.89(s, 9H, -Si-t-Bu), 4.60(s, 2H, H-6), 7.33(d, 2H, J=4.8Hz, H-8 and H-12), 7.43(s, 2H, H-2 and H-5), 7.48(d, 2H, J=4.8Hz, H-9 and H-11); $^{13}$C NMR(CDCl$_3$, 75MHz) $\delta$ -5.30(q), 18.25(s), 25.82(q), 56.16(t), 124.14(s), 125.43(s), 128.73(d), 129.16(d), 130.83(s), 132.90(s), 140.06(d), 141.98(d); IR(neat) cm$^{-1}$ 1515(C=C), 1092.6(C=O); mass spectrum 265(M$^+$-t-Bu), 230(M$^+$-t-Bu -Cl).
4.4.0 Lead Tetraacetate Oxidation Experimental

2(t-Butyldimethylsilyl)furan (126)

General Lithiation Procedure 5

Furan 85 (5g, 73.4mmol) in THF (25ml) was cooled to -78°C and n-butyllithium (32.30ml, 2.5M in hexane, 80.74mmol) was slowly added over 2 minutes. The mixture was then warmed to 0°C and stirred for 1 hour before t-butyldimethylsilyl chloride (12.17g, 80.74mmol) in THF (20ml) was added. After an additional 2 hours at room temperature, saturated ammonium chloride (30ml) was added, the mixture was extracted (3X) with diethyl ether, dried (Na₂SO₄) and the solvent removed in vacuo to afford after distillation furan 126(94%). bp. 65-67/20mm; ¹H NMR(CDCl₃, 300MHz) δ 0.23(s, 9H, -Si-Me), 0.93(s, 9H, -Si-t-Bu), 6.38(dd, 1H, J=3Hz,3Hz, H-4), 6.63(d, 1H, J=3Hz, H-3), 7.65(d, 1H, J=3Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -6.27(q), 16.83(s), 26.34(q), 109.19(d), 120.67(d), 146.62(d), 158.68(s); IR(neat) cm⁻¹ 1551(C=C); mass spectrum 182(M⁺), 125(M⁺-t-Bu).

2-(Triethylsilyl)furan (135)
General lithiation procedure 5 was used with triethylsilyl chloride (0.253g, 1.68mmol) to afford after distillation furan 135(92%). bp. 70³C/20mm; ¹H NMR(CDCl₃, 300MHz) δ 1.76(t, 6H, J=8Hz, H-6), 0.92(q, 9H, J=8Hz, H-7), 6.38(dd, 1H, J=2Hz,2Hz, H-4), 6.62(d, 1H, J=2Hz, H-3), 7.63(d, 1H, J=2Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ 3.28(t), 7.23(q), 109.10(d), 120.48(d), 146.55(d), 158.19(s); IR(neat) cm⁻¹ 1550(C=C); mass spectrum 182(M⁺), 153(M⁺-Et), 125(M⁺-Et-Et +H⁻).

2-(Dimethylphenylsilyl)furan (136)

General lithiation procedure 5 was used with dimethylphenylsilyl chloride (0.449g, 2.63mmol) to afford after distillation furan 136(89%). bp.105³C/20mm; ¹H NMR(CDCl₃, 300MHz) δ 0.59(s, 6H, H-6 and H-7), 6.41(dd, 1H, J=2Hz,2Hz, H-4), 6.72(d, 1H, J=2Hz, H-3), 7.40(m, 3H, H-9, H-11 and H-13), 7.60(m, 2H, H-10 and H-12), 7.71(d, 1H, J=2Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -2.89(q), 109.42(d), 121.03(d), 127.86(d), 129.37(d), 133.93(d), 136.98(s), 147.12(d), 158.17(s); IR(neat) cm⁻¹ 1550(C=C); mass spectrum 202(M⁺), 187(M⁺-Me).
2-(Diphenylmethylsilyl)furan (137)

General lithiation procedure 5 was used with diphenylmethylsilyl furan (1.00g, 4.30mmol) to afford after distillation furan 137(96%). bp. 114-115°C/0.33mm; 1H NMR(CDCl₃, 300MHz) δ 0.90(s, 3H, H-7), 6.48(dd, 1H, J=2Hz,2Hz, H-4), 6.80(d, 1H, J=2Hz, H-3), 7.43(m, 6H, H-8, H-10 and H-12), 7.62(m, 4H, H-9 and H-11), 7.80(d, 1H, J=2Hz, H-5); 13C NMR(CDCl₃, 75MHz) δ 3.76(q), 109.73(d), 123.08(d), 128.10(d), 129.86(d), 135.14(d), 147.91(d), 157.60(s); IR(neat) cm⁻¹ 1427(C=C); mass spectrum 264(M⁺), 249(M⁺-Me).

2-(t-Butylphenylsilyl)furan (138)
General lithiation procedure 5 was used with t-butyldiphenylsilyl chloride (0.359 g, 1.31 mmol) to afford furan 138 (90%). bp. 112-115°C/0.3 mm; \( ^1 \text{H} \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 1.17 (s, 9H, -Si-t-Bu), 6.41 (dd, 1H, J=2 Hz, 2 Hz, H-4), 6.63 (d, 1H, J=2 Hz, H-3), 7.37 (m, 6H, H-7, H-9 and H-11), 7.61 (m, 4H, H-8 and H-10), 7.79 (d, 1H, J=2 Hz, H-5); \( ^{13} \text{C} \) NMR (CDCl\(_3\), 75 MHz) \( \delta \) 18.64 (s), 27.73 (q), 109.38 (d), 124.46 (d), 127.63 (d), 129.43 (d), 133.71 (s), 136.15 (d), 147.52 (d), 155.89 (s); IR (neat) cm\(^{-1}\) 1463 (C=C), 1424 (C=C); mass spectrum 306 (M\(^+\)), 249 (M\(^+\)-t-Bu).

