EXOCYCLIC ALKENE SYNTHESIS VIA
STEREOSELECTIVE RADICAL CYCLIZATIONS

by
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Department of Chemistry

We accept this thesis as conforming
to the required standard

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The stereoselectivity of radical cyclizations of stabilized radicals to alkynyl esters was investigated. In most cases, reactions mediated by tri(n-butyl)tin hydride afforded predominantly E-exocyclic alkenes, whereas reactions mediated by tris(trimethylsilyl)silane afforded predominantly Z-exocyclic alkenes. In the case of cyclizations to the tetrahydropyran derivatives, the stereoselectivity could be improved by increased substitution α to the exocyclic double bond. For example, reaction of 37 with tris(trimethylsilyl)silane in refluxing benzene produced nearly equal amounts of 52 and 53, whereas 72 was selective for the Z-exocyclic alkene 76.

The formation of exocyclic alkenes via cyclization of secondary alkyl radicals to both (E)- and (Z)-bromo, iodo, and tri(n-butyl)stannyl-α,β-unsaturated esters was investigated. In many cases reactions were highly stereoselective. For example, the vinyl bromide 125 cyclized to afford predominantly the (E)-exocyclic alkene 123. Unlike its analogous vinyl bromide, the vinyl iodide 155 cyclized to afford predominantly the (Z)-exocyclic alkene 124.
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LIST OF ABBREVIATIONS

Ac ............................................. acetyl
AIBN ........................................ 2,2'-azobisisobutyronitrile
Anal .......................................... analysis
Bu ............................................. butyl
calcd ......................................... calculated
CI ............................................... chemical ionization
d ................................................ doublet
DCI ............................................. desorption chemical ionization
dd ............................................... double doublet
DHP ............................................ dihydropyran
DIBAL ........................................ diisobutylaluminum hydride
DMF ........................................... dimethylformamide
DMSO .......................................... dimethyl sulfoxide
EDA ........................................... ethylenediamine
EI ............................................... electron ionization
equiv ......................................... equivalent(s)
Et ............................................... ethyl
GC ............................................... gas chromatography
gem ........................................... geminal
HRMS .......................................... high resolution mass spectrometry
IR ............................................... infrared
J .................................................... coupling constant
LDA ............................................ lithium diisopropylamide
LUMO .......................................... lowest unoccupied molecular orbital
LRMS .......................................... low resolution mass spectrometry
m ............................................... multiplet
M+ ............................................... molecular ion
Me ............................................... methyl
min ............................................ minute(s)
m/z ........................................ mass to charge ratio
n........................................... normal
NMR ........................................ nuclear magnetic resonance
NOE ........................................ nuclear Overhauser enhancement
p.............................................. para
Ph ............................................. phenyl
PhH .......................................... benzene
PhMe ......................................... toluene
PPTs .......................................... pyridinium p-toluenesulfonate
py ............................................. pyridine
q.............................................. quartet
qn ............................................. quintet
s.............................................. singlet
SOMO ......................................... singly occupied molecular orbital
t.............................................. triplet
t.............................................. tertiary
TBDMS ........................................ t-butyldimethylsilyl
THF ........................................... tetrahydrofuran
THP ........................................... tetrahydropyran
TLC ........................................... thin layer chromatography
TMS ........................................... trimethylsilyl
Ts.............................................. toluenesulfonyl
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I thank my research supervisor Professor Larry Weiler for his guidance and encouragement during the course of this work.

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Special thanks go to my coworkers, whose helpful advice and timely lightheartedness provided a much appreciated positive atmosphere in the laboratory.

I also thank Janet Gamlin for her understanding and encouragement.

Finally, I thank my parents for making this all possible.
DEDICATION

To my parents.
CHAPTER 1
INTRODUCTION

The history of radical chemistry dates back to 1900 when Gomberg discovered the triphenylmethyl radical.¹ In the 1920's Paneth and Hofeditz showed that less stabilized alkyl radicals also exist and measured the lifetime of these radicals in the gas phase.² The first report of the use of a radical reaction in organic synthesis was in 1937, when Hey and Waters described the phenylation of aromatic compounds by benzoyl peroxide as a radical reaction.³ In that same year, Kharasch et al. recognized that the anti-Markovnikov addition of hydrogen bromide to alkenes proceeds via a radical chain process.⁴ As the level of understanding of the structure and reactivity of organic radicals has increased, so too has the application of radical reactions to problems in synthesis.

Several features of radical reactions make them particularly useful in synthesis. They are often highly chemo-, regio-, and stereoselective. The mild, neutral reaction conditions tolerate many oxygenated functional groups without the need for protection. In addition, steric crowding, particularly at the radical center, is often tolerated, making radical reaction useful for the formation of hindered carbon-carbon bonds.

The following is an examination of some of the basic principles of radical reactions.

1.1 Basic Principles

Several reviews outline the basic principles of free radical reactions.⁵⁻¹⁰ Radicals are species with at least one unpaired electron. Because of the high reactivity of radicals, radical-radical reactions occur at diffusion controlled rates with poor selectivity, severely limiting their synthetic usefulness. Chain reactions are often the preferred strategy for reactions between radicals and non-radicals. Chain reactions maintain a low concentration of radicals over the course of a reaction. In this way, radical-radical combination is kept to a minimum.

For a radical chain reaction to be successful at producing a desired product, the selectivity of the radicals in the chain must differ to such a degree that the desired
reaction dominates the various competitive reactions. When planning a radical chain reaction it is important to consider the electronic nature of the radical. Simple alkyl radicals and those that are substituted with electron-donating groups are considered nucleophilic and as such seek electron poor addition or abstraction sites. In contrast, alkyl radicals substituted with electron-withdrawing groups are electrophilic and prefer to react at sites of higher electron density. In the case of heteroatom-centered radicals, radicals centered on atoms more electronegative than carbon are considered electrophilic while those on atoms less electronegative than carbon form nucleophilic radicals. Therefore, an alkoxy radical (RO·) and bromine atom are considered electrophilic and tri(n-butyl)tin radical is considered nucleophilic.