2-(Tri-n-butylsilyl)furan (139)

General lithiation procedure 5 was used with tributyldisilylcibroide (0.219 g, 0.932 mmol) to afford after distillation furan 139 (96%). bp. 82-83°C/0.1 mm; \( ^1 \text{H} \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 0.78 (m, 6H, H-6), 0.89 (m, 9H, H-9), 1.32 (m, 12H, H-7 and H-8), 6.37 (dd, 1H, J=2 Hz, 2 Hz, H-4), 6.61 (d, 1H, J=2 Hz, H-3), 7.65 (d, 1H, J=2 Hz, H-5); \( ^{13} \text{C} \) NMR (CDCl\(_3\), 75 MHz) \( \delta \) 11.98 (t), 13.75 (q), 25.97 (t), 26.63 (t), 109.14 (d), 120.28 (d), 146.47 (d), 158.79 (s); IR (neat) cm\(^{-1}\) 2923 (s) (C-H), 1550 (C=C); mass spectrum 266 (M\(^+\)), 209 (M\(^+\)-Bu).

2-(Triisopropylsilyl)furan (140)
General lithiation procedure 5 was used with triisopropylsilyl chloride (0.573g, 2.97mmol) to afford after distillation furan 140(94%). bp. 123-125°C/20mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 1.08(d, 18H, J=7Hz, H-7 and H-8), 1.32(m, 3H, J=7Hz, H-6), 6.39(dd, 1H, J=2Hz, J=2Hz, H-4), 6.68(d, 1H, J=2Hz, H-3), 7.68(d, 1H, J=2Hz, H-5); \(^{13}\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) 11.07(d), 18.54(q), 108.97(d), 121.38(d), 146.40(d), 158.87(s); IR(neat) cm\(^{-1}\) 2945(s)(C-H), 1550(C=C); mass spectrum 224(M\(^+\)), 181(M\(^+\)-i-Pr).

2-Acetoxy-3-(t-butyldimethylsilyl)-\(\Delta^3\)-butenolide (127)

![Chemical Structure](image)

**General Lead Tetraacetate Oxidation Procedure 6**

Furan 126 (0.312g, 1.71mmol) and lead tetraacetate (1.67g, 3.76mmol) were mixed in acetic acid (5ml). After 20 minutes at 70°C, the solution was cooled to room temperature and the acid neutralized with saturated sodium bicarbonate. Diethyl ether was added, the solution was filtered through celite, extraction with diethyl ether dried (Na\(_2\)SO\(_4\)) and the solvent removed in vacuo. After silica gel chromatography (petroleum ether:ethyl acetate 20:1), compound 127 was obtained (60%). \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 0.21(s, 6H, -Si-Me), 0.90(s, 9H, -Si-t-Bu), 2.12(s, 3H, Ac), 6.86(d, 1H, J=1Hz, H-2), 7.33(d, 1H, J=1Hz, H-4); \(^{13}\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) -6.52(q), -6.40(q), 16.47(s), 20.65(q), 26.36(q), 93.79(d), 137.91(s), 158.23(d), 169.08(s), 172.9(s); IR(KBr pellet) cm\(^{-1}\) 1769(C=O), 1467(C=C); mass spectrum 257(MH\(^+\)), 199 (M\(^+\)-t-Bu), 197(M\(^+\)-OAC); UV(CHCl\(_3\)) \(\lambda_{\text{max}}\)=220nm, \(\varepsilon=130\text{Lmol}^{-1}\text{cm}^{-1}\).
4-Acetoxy-4-(t-butyldimethylsilyl)-Δ²-butenolide (128)

General lead tetraacetate oxidation procedure 6 was used on furan 126 to also afford compound 128 (30%). bp. 95-102⁰C/20mm; ¹H NMR(CDCl₃, 300MHz) δ 0.04(s, 3H, -Si-Me), 0.05(s, 3H, -Si-Me), 0.98(s, 9H, -Si-t-Bu), 2.02(s, 3H, Ac), 6.11(d, 1H, J=3Hz, H-2), 7.59(d, 1H, J=3Hz, H-3); ¹³C NMR(CDCl₃, 75MHz) δ -8.30(q), -7.83(q), 17.51(s), 26.87(q), 107.48(s), 120.68(d), 155.03(d), 169.17(s), 170.59(s); mass spectrum 199(M⁺-t-Bu); UV(CHCl₃) λ_max=218nm, ε=17200Lmol⁻¹cm⁻¹.

2-Hydroxy-3-(t-butyldimethylsilyl)-Δ³-butenolide (127a)

The butenolide 127 (0.020g, 0.078mmol) was dissolved in methanol (5ml) and stirred with potassium carbonate (0.011g, 0.078mmol) for one hour. Water (2ml) was added and the solution carefully neutralized with 1% HCl. The mixture was extracted (3X) with ether and the solvent removed in vacuo to afford, after distillation, compound
127a (85%). bp. 74-76°C/0.1mm; \(^1\)H NMR (CDCl\(_3\), 300MHz) \(\delta\) 0.22 (s, 6H, -Si-Me), 0.91 (s, 9H, -Si-t-Bu), 6.12 (s, 1H, H-2), 7.32 (s, 1H, H-4); \(^1\)C NMR (CDCl\(_3\), 75MHz) \(\delta\) -6.42 (q), -6.31 (q), 16.47 (s), 20.40 (q), 93.85 (s), 98.09 (d), 137.04 (s), 160.7 (d), 173.76 (s); IR (neat) cm\(^{-1}\) 3445 (b) (OH), 1755 (C=O), 1152 (C-O).

**2-Acetoxy-3-(triethyлsilyl)-\(\Delta^3\)-butenolide (142)**

![Chemical structure](image)

General lead tetraacetate oxidation procedure 6 was used on silylfuluramic acid to afford, after silica gel chromatography and distillation, compound 142 (5%). bp. 60-62°C/0.1mm; \(^1\)H NMR (CDCl\(_3\), 300MHz) \(\delta\) 0.73 (q, 6H, J=6Hz, -Si-CH\(_2\)), 0.93 (t, 9H, J=6Hz, -CH\(_2\)-CH\(_3\)), 2.13 (s, 3H, OAc), 6.87 (d, 1H, J=1Hz, H-2), 7.32 (d, 1H, J=1Hz, H-4); \(^1\)C NMR (CDCl\(_3\), 75MHz) \(\delta\) 2.46 (t), 7.06 (q), 26.33 (q), 94.03 (d), 137.43 (s), 157.93 (d), 169.13 (d), 172.83 (s).

**2-Acetoxy-3-(tri-n-butylsilyl)-\(\Delta^3\)-butenolide (143)**

![Chemical structure](image)
General lead tetraacetate oxidation procedure 6 was used on silylfuran 139 to afford, after silica gel chromatography and distillation butenolide 143 (5%). bp. 68-70°C/0.1mm; $^1$H NMR(CDCl₃, 300MHz) $\delta$ 0.78(m, 6H, -Si-CH₂), 0.87(m, 9H, -CH₂-CH₃), 1.34(m, 12H, -Si-CH₂-CH₂-CH₃), 6.88(d, 1H, J=1Hz, H-2), 7.31(d, 1H, J=1Hz, H-4); $^{13}$C NMR(CDCl₃, 75MHz) $\delta$ 11.87(t), 13.73(q), 25.97(t), 26.65(q), 94.10(d), 137.85(s), 156.98(d), 169.30(s), 173.03(s).

2-Acetoxy-3-(triisopropylsilyl)-A₃-butenolide (144)

```
\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{AcO}} node at (1,0) {2} node at (1.5,0) {3} node at (1.5,1.5) {Si(i-Pr)₃} node at (0,1.5) {1} node at (0.5,1.5) {O} node at (1,0) {2} node at (2,1.5) {O} node at (2.5,1.5) {4} node at (3,1.5) {5};
\end{tikzpicture}
\end{center}
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General lead tetraacetate oxidation procedure 6 was used on silylfuran 140 to afford, after silica gel chromatography and distillation, butenolide 144 (15%). bp. 70-72°C/0.3mm; $^1$H NMR(CDCl₃, 300MHz) $\delta$ 1.02(d, 18H, J=6Hz, -Si-CH-CH₃), 1.87(m, 3H, J=6Hz, -Si-CH), 2.18(s, 3H, Ac), 6.92(d, 1H, J=1Hz, H-2), 7.39(d, 1H, J=1Hz, H-4); $^{13}$C NMR(CDCl₃, 75MHz) $\delta$ 11.01(d), 18.72(q), 26.21(q), 93.88(d), 136.95(s), 158.33(d), 169.02(s), 172.98(s).
4-Acetoxy-4-(triisopropylsilyl)-Δ²-butenolide (145)

The above procedure also yielded butenolide (145) (10%). bp. 65-69°C/0.4mm; ¹H NMR (CDCl₃, 300MHz) δ 1.03 (d, 18H, J=6Hz, -Si-CH₂CH₃), 1.27 (m, 3H, J=6Hz, -Si-CH), 2.02 (s, 3H, Ac), 6.13 (d, 1H, J=3Hz, H-2), 7.68 (d, 1H, J=3Hz, H-3); ¹³C NMR (CDCl₃, 75MHz) δ 11.12 (d), 18.25 (q), 27.03 (q), 107.22 (s), 121.06 (d), 155.20 (d), 169.35 (s), 171.00 (s).

2-Acetoxy-3-(trimethylsilyl)-Δ³-butenolide (146)

General lead tetraacetate oxidation procedure 6 was used on silylfuran (141) to provide, after silica gel chromatography and distillation, butenolide (146) (10%). bp. 55-58°C/0.05mm; ¹H NMR (CDCl₃, 300MHz) δ 0.24 (s, 9H, -Si-Me), 2.13 (s, 3H, Ac), 6.87 (d, 1H, J=1Hz, H-2), 7.30 (d, 1H, J=1Hz, H-4); ¹³C NMR (CDCl₃, 75MHz) δ 0.56 (q), 26.35 (q), 95.03 (d), 137.45 (s), 158.33 (d), 168.45 (s), 172.50 (s).
3-(Acetoxyethyl)-2-(t-butyldimethylsilyl)furan (134)

Furan 49 (0.413g, 1.94mmol), acetic anhydride (0.22ml, 2.33mmol) and N,N-dimethylaminopyridine (0.285g, 2.33mmol) were dissolved in dichloromethane (10ml). After 6 hours at room temperature, 5% sodium carbonate was added until the bubbling had ceased. The mixture was extracted with ethyl acetate and the solvent removed in vacuo to afford, after distillation furan 134(93%). bp. 70°C/0.2mm; $^1$H NMR(CDCl$_3$, 300MHz) δ 0.25(s, 6H, -Si-Me), 0.86(s, 9H, -Si-t-Bu), 2.01(s, 3H, Ac), 4.98(s, 2H, H-6), 6.39(d, 1H, J=3Hz, H-4), 7.55(d, 1H, J=3Hz, H-5); $^{13}$C NMR(CDCl$_3$, 75MHz) δ -5.96(q), 17.19(s), 20.80(q), 26.17(q), 59.46(t), 111.21(d), 130.86(s), 146.56(d), 156.64(s), 170.75(s); IR(neat) cm$^{-1}$ 1743(C=O), 1048(C-O).
4.5.0 Halenaquinone Experimental

2-(t-Butyldimethylsilyl)-3-(hydroxymethyl)-4-iodofuran (190)

![Chemical Structure](image)

To the dianion of compound 49 (1.3g, 3.8mmol) produced by general lithiation procedure 2 was added iodine (1.1g, 4.2mmol) in DME (20ml) to afford compound 190(95%). mp: 67-69\(^\circ\)C; bp: 84-86\(^\circ\)C/0.02mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 0.27(s, 6H, -Si-Me), 0.87(9s, 9H, -Si-t-Bu), 4.45(s, 2H, H-6), 7.56(s, 1H, H-5); \(^{13}\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) -5.64(q), 17.20(s), 26.42(q), 56.75(t), 69.42(s), 136.38(s), 149.68(d); IR(KBr pellet) cm\(^{-1}\) 3388(OH), 1047(C-O); mass spectrum 338(M\(^+\)), 281(M\(^+\)-t-Bu).