1.2 Radical Addition Reactions

The vast majority of free radical reactions used for carbon-carbon bond formation involve the addition of a radical to a multiple bond, the driving force of the addition being the formation of a strong σ-bond at the expense of a weaker π-bond. The regiochemistry of addition is sensitive to substituent effects, both on the attacking radical itself and on the α- and β-positions of the unsaturated acceptor. The addition of electron-donating substituents at the radical center increases the nucleophilicity of the radical, and as a result leads to an increase in the rate of addition to an electron-deficient olefin. This is illustrated by the following data for addition to diethylvinylphosphonate (Table I). It is interesting to note that this electronic effect offsets both the increased stability of the attacking radical and any steric hindrance to addition that might be expected.

Table I. Relative Rates of Addition of Nucleophilic Radicals to H₂C=CHPO(OEt)₂ (from ref 11 and 12).

<table>
<thead>
<tr>
<th>R</th>
<th>CH₃</th>
<th>CH₂CH₃</th>
<th>CH₂OCH₃</th>
<th>CH(CH₃)₂</th>
<th>C(CH₃)₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>k_rel</td>
<td>1</td>
<td>1</td>
<td>2.7</td>
<td>4.8</td>
<td>24</td>
</tr>
</tbody>
</table>
Electron-withdrawing groups on an olefin can effect the relative rates of addition even more significantly. As the data in Table II illustrate, the rate of addition of a radical to an alkene is greatly accelerated by the presence of strongly electron-withdrawing groups on the alkene.

**Table II.** Effect of Electron-Withdrawing Group on Relative Rate of Addition of Cyclohexyl Radical to an Alkene (from ref 13).

<table>
<thead>
<tr>
<th>E</th>
<th>C_4H_9</th>
<th>H</th>
<th>Cl</th>
<th>Ph</th>
<th>CO_2CH_3</th>
<th>CN</th>
<th>CHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>k_rel</td>
<td>1</td>
<td>3.75</td>
<td>30</td>
<td>250</td>
<td>1675</td>
<td>6000</td>
<td>8500</td>
</tr>
</tbody>
</table>

An electron-withdrawing group also influences the regioselectivity of radical addition, directing an attacking nucleophilic radical to itself, as one would predict from a polar transition state. However, steric effects resulting from alkene substitution also have a pronounced influence on the regioselectivity of radical additions to alkenes. The magnitude of these effects is illustrated by the data in Table III.
Table III. Steric Effects on Addition Regioselectivity: Addition of Dicyanomethyl Radical to Various Alkenes (from ref 14).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>% addition to</th>
<th>k_{rel}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C_a</td>
<td>C_b</td>
</tr>
<tr>
<td>1</td>
<td>a b</td>
<td>≥95</td>
<td>≤5</td>
</tr>
<tr>
<td>2</td>
<td>a b</td>
<td>≥95</td>
<td>≤5</td>
</tr>
<tr>
<td>3</td>
<td>a b</td>
<td>ca. 50</td>
<td>ca. 50</td>
</tr>
<tr>
<td>4</td>
<td>a b</td>
<td>≥95</td>
<td>≤5</td>
</tr>
<tr>
<td>5</td>
<td>a b</td>
<td>≤5</td>
<td>≥95</td>
</tr>
</tbody>
</table>

1.3 **Exo versus Endo Cyclization**

Radical cyclization is used extensively in synthesis, and thorough summaries outlining important considerations for these reactions are available.5,6,9,10,15,16 Both 5-hexenyl and 6-heptenyl radicals exhibit a marked preference to add to the alkene in an exo-fashion to yield the cycloalkylcarbinyl radicals, which are the less thermodynamically stable products.17 Radical ring closures are known to be under kinetic and stereoelectronic, rather than thermodynamic, control. The preference for exo ring closure of the 5-hexenyl radical can be explained by invoking a chair-like transition state, as depicted in Figure 1. The angle of attack in the exo-transition state (106°) is nearer to the preferred angle for unconstrained bimolecular additions (109°) than in the endo-transition state (94°). Thus, endo-cyclization is less favourable due to poorer overlap between the SOMO of the radical and the LUMO of the alkene. A comprehensive discussion of the factors that control the cyclization of the 5-hexenyl radical can be found in a recent review by Curran.15 Computer calculations have shown that the relative strain energy in the transition state leading to exo-cyclization of
the 5-hexenyl radical is 2.8 kcal/mol lower than that in the corresponding endo-cyclization.\textsuperscript{18}

Figure 1. Computer generated models of exo- and endo-cyclizations of 5-hexenyl radical (from ref 18,19).

The rate of $\omega$-alkenyl radical ring closure by both exo- and endo- modes depends on substitution on the alkene and on the alkyl chain. Experimental kinetic data for representative examples are given in Table IV.