3-(Hydroxymethyl)-4-iodofuran (191)

![Chemical Structure](image)

Furan 190 (0.85g, 2.5mmol) was dissolved in THF (20ml) to which tetra-n-butylammonium fluoride (2.8ml, 1.0M in THF, 2.8mmol) was added. After 12 hours at 25\(^\circ\)C, water (20ml) was added and the organic layer extracted with ethyl acetate. The solvent was removed \textit{in vacuo} to afford, after distillation furan 191(94%). bp. 65\(^\circ\)C/0.04mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 2.98(bs, 1H, OH), 4.37(s, 2H, H-6),
7.33(s, 1H, H-2 or H-5), 7.36(s, 1H, H-5 or H-2); $^{13}$C NMR(CDCl$_3$, 75MHz) δ 56.75(t), 67.04(s), 126.99(s), 140.85(d), 145.89(d); IR(neat) cm$^{-1}$ 3433(OH), 1068(C-O); mass spectrum 225(M$^+$).

4-Iodo-3-furaldehyde (180)

![Chemical structure of 4-Iodo-3-furaldehyde](image)

**General Swern Oxidation Procedure 7**

A mixture of methylene chloride (3ml) and oxalyl chloride (0.12ml, 1.36mmol) was cooled to -78°C to which DMSO (0.19ml, 2.72mmol) was added. After two minutes the alcohol 191 (0.28g, 1.24mmol), dissolved in methylene chloride (1ml), was added over 2 minutes. After an additional 15 minutes, triethylamine (0.86ml, 6.18mmol) was added and the solution warmed to 0°C. Water (5ml) was added and the mixture extracted with methylene chloride. The organic layers were washed with saturated brine, 1% HCl, 5% Na$_2$CO$_3$ and water affording, after distillation aldehyde 180(95%). bp. 57-60/0.04mm; $^1$H NMR(CDCl$_3$, 300MHz) δ 7.48(d, 1H, J=1Hz, H-5), 7.99(d, 1H, J=1Hz, H-2), 9.85(s, 1H, H-6); $^{13}$C NMR(CDCl$_3$, 75MHz) δ 62.17(s), 126.54(s), 147.82(d), 151.06(d), 184.84(d); IR(neat) cm$^{-1}$ 1690(s) (C=O); mass spectrum 222(M$^+$).
3-[1-Cyano-1-(trimethylsilyloxy)methyl]-4-iodofuran (192)

General Cyanohydrin Procedure 8

A mixture of furan aldehyde 180 (0.34g, 1.53mmol) and trimethylsilyl cyanide (0.25ml, 1.82mmol) was stirred at room temperature with one crystal of zinc iodide for 10 minutes. The excess trimethylsilyl cyanide was removed in vacuo affording, after distillation, furan 192 (95%). bp. 78-80°C/0.04mm; 1H NMR(CDCl3, 300MHz) δ 0.25(s, 9H, -Si-Me), 5.30(s, 1H, H-6), 7.44(d, 1H, J=2Hz, H-2 or H-5), 7.60(d, 1H, J=2Hz, H-5 or H-2); 13C NMR(CDCl3, 75MHz) δ -0.19(q), 57.23(d), 54.92(s), 117.75(s), 124.13(s), 142.18(d), 146.99(d); IR(neat) cm⁻¹ 1096(C=O); mass spectrum 306(M⁺), 221(M⁺-TMSCN).

3-[1-Cyano-1-[1-(ethoxy)ethyl]oxy)methyl]-4-iodofuran (193)
The furan 192 (0.38g, 1.17mmol), ethyl vinyl ether (0.13ml, 1.46mmol), water (0.5ml) and one crystal of p-toluene sulfonic acid were stirred in THF (5ml). After 1 hour at 25°C, water (10ml) was added and the mixture extracted with diethyl ether. The solvent was removed in vacuo affording, after distillation, furan 193(85%). bp. 85-90°C/0.04mm; 1H NMR(CDCl₃, 300MHz) δ 1.23(t, 1.5H, J=4Hz, H-11), 1.25(t, 1.5H, J=4Hz, H-11), 1.43(d, 1.5H, J=5Hz, H-9), 1.45(d, 1.5H, J=5Hz, H-9), 3.65(q, 1H, J=4Hz, H-10), 3.70(q, 1H, J=4Hz, H-10), 5.05(q, 0.5H, J=5Hz, H-8), 5.10(q, 0.5H, J=5Hz, H-8), 5.21(s, 0.5H, H-6), 5.40(s, 0.5H, H-6), 7.47(s, 1H, H-2 or H-5), 7.68(s, 1H, H-5 or H-2); 13C NMR(CDCl₃, 75MHz) δ 14.97(q), 15.19(q), 19.41(q), 19.56(q), 58.29(t), 59.39(t), 60.59(t), 61.22(t), 65.37(s), 98.98(d), 100.99(d), 116.61(s), 117.34(s), 122.33(s), 122.65(s), 142.85(d), 143.17(d), 147.17(d), 147.26(d); IR(neat) cm⁻¹ 1079(C-O); mass spectrum 321(M⁺), 277(M⁺-OEt +H), 232(M⁺-OEt-OEt).

3-[1-Cyano-1-[1-(ethoxy)ethyloxy]-2-oxopent-3-enyl]-4-iodofuran (195)