\textbf{Table IV.} Experimental Kinetic Data for Ring Closure of $\omega$-Alkenyl and Related Radicals (from ref 18).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Radical</th>
<th>$k$ (exo)$^a$</th>
<th>$k$ (endo)$^a$</th>
<th>$k$(exo)/$k$(endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\overset{\cdot}{(\text{CH}_2)_3}$</td>
<td>$2.3 \times 10^5$</td>
<td>$4.1 \times 10^3$</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>$\overset{\cdot}{(\text{CH}_2)_4}$</td>
<td>$5.2 \times 10^3$</td>
<td>$8.3 \times 10^2$</td>
<td>6.3</td>
</tr>
<tr>
<td>3</td>
<td>$\overset{\cdot}{(\text{CH}_3)_2}$</td>
<td>$6.1 \times 10^3$</td>
<td>$9.0 \times 10^3$</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>$\overset{\cdot}{(\text{CH}_2)_2}$</td>
<td>$5.2 \times 10^6$</td>
<td>$&lt;1 \times 10^5$</td>
<td>&gt;52</td>
</tr>
<tr>
<td>5</td>
<td>$\overset{\cdot}{(\text{CH}_2)_2}$</td>
<td>$8.5 \times 10^6$</td>
<td>$&lt;1 \times 10^5$</td>
<td>&gt;85</td>
</tr>
<tr>
<td>6</td>
<td>$\overset{\cdot}{(\text{CH}_2)_2}$</td>
<td>$2.8 \times 10^4$</td>
<td>$&lt;6 \times 10^2$</td>
<td>&gt;47</td>
</tr>
</tbody>
</table>

$^a$ rate constants at 25 °C in s$^{-1}$
1.4 Selectivity in Cyclization of Substituted 5-Hexenyl Radicals

The ring closure of substituted 5-hexenyl systems is often stereoselective, and guidelines for predicting the stereochemistry in these systems have been put forth by Beckwith:20

- 1- or 3-substituted hexenyl radicals preferentially give cis-cyclopentyl products.
- 2- or 4-substituted hexenyl radicals preferentially give trans-cyclopentyl products.

The magnitude of this effect is illustrated by the examples in Figure 2.

![Figure 2. Stereoselective substituted 5-hexenyl radical cyclization (from ref 21).](image)

The Beckwith model provides a rationale for the preference of cis or trans product by considering the possible chair-like transition states.18,21a The substituents on carbon atoms 2, 3, or 4 will preferentially occupy equatorial positions, and therefore control the stereoselectivity. Houk and Spellmeyer advanced the understanding of the stereoselectivity in these cyclizations through calculations of possible transition states for these reactions.19 Figure 3 illustrates the possible transition state structures for the exo-cyclization of a 3-substituted 5-hexenyl radical. The relative energies, derived from force field calculations, agree with the Beckwith model's prediction that the major cis
product arises via the chair transition state A. However, the calculations indicate that
the minor trans product arises both from the chair transition state B and the boat
transition state D. RajanBabu and coworkers have provided experimental support for
the postulated energetic importance of boat transition states.22

![Diagram of cyclization reaction]

Figure 3. Houk/Spellmeyer model for cyclization of a 3-substituted 5-hexenyl radical
(from ref 19).

1.5 Analysis of a Chain Reaction Mechanism

Methods for conducting radical chain reactions can be classified into four
categories: the metal hydride method, the fragmentation method, the thiohydroxamate
method, and the atom transfer method. Detailed descriptions of each method can be
found in many of the reviews cited earlier. Radical chain reactions comprise initiation,
propagation, and termination steps. Initiation is a process by which non-radicals are
converted to the radicals required for the chain reaction. The propagation steps are the
steps in which the chain reaction converts starting materials into products. Termination
involves quenching the chain reaction by radical-radical combination. The tri(n-butyl)tin
hydride mediated addition of an alkyl halide to an alkene serves as an example of a radical chain reaction (eq 1).

\[
\text{E} + \text{R-X} \xrightarrow{\text{Bu}_3\text{SnH}} \text{R} - \text{E} + \text{Bu}_3\text{SnX} \quad (1)
\]

The chain reaction mechanism of the above reaction equation is apparent when the reaction is presented as in Figure 4. A single cycle of the chain begins with tri(n-butyl)tin radical abstraction of the halide, producing tri(n-butyl)tin halide and an alkyl radical. Addition of the alkyl radical to the alkene generates the adduct alkyl radical. Hydrogen transfer from tri(n-butyl)tin hydride to the adduct alkyl radical affords the addition product and a new tri(n-butyl)tin radical to continue the chain reaction. When examining chain reactions in this manner, it is important to keep in mind that all of the radical and non-radical species are present in the reaction mixture simultaneously. Therefore, when designing reactions of this type, it is necessary to consider the relative rates of the various pathways available to each of the radical species. Much has been discovered about how reaction substrates and reaction conditions can be manipulated in order to influence the desired reaction outcome.

Figure 4. The tin hydride mediated addition of an alkyl halide to an alkene (from ref 5).
The tri(n-butyl)tin radical can undergo alkene addition (eq 2) or halogen abstraction from the alkyl halide (eq 3). Addition of tri(n-butyl)tin radical to the alkene is reversible due to the weak carbon-tin bond (ca. 65 Kcal/mol). Therefore, competition between these pathways depends on the rate of abstraction of the halide. Bromides and iodides are the most useful alkyl halides for radical reactions. The desired halogen abstraction pathway can be made more favourable by switching from an alkyl bromide to a more reactive alkyl iodide. Tri(n-butyl)tin radical abstracts iodine about 100 times faster than it abstracts bromine from alkyl halides.

Beckwith and Pigou have established a reactivity scale for tri(n-butyl)tin radical which is useful in synthetic planning. Iodine is often the preferred precursor, as the rate constant for iodine atom abstraction approaches the diffusion-controlled limit.

The alkyl radical can compete between hydrogen abstraction from tri(n-butyl)tin hydride (eq 4) and alkene addition (eq 5). Hydrogen abstraction can be minimized by maintaining a low concentration of tri(n-butyl)tin hydride throughout the duration of the reaction. Low tin hydride concentration can be maintained by the use of a syringe pump to perform a slow, controlled addition of tri(n-butyl)tin hydride. Another method uses a catalytic amount of tri(n-butyl)tin chloride and NaBH₃CN for the in situ generation of tri(n-butyl)tin hydride. An electron-withdrawing substituent on the alkene will accelerate addition by nucleophilic alkyl radicals. Also, substituents at the radical center will accelerate addition, while having little effect on the rate of hydrogen abstraction. Thus, proper substitution of the radical center and the alkene can help control the reactivity of the alkyl radical.
R• + Bu₃SnH → Bu₃Sn• + R-H

R• + E → R-E

The adduct alkyl radical can compete between alkene addition and hydrogen abstraction from tri(n-butyl)tin hydride. An electron-withdrawing substituent on the alkene will render the adduct radical electrophilic, and therefore addition to a second electron-poor alkene (eq 6) will be slow relative to hydrogen abstraction (eq 7).