General swern oxidation procedure 7 was performed on the alcohol 194 (57.2mg, 0.15mmol) to afford after distillation furan 195(85%). bp. 105-107°C/0.08mm; 1H NMR(CDCl₃, 300MHz) δ 1.18(t, 3H, J=4Hz, H-14), 1.45(d, 3H, J=5Hz, H-12), 1.93(dd, 3H, J=3Hz,6Hz, H-10), 3.51(q, 2H, J=4Hz, H-13), 5.07(q, 1H, J=4Hz, H-11), 6.53(m, 1H, J=10Hz,6Hz,3Hz, H-8), 7.21(m, 1H, J=10Hz,6Hz,3Hz, H-9), 7.47(s, 1H, H-2 or H-5), 7.53(s, 1H, H-5 or H-2); 13C NMR(CDCl₃, 75MHz) δ 14.42(q), 14.77(q), 18.70(q), 18.80(q), 20.14(q), 20.85(q), 62.17(s), 62.36(t), 62.78(t), 99.44(d), 99.94(d), 114.62(s), 115.06(s), 120.77(s), 121.92(s), 123.98(d), 124.46(d), 124.78(d), 125.09(d), 125.77(d), 126.24(d), 127.18(d).
143.63(d), 146.78(d), 148.24(d), 148.31(d), 148.99(d), 186.94(s), 187.18(s); IR(neat) cm⁻¹ 1708(C=O), 1099(C-O).

2-(t-butyldimethylsilyl)-3-formyl-4-iodofuran (186)

General Swern oxidation procedure 7 was performed on alcohol 190 (0.2048g, 0.61mmol) to afford after distillation furan 186 (92%). bp. 78-80°C/0.03mm; ¹H NMR(CDCl₃, 300MHz) δ 0.31(s, 6H, -Si-Me), 0.87(s, 9H, -Si-t-Bu), 7.60(s, 1H, H-5), 9.95(s, 1H, H-6); ¹³C NMR(CDCl₃, 75MHz) δ -5.0(q), 17.35(s), 26.19(q), 62.90(s), 134.07(s), 134.71(s), 149.76(s), 150.86(d), 186.06(d); IR(neat) cm⁻¹ 1689(C=O), mass spectrum 279(M⁺-t-Bu).

2-(t-butyldimethylsilyl)-3-[1-cyano-1-[trimethylsilyloxy]methyl]-4-iodofuran (184)
General cyanohydrin procedure 8 was used on furan aldehyde 186 (0.110 g, 0.327 mmol) to provide after distillation furan 184 (96%). bp. 93-95°C/0.05 mm; ¹H NMR(CDCl₃, 300 MHz) δ 0.25 (s, 9H, -Si(8)-Me), 0.313 (s, 3H, -Si(9)-Me), 0.315 (s, 3H, -Si(9)-Me), 0.90 (s, 9H, -Si(9)-t-Bu), 5.49 (s, 1H, H-6), 7.60 (s, 1H, H-5); ¹³C NMR(CDCl₃, 75 MHz) δ -5.68 (q), -5.58 (q), -0.19 (q), 17.51 (s), 26.37 (q), 57.32 (d), 65.78 (s), 188.18 (s), 132.67 (s), 150.47 (d), 158.98 (s); IR (neat) cm⁻¹ 2365 (CN), 1010 (C-O); mass spectrum 378 (M⁺-t-Bu), 279 (M⁺-t-Bu - TMSCN + H).

1-(3-Furyl)-4-penten-1-one (209)

General Swern oxidation procedure 7 was used on furan alcohol 208 (0.282 g, 1.85 mmol) to afford after distillation furan 209 (84%). bp. 70-73°C/0.06 mm; ¹H NMR(CDCl₃, 300 MHz) δ 2.43 (dt, 2H, J=6 Hz, 5 Hz, H-8), 2.82 (t, 2H, J=5 Hz, H-7), 5.00 (m, 2H, H-10), 5.82 (m, 1H, J=6 Hz, H-9), 6.76 (d, 1H, J=1 Hz, H-4), 7.44 (d, 1H, J=1 Hz, H-5), 8.01 (s, 1H, H-2); ¹H NMR(CDCl₃, 300 MHz) δ 27.86 (t), 39.28 (t), 108.38 (d), 115.14 (t), 127.49 (s), 136.88 (d), 144.01 (d), 146.96 (d), 193.96 (s).

1-(3-Furyl)-4-hydroxy-5-iodopentan-1-one (210)
The furan olefin 208 (0.103g, 0.686mmol), iodine (0.350g, 1.372mmol), potassium iodate (0.15b, 0.686mmol) were stirred in a solvent mixture of acetic acid (0.3ml), water (8.8ml) and 1,4-dioxane (2.2ml). After 30 minutes at 25°C the mixture was extracted with chloroform (3X), dried (Na₂SO₄) and the solvent removed In vacuo to afford the iodoxydrol 210(96%). bp. 75°C(d); \(^1\)H NMR(CDCl₃, 300MHz) δ 1.81(m, 2H, H-8), 2.10(m, 2H, H-10), 2.95(m, 2H, H-7), 3.31(m, 1H, H-9), 6.75(d, 1H, J=1Hz, H-4), 7.43(d, 1H, J=1Hz, H-5), 8.06(s, 1H, H-2); \(^1\)C NMR(CDCl₃, 75MHz) δ 14.94(t), 30.35(t), 36.14(t), 70.11(d), 108.41(d), 127.34(s), 144.15(d), 147.31(d), 194.77(s).

1-[3-(4-Iodofuryl)]-4-penten-1-one (211)

General Swern oxidation procedure 7 was used on the corresponding C-6 alcohol of compound 211 (1.507g, 5.46mmol) to afford the furan 211(98%). bp.78-79°C/0.02mm; \(^1\)H NMR(CDCl₃, 300MHz) δ 2.41(m, 2H, H-8), 2.82(m, 2H, H-7), 5.02(m, 2H, H-10), 5.83(m, 1H, H-9), 7.45(s, 1H, H-5), 7.99(s, 1H, H-2); \(^1\)H NMR(CDCl₃, 300MHz) δ 27.70(t), 39.99(t), 62.64(s), 155.49(t), 125.91(s), 136.85(d), 136.86(d), 148.26(d), 193.01(s); IR(neat) cm⁻¹ 1684(C=O), 1541(C=C); mass spectrum 276(M⁺) 221(M⁺-CH₂-CH₂-CH=CH₂).
1-[3-(4-iodofuryl)]-1-(t-butyldimethylsilyloxy)-4-pentene (212)

General silylation procedure 1 was used on the corresponding alcohol of compound 212 (0.413g, 1.05mmol) to afford after distillation furan 212(91%). bp.85-86°C/0.08mm; ¹H NMR(CDCl₃, 300MHz) δ -0.92(s, 3H, -Si-Me), 0.03(s, 3H, -Si-Me), 0.91(s, 9H, -Si-t-Bu), 1.80(m, 2H, H-8), 2.12(m, 2H, H-7), 4.59(t, 1H, J=4Hz, H-6), 4.98(m, 2H, H-10), 5.82(m, 1H, H-9), 7.25(s, 1H, H-2 or H-5), 7.38(1H, H-5 or H-2); ¹³C NMR(CDCl₃, 75MHz) δ -4.98(q), -4.5(q), 8.12(s), 25.83(q), 29.28(t), 37.76(t), 65.49(s), 68.27(d), 114.62(t), 130.92(s), 138.34(s), 140.47(d), 145.71(d), IR(neat) cm⁻¹ 1091(C-O).

4-(p-Toluenesulfonyl)-1-butyne (218)

The alcohol 3-butyln-1-ol (0.500ml, 7.13mmol), DMAP (0.89g, 7.84mmol) and TsCl (1.39g, 7.84mmol) were stirred in dichloromethane (8ml) for 18 hours. The solution was poured into water (10ml), extracted with dichloromethane (3X), washed with 2N HCl, dried (Na₂SO₄) and the solvent removed in vacuo to afford the tosylate.
218 (>99%). bp. 75°C(d); \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 1.95(t, 1H, J=1Hz, H-4), 2.43(s, 3H, H-11), 2.53(dt, 2H, J=7Hz,1Hz, H-2), 4.03(t, 2H, J=7Hz, H-1), 7.32(d, 2H, J=9Hz, H-7 and H-9), 7.79(d, 2H, J=9Hz, H-6 and H-10); \(^13\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) 19.43(t), 21.65(q), 67.42(t), 70.76(s), 78.36(d), 127.99(d), 129.89(d), 132.77(s), 145.00(s).

**4-Iodo-1-butyne (219)**

![Diagram of 4-Iodo-1-butyne](image)

**General Halogen-Tosylate Exchange Procedure 9**

The tosylate 218 (0.607g, 2.71mmol) and sodium iodide (1.22g, 13.55mmol) were stirred in refluxing acetone (5ml) for 24 hours. The solvent was removed by proper distillation affording after distillation the iodide 219(67%). bp. 45°C/20mm; \(^1\)H NMR(CDCl\(_3\), 300MHz) \(\delta\) 2.13(t, 1H, J=2Hz, H-4), 2.74(dt, 2H, J=2Hz,5Hz, H-2), 3.19(t, 2H, J=5Hz, H-1); \(^13\)C NMR(CDCl\(_3\), 75MHz) \(\delta\) 0.88(t), 23.62(t), 70.18(s), 82.66(d).

**1-(Trimethylsilyl)-4-iodo-1-butyne (228)**

![Diagram of 1-(Trimethylsilyl)-4-iodo-1-butyne](image)
General halogen-tosylate exchange procedure 9 was used with compound 227 and lithium iodide at room temperature to afford iodide 228(85%). bp. 47-50°C/0.01mm; $^1$H NMR(CDCl$_3$, 300MHz) $\delta$ 0.12(s, 9H, -Si-Me), 2.77(t, 2H, J=6Hz, H-3), 3.21(t, 2H, J=6Hz, H-4).

1-(Trimethylsilyl)-4-bromo-1-butyne (229)

![Structure of 1-(Trimethylsilyl)-4-bromo-1-butyne (229)]

General halogen-tosylate exchange procedure 9 was used with compound 227 and lithium bromide at room temperature to afford bromide 229(98%). bp. 70-75°C/10mm; $^1$H NMR(CDCl$_3$, 300MHz) $\delta$ 0.13(s, 9H, -Si-Me), 2.75(t, 2H, J=5Hz, H-3), 3.40(t, 2H, J=5Hz, H-4).

5-[3-(4-Iodofuryl)]-5-hydroxy-1-(trimethylsilyl)-1-pentyne (231)

![Structure of 5-[3-(4-Iodofuryl)]-5-hydroxy-1-(trimethylsilyl)-1-pentyne (231)]

The alkyne bromide 229 (0.69g, 3.90mmol) in THF (5ml) was slowly dropped into magnesium metal (13g, 195mmol) in THF (70ml) over 5 minutes and stirred for one hour at room temperature. The grey suspension was transferred to another flask
and cooled to 0°C to which the aldehyde 180 in THF(5ml) was added. After 30 minutes, saturated ammonium chloride (30ml) was added, the mixture extracted (3X) with ethyl acetate, dried (Na₂SO₄) and the solvent removed in vacuo to afford after distillation compound 231(96%). bp. 100-105°C/0.04mm; ¹H NMR(CDCls, 300MHz) δ 0.12(s, 9H, -Si-Me), 1.97(m, 2H, H-8), 2.39(m, 2H, H-7), 4.73(bs, 1H, H-6), 7.36(s, 1H, H-2 or H-5), 7.41(s, 1H, H-5 or H-2); ¹³C NMR(CDCls, 75MHz) δ 0.17(q), 16.41(t), 35.20(t), 65.82(s), 67.07(d), 85.84(s), 106.24(s), 129.77(s), 140.13(d), 146.12(d); IR(neat) cm⁻¹ 3411(b)(OH), 2172(C=C), 1047(C-O).

2-(t-Butyldimethylsilyl)-3-(1-hydroxy-3-butenyl)-4-iodofurane (235)

General Grignard Procedure 10