R-E + E → R-E

R-E + Bu₃SnH → Bu₃Sn• + R-E

The most commonly used initiators undergo thermally or photochemically promoted homolytic bond cleavage to give two radicals. 2,2'-Azobisisobutyronitrile (AIBN) is the most commonly employed initiator. Exposure of AIBN to heat or light effects its decomposition to two isobutyronitrile radicals (eq 8). AIBN has a half-life of 1 hour at 80 °C and is useful over the temperature range 60-120 °C.29

\[ \text{N}=\text{N} \rightarrow 2 \text{N} + N_2 \]

An initiator that has been finding increasing application in organic synthesis is triethylborane. It is usually added to a reaction as a commercially available 1.0 M solution in hexanes. Triethylborane reacts readily with oxygen, generating ethyl radicals which may be responsible for its initiator property.30 Triethylborane is
particularly attractive because it can effectively generate radicals at low as well as high temperatures.\textsuperscript{31}

1.6 Example of Application of Radical Cyclization in Natural Product Synthesis

An impressive use of radical cyclization is Curran’s tandem radical cyclization approach to linear and angular triquinanes.\textsuperscript{32} The general strategy involves a preformed central cyclopentene ring which serves as the “relay” for the tandem addition reaction, and also ensures the correct stereochemical outcome. The application of this methodology to the synthesis of hirsutene is shown below.

Several features of this reaction are noteworthy. First, the reaction is very efficient, and hirsutene is produced in 80% yield in a single step from the relatively simple \textit{trans}-3,5-disubstituted cyclopentene \textbf{1} upon reaction with tri(n-butyl)tin hydride. This reaction also demonstrates that radicals are well suited for the formation of sterically hindered carbon-carbon bonds. As can be seen above, the initially-formed radical \textbf{2}, which is flanked by a \textit{gem}-dimethyl group on the \textit{\alpha}-carbon, adds efficiently to the alkene to afford the tertiary radical \textbf{3}. In turn, radical \textbf{3} adds to the alkyne to give the vinyl radical \textbf{4}, forming a quaternary center in the process. Finally, radical \textbf{4} abstracts a hydrogen atom from tri(n-butyl)tin hydride to afford hirsutene, and the chain-carrying tri(n-butyl)tin radical.
1.7 Methods for Stereoselective Exocyclic Double Bond Formation via Radical Cyclization

An application of radical chemistry which is of particular interest to our group is for the stereoselective synthesis of alkenes. We are particularly interested in combining the efficient radical cyclization to 5- and 6-membered rings with methods to stereoselectively produce exocyclic alkenes. The first reported example of such a reaction was by Ohnuki et al.\textsuperscript{33} Reaction of 5 with tri(n-butyl)tin hydride afforded a 48% yield of the exocyclic alkenes 6 and 7. Resolution of the $^1$H NMR signals of the allylic methylenes using the chemical shift reagent tris(dipivalomethanato)europium allowed the ratio of 6 and 7 to be determined as 96:4.

```
EtO=CCl
D D
5    Bu$_3$SnH
```

```
ET
D D
6

OEt
D D
7

96 : 4
```

The almost exclusive formation of the $E$-isomer suggested that the radical center which has attacked the acetylenic bond and the newly generated half-filled sp$^2$ hybrid orbital are disposed in a trans orientation in the initial vinylic radical (Figure 5). Hydrogen transfer to the vinyl radical at a significantly higher rate than that of vinyl radical inversion is thought to be responsible for the high stereoselectivity of the addition. Rationale offered to account for the small amount of $Z$-isomer include the possible slow isomerization of $E$- and $Z$-bent configurations of the radical, or product isomerization by the tri(n-butyl)tin radical.\textsuperscript{34}

```
OEt
D D
```

Figure 5. Stereochemistry of initial vinyl radical upon cyclization of the radical derived from 5.
This result was in good agreement with the Wedegaertner et al. observation of stereoselective addition of ethyl mercaptan to ethoxyacetylene (Figure 6).\textsuperscript{35} This intermolecular addition afforded initial \textit{cis/trans} product ratio of greater than 100. Here again, chain transfer is thought to be much more rapid than isomerization of the vinyl radical, therefore the product composition is given by the ratio of the rate constants of the initial additions to give the \textit{cis}- and \textit{trans}-vinyl radicals. The \textit{cis/trans} product ratio gradually decreased throughout the course of the reaction. This was attributed to isomerization of the products by thiyl radicals.

\begin{center}
\begin{align*}
\text{EtS}\ast + \ & \text{H} \equiv \text{OEt} \\
\downarrow \ & \downarrow \\
\text{EtS} \equiv \text{OEt} & \quad \text{EtS} \equiv \text{OEt} \\
\quad \quad \text{slow} & \quad \quad \text{fast} \\
\downarrow & \downarrow \\
\text{EtS} \equiv \text{OEt} & \quad \text{EtS}\ast \\
\quad \quad \text{EtS}\ast & \quad \quad \text{EtS} \equiv \text{OEt}
\end{align*}
\end{center}

\textbf{Figure 6.} Rationale for the stereoselective addition of ethyl mercaptan to ethoxyacetylene.

Ohnuki et al. also showed that the phenyl substituted acetylenic compound 8 underwent tri(n-butyl)tin hydride mediated cyclization to afford equal amounts of the \textit{E} and \textit{Z} isomeric products 9 and 10.\textsuperscript{36}
In this case the cyclization is proposed to yield the vinyl radical in a linear form. Thus, hydrogen abstraction would occur with equal probability from both sides of the vinyl radical. This is in agreement with the observation by Bennett and Howard that the electron spin resonance spectrum of the α-styryl radical is more consistent with a π-type radical rather than a σ-type radical.\(^{37}\)

![Figure 7. Linear stereochemistry of α-styryl type radicals.](image)

Alkyl and unsubstituted vinyl radicals are believed to be bent and are undergoing rapid inversion. Electron spin resonance investigations have shown that at low temperatures the unsubstituted vinyl radical possesses a nonlinear configuration which undergoes facile inversion.\(^{38}\) The stereoselectivity from alkyl substituted vinyl radicals results from the relative transition state energies for hydrogen transfer. As the effective size of the alkyl group or of the hydrogen source is increased, stereoselectivity increases.\(^{39}\)

Munt and Thomas reported a different approach to the stereoselective formation of exocyclic alkenes.\(^{40}\) They chose compounds 11 and 12 as cyclization precursors. Each compound, when reacted with tri(n-butyl)tin hydride, afforded 15 and 16 in 80:20 ratio. These results were rationalized by an equilibration of the radicals 13 and 14 before cyclization. The stereoselectivity of cyclization is thought to be due to the adjacent carbomethoxy group providing addition steric hindrance to cyclization of the E-radical 14.
Both Baldwin and Russell have used a radical addition-elimination strategy to effect intermolecular vinylation. The general strategy for this radical reaction is shown in Figure 8. An initially formed alkyl radical adds to an alkene which bears a suitable leaving group Q. An electron-withdrawing substituent E on the alkene directs the regiochemistry of the addition. The resulting radical fragments by eliminating the leaving group and regenerating the alkene. The net result is a vinylation of the alkyl radical.
Figure 8. General strategy of addition-elimination reaction.

For example, Baldwin and Kelly studied reactions of alkyl radicals with E- and Z-vinyl stannanes (Figure 9). They found the reactions to be selective for the E-alkene product independent of the geometry of the starting vinyl stannane. They also found that primary, secondary and tertiary alkyl radicals could participate in the addition-elimination sequence.

Figure 9. E-Selective addition-elimination reactions (from ref 41).

In addition totrialkylstannyl groups, Russell and co-workers have found that phenylsulphonyl, phenylsulphinyl, and phenylthio groups, as well as halides and mercuric halides are suitable leaving groups for the addition-elimination reaction. In contrast to the work of Baldwin, Russell discovered that in some cases the product alkene geometry did depend on the stereochemistry of the vinyl derivative used
(Figure 10). However, the extent of the selectivity appeared to be dependent upon the substrates used, as well as the reaction conditions employed.\textsuperscript{42b}

![Equation 1](image1.png)

![Equation 2](image2.png)

Figure 10. Stereospecific addition-elimination reaction (from ref 42b).

The Weiler group's history of the investigation of radical cyclization methods began in the mid 1980's. Harris and Weiler reported the use of a radical cyclization as the key step in the synthesis of three components of the boll weevil sex pheromone.\textsuperscript{43} Treatment of each of the vinyl stannanes 17 and 20 with tri(n-butyl)tin hydride afforded a 1:1 ratio of the acyclic reduction product 19 and the exocyclic alkenes 18 and 21. The cyclization was stereospecific and proceeded with high selectivity.
Later it was shown by Lowinger\textsuperscript{44} that reaction of the Z-vinyl stannane 17 with tris(trimethylsilyl)silane resulted in the exclusive formation of the Z-exocyclic alkene 18 in 55\% yield along with 40\% of the acyclic reduction product 19. Under the same conditions, reaction of the E-vinyl stannane 20 resulted in the exclusive formation of the E-exocyclic alkene 21 in 48\% yield along with 40\% of the acyclic reduction product 19. Thus the reactions using tris(trimethylsilyl)silane afforded superior results to those mediated by tri(n-butyl)tin hydride. In each case only a single diastereomer of the exocyclic alkenes was produced, suggesting that isomerization of the cyclic products did not occur under tris(trimethylsilyl)silane conditions. In addition, the ratio of acyclic to cyclic products was decreased, which was in agreement with the report that tris(trimethylsilyl)silane is a poorer hydrogen atom donor than tri(n-butyl)tin hydride.\textsuperscript{45}

The possible mechanism of the addition-elimination reaction sequence put forth by Lowinger\textsuperscript{44} is outlined below. Radical abstraction of the iodine atom affords the
acyclic alkyl radical 22. Cyclization to the alkyl radical intermediate 23, followed by elimination of the tri(n-butyl)tin radical results in formation of the exocyclic alkene 18. The geometry of the alkene is dependent on the relative rates of rotation about the C1-C2 bond and of elimination of the tri(n-butyl)tin substituent. If the rate of elimination of the tri(n-butyl)tin is faster than rotation of the C1-C2 bond in the intermediate 23, then the stereochemistry of the starting alkene is retained in the product.

\[
\begin{align*}
\text{addition} & \quad \text{elimination} \\
17 & \quad \xrightarrow{1} 23 & \quad \xrightarrow{2} 18 + \text{Bu}_3\text{Sn}^* \\
\end{align*}
\]

One complication to the task of synthesizing alkenes stereoselectively by radical cyclization, is their susceptibility to isomerization under radical reaction conditions.\(^{46,47}\) In fact, double bond isomerization by radicals can be useful in synthesis. Thiyls,\(^{47}\) tris(trimethylsilyl)silyl,\(^{48}\) and tri(n-butyl)tin\(^{44}\) radicals add reversibly to double bonds, and through this addition-elimination mechanism, effect isomerization of alkenes.\(^{49}\)

Lowinger found that in some cases, radical mediated isomerization could severely limit the selective production of Z-alkenes.\(^{44}\) For example, the tri(n-butyl)tin hydride mediated radical reaction of the \(E\)-vinyl stannane 24 resulted in a 96:4 ratio of \(E\)- and \(Z\)-exocyclic alkenes.
Reaction of the Z-vinyl stannane 25 resulted in an 84:16 ratio of E- and Z-exocyclic alkenes. Thus, the reactions were not stereospecific since in each case the E-isomer was more prevalent.