The furan aldehyde 186 (1.13g, 3.36mmol) in THF(5ml) was slowly added over 10 minutes to vinyl magnesium bromide (5.04ml, 1.0M in diethyl ether, 5.04mmol) in THF (15ml). After 30 minutes at 25°C, saturated ammonium chloride (20ml) was added, the mixture extracted with ethyl acetate, dried (Na₂SO₄) and the solvent removed in vacuo to afford compound 235(85%). bp. 73°C(d); ¹H NMR(CDCls, 300MHz) δ 0.25(s, 3H, -Si-Me), 0.27(s, 3H, -Si-Me), 0.90(s, 9H, -Si-t-Bu), 1.92(s, 1H, OH), 2.55(m, 1H, H-7), 2.75(m, 1H, H-7), 4.84(m, 1H, H-6), 5.19(m, 2H, H-9), 5.78(m, 1H, H-8), 7.56(s, 1H, H-5); ¹³C NMR(CDCls, 75MHz) δ -5.37(q), -4.97(q), 17.35(s), 26.44(q), 41.67(t), 63.22(s), 67.52(d), 118.22(t), 134.52(d), 137.44(s), 150.63(d), 156.67(s); IR(neat) cm⁻¹ 3540(b)(OH), 1650(C=C), 1090(C-O).
3-[1-(t-Butyldimethylsilyloxy)-3-butenyl]-4-iodofuran (237)

General migration procedure 3 was performed on furan 235 (56.0mg, 0.148mmol) to afford after distillation compound 237 (88%). bp.75-78°C/0.06mm; ¹H NMR(CDCl₃, 300MHz) δ -0.92(s, 3H, Si-Me), 0.06(s, 3H, -Si-Me), 0.91(s, 9H, -Si-t-Bu), 2.49(m, 2H, H-7), 4.61(t, 1H, J=5Hz, H-6), 5.03(m, 2H, H-9), 5.80(m, 1H, H-8), 7.26(s, 1H, H-2 or H-5), 7.38(s, 1H, H-5 or H-2); ¹³C NMR(CDCl₃, 75MHz) δ -4.93(q), -4.65(q), 18.16(s), 25.79(q), 43.06(t), 65.39(s), 68.79(d), 117.37(t), 130.57(s), 134.46(d), 140.57(d), 145.70(d), IR(neat) cm⁻¹ 1467(C=O), 1090(C-O); mass spectrum 378(M⁺), 321(M⁺-t-Bu), 337(M⁺-CH₂-CH=CH₂).

3-[1-(t-Butyldimethylsilyloxy)-4-hydroxybutyl]-4-iodofuran (238)

100
General Hydroboration Procedure 11

Borane methyl sulfide (0.016ml, 2.0M in THF, 0.032mmol) was added to the furan olefin 237 (30.0mg 0.079mmol) in diethyl ether (0.3ml) at -78°C. The mixture was warmed to 0°C and stirred for 1 hour. Ethanol (0.4ml), 3.0M sodium hydroxide (0.032ml) and 30% hydrogen peroxide (0.027ml) were added and the mixture stirred for an additional one hour. Saturated ammonium chloride (2ml) was added, the mixture extracted (3X) with ethyl acetate and, following silica gel chromatography (Petroleum ether:ethyl acetate 9:1) and distillation afforded the alcohol 238(95%). bp. 85-90°C/0.03mm; 1H NMR(CDCl3, 300MHz) δ -0.92(s, 3H, -Si-Me), 0.05(s, 3H, -Si-Me), 1.71(m, 4H, H-7 and H-8), 3.62(t, 2H, J=5Hz, H-9), 4.61(t, 1H, J=5Hz, H-6), 7.28(s, 1H, H-2 or H-5), 7.38(s, 1H, H-5 or H-2).

3-[1-(t-butyldimethylsilyleoxy)-4-oxobutyll]-4-iodofuran (239)

General Swern oxidation procedure 7 was performed on alcohol 235 to afford after distillation aldehyde 239(90%). bp. 96-98°C/0.06mm; 1H NMR(CDCl3, 300MHz) δ -0.07(s, 3H, -Si-Me), 0.03(s, 3H, -Si-Me), 0.87(s, 9h, -Si-t-Bu), 2.05(m, 2H, H-7), 2.45(m, 2H, H-8), 4.66(t, 1H, J=4Hz, H-6), 7.27(s, 1H, H-2 or H-5), 7.36(s, 1H, H-5 or H-2), 9.74(t, 1H, J=2Hz, H-9); 13C NMR(CDCl3, 75MHz) δ -5.02(q), -4.67(q), 18.19(s), 25.86(q), 30.63(t), 39.17(t), 65.50(s), 67.99(d), 130.13(s), 140.93(d), 146.11(d), 202.30(d).
2-(t-Butyldimethylsilyl)-3-(1-hydroxy-3-butenyl)furan (249)

General Grignard procedure 10 was performed on aldehyde 248 to afford the alcohol 249(97%). bp. 63°C(d); ¹H NMR(CDCl₃, 300MHz) δ 0.25(s, 3H, -Si-Me), 0.28(s, 3H, -Si-Me), 0.91(s, 9H, -Si-t-Bu), 1.91(bs, 1H, OH), 2.47(m, 1H, H-7), 4.78(dd, 1H, J=4Hz, 4Hz, H-6), 5.11(m, 2H, H-9), 5.79(m, 1H, H-8), 6.48(d, 1H, H=2Hz, H-4), 7.56(d, 1H, J=2Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -5.59(q), -5.33(q), 17.22(s), 26.37(q), 42.99(t), 66.00(d), 107.89(d), 117.96(t), 134.59(d), 139.08(s), 146.78(d), 154.12(s); IR(neat) cm⁻¹ 3417(b)(OH), 1468(C=O), 1089(C-O); mass spectrum 252(M⁺), 195(M⁺-t-Bu).

2-(t-Butyldimethylsilyl)-3-[1-(t-butyldimethylsilyl)oxy-3-butenyl]furan (250)