The Z-exocyclic alkene was shown to be unstable to the cyclization conditions by exposing pure Z-exocyclic alkene to the tri(n-butyl)tin radical conditions. After 1 hour the ratio of E- and Z-exocyclic alkenes was 98:2.

Investigation into the reactivity of the next higher homologues revealed similar results. The E-vinyl stannane 26 was reacted with tri(n-butyl)tin hydride to selectively produce the E-exocyclic alkene in 82% yield.
As was the case with the lower homologue, the Z-vinyl stannane 27 reacted to give a mixture of $E$- and $Z$-exocyclic alkenes which was richer in the $E$-product.

![Chemical structure](image)

No difference in selectivity for the formation of 6-membered rings was realized for reactions mediated by tris(trimethylsilyl)silane versus tri($n$-butyl)tin hydride. However, tris(trimethylsilyl)silane mediated reactions had the advantage of producing less of the acyclic reduction products.

The following diagram shows how the methyl substituent on the ring may effect the $E$- versus $Z$-isomer selectivity. Abstraction of the iodine atom affords the secondary alkyl radical 28, which cyclizes to give the cyclic radical 29. Elimination of tri($n$-butyl)tin radical from 29 gives the $Z$-exocyclic alkene. However, there is a steric interaction between the methyl group and the ester moiety in 29. This strain can be relieved by bond rotation to give the more stable rotamer 30. Elimination of tri($n$-butyl)tin radical from 30 gives the $E$-exocyclic alkene. The elimination of tri($n$-butyl)tin radical is reversible, thus products are also susceptible to isomerization.
Lowinger and Weiler solved the difficulty in making Z-exocyclic alkenes by using the ring substituent to their advantage.\(^{50}\) Reaction of the acetylene 31 with tri(n-butyl)tin hydride at 80 °C afforded a 98:2 ratio of E-and Z-alkenes. While reaction of 31 with tris(trimethylsilyl)silane at -78 °C afforded an 11:89 ratio of E-and Z-alkenes.
Similar results were obtained for synthesizing the 6-membered ring alkenes. Reaction of 32 with tri(n-butyl)tin hydride at 80 °C afforded a 98:2 ratio of E- and Z-alkenes, while reaction with tris(trimethylsilyl)silane at -78-25 °C afforded 9:91 ratio of E- and Z-alkenes. Thus, by specific choice of reaction conditions, it was possible to prepare either E- or Z-exocyclic alkenes stereoselectively from the same precursors.

The following rationale was offered for the selectivity in these reactions. Abstraction of the iodine atom from 31 affords the secondary alkyl radical 33. Cyclization gives a vinyl radical, which can exist in two isomeric forms, 34 and 35. The final step required in the reaction is the abstraction of a hydrogen atom from the reducing agent, R-H [tri(n-butyl)tin hydride or tris(trimethylsilyl)silane]. For reduction of 34, which leads to the E-exocyclic alkene, the reducing agent must approach the
molecule from the side bearing the methyl group. This is disfavoured because of a steric interaction between the bulky reducing agent and the methyl group. However, for reduction of 35 leading to the Z-exocyclic alkene, the reducing agent approaches the molecule from the side opposite the methyl group. Therefore, in this transition state steric interaction between the bulky reducing agent and the methyl group is avoided. Stereoselective formation of E-alkene using tri(n-butyl)tin hydride results from isomerization of initially formed Z-alkene.
CHAPTER 2
RESULTS AND DISCUSSION

2.1 Heterocyclic Radical Reactions

The work by Lowinger and Weiler,\(^{50}\) described in the Introduction showed that the stereochemistry of exocyclic alkenes could be controlled by the choice of radical reducing agent. The radical cyclizations proceeded in good yields to form both 5- and 6-membered rings. We were interested in investigating the scope and limitations of this method in an effort to expand our understanding of this area of radical chemistry.

Lolkema et al. have shown that substituted tetrahydrofuran and tetrahydropyran derivatives could be synthesized using a radical cyclization methodology.\(^{51}\) Their work investigated the intramolecular addition of stabilized carbon radicals to various unsaturated carbon centers. One such example is shown in eq 9. The authors presented many examples of additions to alkenes, but this was the lone acetylenic substrate reported. The cyclization was reported to proceed in high yield, but with no stereoselectivity.

\[
\begin{align*}
\text{Me} & \quad \text{Bu}_3\text{SnH, AIBN} \\
\text{PhH, } & \Delta \\
\rightarrow & \\
\text{Me} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\text{(9)}^{51}

88% \\
\text{($E:Z = 50:50$)}

We were interested to know if our methods of controlling the stereochemistry of exocyclic alkenes by choice of reducing agent and reaction conditions could be applied for the stereoselective production of exocyclic alkenes in tetrahydrofuran and tetrahydropyran derivatives. We chose compounds 36 and 37 as cyclization substrates.
for this study. Alkynes substituted with a carbomethoxy group were chosen following the substrates on which the stereoselective methodology had been developed. Also, the ester group provides an additional handle for further synthetic transformations. Such a handle could conceivably be important for the use of this method in the synthesis of more complex molecules.

2.1.1 Synthesis of Dimethyl 6-Oxa-7-(phenylthio)-2-octynedioate (36) and Dimethyl 7-Oxa-8-(phenylthio)-2-nonynedioate (37)

Cyclization substrates 36 and 37 were synthesized as illustrated in Scheme I. 3-Butyn-1-ol (38) and 4-pentyn-1-ol (39) were commercially available starting substrates for the syntheses of 36 and 37, respectively. The hydroxyl group was protected by conversion to 4-(2-tetrahydropyranyloxy)-1-butyne (40) and 5-(2-tetrahydropyranyloxy)-1-pentyne (41).

![Scheme I](image)

The alkyne was deprotonated by methyllithium and addition of methyl chloroformate afforded methyl 5-(2-tetrahydropyranyloxy)-2-pentyenoate (42) and methyl
6-(2-tetrahydropyranloxy)-2-hexynoate (43). This acylation was followed by infrared spectroscopy in which the C-H bond ca. 3300 cm\(^{-1}\) of the starting material was replaced by a C=O bond ca. 1710 cm\(^{-1}\) and the acetylenic bond at ca. 2240 cm\(^{-1}\) was much more intense in the products 42 and 43. The hydroxyl group was deprotected by hydrolysis of the acetal using acidic methanol to afford methyl 5-hydroxy-2-pentynoate (44) and methyl 6-hydroxy-2-hexynoate (45). Following the method of Lolkema et al.,\(^{51}\) each of the alcohols 44 and 45 was reacted with methyl 2-chloro-2-(phenylthio)acetate (48) to yield radical cyclization substrates 36 and 37. Intermediate 48 was prepared according to the procedures shown in Scheme II.\(^{52}\) An important feature in the conversion of 44 and 45 to 36 and 37 is to carefully deoxygenate the benzene solvent. Traces of oxygen may react with the activated zinc acetate reagent thereby preventing the desired coupling reaction.

\[
\text{PhS} - \text{CO}_2\text{H} \xrightarrow{\text{i}} \text{PhS} - \text{CO}_2\text{Me} \xrightarrow{\text{ii}} \text{Cl} \text{PhS} - \text{CO}_2\text{Me} 
\]

Scheme II. i. MeOH, \(p\)-TsOH-H\(_2\)O, 93%; ii. N-chlorosuccinimide, CCl\(_4\) 76%.

With the desired radical precursors in hand, we proceeded to investigate their cyclization.

2.1.2 Cyclization of Compound 36

Substrate 36 underwent cyclization in a 5-exo fashion to yield the tetrahydrofurans 49 and 50.
The results of the cyclizations of compound 36 to compounds 49 and 50 are summarized in Table V. Initial reactions were focused on the use of tri(n-butyl)tin hydride as the radical reducing agent. Selectivity for the E-isomer was expected for tri(n-butyl)tin hydride mediated reactions.

**Table V. Tri(n-butyl)tin Hydride and Tris(trimethylsilyl)silane Mediated Cyclizations of Compound 36.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent</th>
<th>Initiator</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E:Z Ratio&lt;sup&gt;b&lt;/sup&gt; (49:50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>AIBN</td>
<td>PhH</td>
<td>80</td>
<td>72</td>
<td>62:38</td>
</tr>
<tr>
<td>2</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>PhH</td>
<td>80</td>
<td>95</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>PhH</td>
<td>25</td>
<td>82</td>
<td>66:34</td>
</tr>
<tr>
<td>4</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>AIBN</td>
<td>PhH</td>
<td>80</td>
<td>82</td>
<td>22:78</td>
</tr>
<tr>
<td>5</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>PhH</td>
<td>80</td>
<td>90</td>
<td>19:81</td>
</tr>
<tr>
<td>6</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>PhH</td>
<td>25</td>
<td>82</td>
<td>15:85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC analysis using tetradecane as internal standard.

<sup>b</sup> Determined by GC analysis.

The procedure for the reaction in Entry 1 was carried out as follows. A solution of compound 36 (0.2 M), 2.0 equiv. of tri(n-butyl)tin hydride, 0.1 equiv. of AIBN and tetradecane in deoxygenated benzene was heated at reflux and monitored by GC analysis, using the tetradecane as internal standard. After 6 hours, GC analysis indicated that no starting material remained and that 49 and 50 were produced in 72% yield and in a 62:38 ratio. Chromatographic separation and purification of compounds 49 and 50 was complicated by the silica gel promoted tautomerization of the exocyclic alkenes to the endocyclic alkene 51.

The tautomerization was slowed by the addition of formic acid to the chromatographic eluent. The C=C IR band ca. 2240 cm<sup>-1</sup> of the starting material was replaced by C=C band ca. 1670 cm<sup>-1</sup> in the cyclic products. The very weak C=C band for 51 was consistent with a tetrasubstituted alkene. The measured masses for compounds 49, 50 and 51 suggested they were isomers of C<sub>9</sub>H<sub>12</sub>O<sub>5</sub>. The absence of
vinyl protons in the $^1$H NMR spectrum of 51 was consistent with the assigned endocyclic alkene structure.

![Diagram of compound 51](image)

The stereochemistry of the exocyclic alkenes was assigned by analysis of their $^1$H and nuclear Overhauser enhancement (NOE) NMR spectral data. The $^1$H NMR spectrum of compound 49 exhibited a two-proton multiplet at $\delta$ 3.02-3.20 assigned to the allylic methylene hydrogens and a one-proton doublet at $\delta$ 4.95 assigned to the allylic methine hydrogen. The analogous signals in the $^1$H NMR spectrum of compound 50 were two one-proton multiplets at $\delta$ 2.78 and $\delta$ 2.86 and a one-proton triplet at $\delta$ 5.42. Comparison of each of these analogous signals suggests that the lower field resonance for the methylene in compound 49 and for the methine in compound 50, were a result of deshielding due to the spatially adjacent carbomethoxy group. Compound 49 exhibited an NOE to the methine proton at $\delta$ 4.95 upon irradiation of the vinyl proton at $\delta$ 6.10. Similarly, irradiation of the vinyl proton at $\delta$ 6.02 of compound 50 exhibited a weak NOE to the methylene protons at $\delta$ 2.78 and 2.86.