General silylation procedure 1 was performed on compound 249 to provide after distillation compound 250 (80%). bp. 82-83°C/0.04mm; ¹H NMR(CDCl₃, 300MHz) δ 0.02(s, 6H, -Si-Me), 0.24(s, 6H, -Si-Me), 0.85(s, 9H, -Si-t-Bu), 0.91(s, 9H, -Si-t-Bu), 2.29(m, 1H, H-7), 2.41(m, 1H, H-7), 4.80(t, 1H, J=4Hz, H-6), 5.02(m, 2H, H-9), 5.80(m, 1H, H-8), 6.48(d, 1H, J=2Hz, H-4), 7.52(d, 1H, J=2Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -5.21(q), -4.69(q), -4.49(q), 17.51(s), 18.21(s), 25.79(q), 26.67(q), 45.81(t), 67.78(d), 109.06(d), 116.72(t), 135.59(d), 141.47(s), 146.11(d), 151.50(s); IR(neat) cm⁻¹ 1469(C=C), 1081(C-O); mass spectrum 366(M⁺), 325(M⁺-CH₂-CH=CH₂), 309(M⁺-t-Bu).

2-(t-Butylidimethylsilyl)-3-[1-(t-butylidimethylsilyl)oxy-4-hydroxybutyl]furan (251)

![Structural diagram](image)

General hydroboration-oxidation procedure 11 was performed on compound 250 (0.213g, 0.562mmol) to afford after silica gel chromatography (petroleum ether:ethyl acetate 5:1) alcohol 251 (80%). bp. 56°C(d); ¹H NMR(CDCl₃, 300MHz) δ -0.88(s, 3H, Si-Me), 0.02(s, 3H, -Si-Me), 0.22(s, 6H, -Si-Me), 0.83(s, 9H, -Si-t-Bu), 0.90(s, 9H, -Si-t-Bu), 1.63(m, 4H, H-7 and H-8), 3.61(m, 2H, H-9), 4.81(t, 1H, J=4Hz, H-6), 6.47(d, 1H, J=3Hz, H-4), 7.51(d, 1H, J=3Hz, H-5); ¹³C NMR(CDCl₃, 75MHz) δ -5.29(q), -4.84(q), -4.51(q), 17.48(s), 18.15(s), 25.76(q), 26.60(q), 28.96(t), 37.59(t), 62.96(t), 67.46(d), 109.25(d), 141.57(s), 146.04(d), 151.43(s); IR(neat) cm⁻¹ 3450(b)(OH), 1052(C-O), 1086(C-O).
General Swern oxidation procedure 7 was performed on compound 251 to afford after distillation compound 252 (90%). bp. 125-127°C/0.02mm; \textsuperscript{1}H NMR(CDC\textsubscript{3}, 300MHz) $\delta$ -0.16(s, 3H, -Si-Me), -0.01(s, 3H, -Si-Me), 0.23(s, 3H, -Si-Me), 0.25(s, 3H, -Si-Me), 0.84(s, 9H, -Si-t-Bu), 0.90(s, 9H, -Si-t-Bu), 1.92(m, 2H, H-7), 2.51(m, 2H, H-8), 4.87(t, 1H, J=6Hz, H-6), 6.42(d, 1H, J=3Hz, H-4), 7.51(d, 1H, J=3Hz, H-5), 9.76(t, 1H, J=1Hz, H-9); \textsuperscript{13}C NMR(CDC\textsubscript{3}, 75MHz) $\delta$ -5.34(q), -4.93(q), -4.55(q), 17.46(s), 18.09(s), 25.73(q), 26.59(q), 33.43(t), 40.09(t), 66.47(d), 109.09(d), 140.93(s), 146.21(d), 157.50(s), 202.33(d); IR(neat) cm\textsuperscript{-1} 1726(C=O), 1087(C-O).
5.0.0 References

5. Quintard, J.-P.; Elissando, B.; Pereyre, M.
7. Arukwe, J.; Benneche, T.; Undheim, K.
8. Majeed, A.J.; Antonsen, O.; Benneche, T.; Undheim, K.
   Tetrahedron 1989, 45, 993
15. McKean, D.R.; Parrinello, G.; Renaldo, A.F.; Stille, J.K.
    d) Milstein, D. Organometallics 1982, 1, 888
19. Dimroth, O.; Friedmann, O.; Hammerer, H. Ber 1920, 53, 481
    Academic Press, 1965, p.283
22. Finch, N.; Gemendin, C.W.; Hsu, J.H.; Taylor, W.J.
    J. Am. Chem. Soc. 1963, 85, 1520

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32. a)Ohta, K. Agric. Biol. Chem. 1977, 41, 2105
37. Keay, B.A.; Rogers, C., unpublished results
42. Kalman, J.R.; Pinhey, J.T.; Sternhell, S. Tet. Lett. 972, 23, 5369
46. Kemp, C.; Mason, S.F. Tetrahedron 1966, 22, 629


52. Keay, B.A.; Bontront, J.-L. J.; unpublished results


60. a) Marinovic, N.N.; Ramanathan, H. *Tet. Lett.* **1983**, *24*, 1871;


63. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*
   3rd Ed.; Wiley Interscience, 1985, p.819

64. Coyle, J.D. *Intro to Organic Photochemistry* J.W. Wiley & Sons, 1986, p.73


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APPENDIX

Presentation of the Work Presented Herein

1. The Preparation of 3,4-Disubstitutedfurans, J.-L. Bontront and B.A. Keay,

2. Approaches Towards 4,5,6,7-Tetrahydroisobenzofurans.
J.-L. Bontront and B.A. Keay,
72nd Canadian Chemical Conference, 1989.

Publications Resulting from Other Research

1. B.A.Keay, C.Rogers, J.-L.J.Bontront, "Wagner Meerwein Rearrangements of
Substituted 11-Oxatricyclo[6.2.1.0^{1,6}]undec-9-enes", J.C.S., Chemical
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