![Diagram of compounds 49 and 50](image)

The reaction in Entry 4, in which tris(trimethylsilyl)silane was used in place of tri(n-butyl)tin hydride, was performed using the same procedure as for the reaction in Entry 1. After 6 hours, GC analysis indicated 11% of the starting material remained and an 82% yield of 49 and 50 in 22:78 ratio.
The reactions in Entries 1 and 4 displayed selectivities consistent with earlier findings. The tri(n-butyl)tin hydride reaction was selective for the E-isomer, while the tris(trimethylsilyl)silane reaction was selective for the Z-isomer. Encouraged by these results, reaction conditions were explored with the goal of improving the selectivity.

The reactions in Entries 2 and 3 show the effect of temperature on the selectivity. The reaction in Entry 2 was analyzed after 10 minutes, GC analysis indicated that none of the starting material remained and a 95% yield of 49 and 50 in a 75:25 ratio. The same procedure was used for the room temperature reaction in Entry 3. After 4 hours, GC analysis indicated that only a trace of the starting material remained and an 82% yield of 49 and 50 in a 66:34 ratio.

This same procedure was used for the reactions in Entries 5 and 6, with the exception that 1.5 equiv. of tris(trimethylsilyl)silane was used in place of tri(n-butyl)tin hydride. After 10 minutes, GC analysis indicated the reaction in Entry 5 was complete and had produced a 90% yield of 49 and 50 in a 19:81 ratio. For the room temperature reaction in Entry 6, after 20 minutes GC analysis indicated that only a trace of starting material remained and an 82% yield of 49 and 50 in a 15:85 ratio. As expected the reactions were faster at the higher temperature.

Comparison of the selectivity of the tri(n-butyl)tin hydride mediated reactions in Entries 2 and 3 show that the preferred E-isomer selectivity decreased from an E:Z ratio of 75:25 for reaction at 80 °C to 66:34 for reaction at 25 °C. This decrease in selectivity may be a result of the longer reaction time required for complete consumption of the starting material at the lower temperature. The longer reaction time may have resulted in isomerization of the products by tri(n-butyl)tin radicals, thus effecting the isomer ratio.

Lowinger has shown that diminished selectivity at longer reaction times could be due to isomerization of the initially formed product under the reaction conditions. For the reaction of 20 to 21 and 18, the stereoselectivity in favour of compound 21 was found to be >98:1 after 20 minutes, but only 4:1 after 140 minutes. In a separate experiment he showed that the cyclic product 21 could be isomerized by reaction with tri(n-butyl)tin hydride and AIBN in refluxing benzene. After 2 hours, GC analysis indicated that a 1:1 mixture of compounds 21 and 18 was present.
Comparison of the tris(trimethylsilyl)silane mediated reactions in Entries 5 and 6 shows that the preferred Z-isomer selectivity increased slightly from an E:Z ratio of 19:81 for reaction at 80 °C to a 15:85 for reaction at 25 °C. That the selectivity was improved at the lower reaction temperature, even with the longer reaction time required for complete consumption of starting material, was consistent with earlier findings that suggest that less isomerization occurred under tris(trimethylsilyl)silane reaction conditions. For example, Lowinger found that reaction of compound 20 with tris(trimethylsilyl)silane was highly stereoselective and that no isomerization of the cyclic product 21 occurred under these conditions. Reactions using triethylborane/air to initiate cyclization of compound 36 at temperatures at 0 °C or lower failed to proceed to any appreciable extent, even after multiple initiations.
2.1.3 Cyclization of Compound 37

The results of the cyclizations of compound 37 to compounds 52 and 53 are summarized in Table VI.

![Structural diagram](image)

**Table VI.** Tri(n-butyl)tin Hydride and Tris(trimethylsilyl)silane Mediated Cyclizations of Compound 37.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reducing Agent</th>
<th>Initiator</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E:Z Ratio&lt;sup&gt;b&lt;/sup&gt; (52:53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>AIBN</td>
<td>PhH</td>
<td>80</td>
<td>39</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>PhH</td>
<td>80</td>
<td>8</td>
<td>50:50</td>
</tr>
<tr>
<td>3</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>AIBN</td>
<td>PhH</td>
<td>80</td>
<td>54</td>
<td>43:57</td>
</tr>
<tr>
<td>4</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>PhH</td>
<td>80</td>
<td>47</td>
<td>48:52</td>
</tr>
</tbody>
</table>

<sup>a</sup> Product yields were determined by GC analysis using tetradecane as internal standard.

<sup>b</sup> Isomer ratios were determined by gas chromatography.

<sup>c</sup> A syringe pump was used to slowly add tri(n-butyl)tin hydride to a solution of substrate 37 and azobis(isobutyronitrile) in refluxing benzene.

The reaction in Entry 1 was performed by the slow continuous addition of tri(n-butyl)tin hydride solution in benzene over 4 hours. After a further 1 hour, GC analysis indicated that no starting material remained and a 39% yield of 52 and 53 in a 50:50 ratio. Performing the reaction without the syringe pump addition of the reagents afforded equal amounts of the heterocycles in 18% yield.

The stereochemistry of the exocyclic alkenes was assigned by analysis of their <sup>1</sup>H and nuclear Overhauser enhancement (NOE) NMR spectral data. The <sup>1</sup>H NMR spectrum of compound 52 exhibited a one-proton doublet of triplets at δ 3.39 and a
one-proton multiplet at $\delta 2.61$ assigned to the allylic methylene hydrogens and a one-proton singlet at $\delta 4.58$ assigned to the allylic methine hydrogen. The analogous signals in the $^1$H NMR spectrum of compound 53 were a two-proton multiplet at $\delta 2.40$ and a one-proton singlet at $\delta 6.29$. Comparison of each of these analogous signals suggests that the lower field resonance for one of the methylene protons in compound 52 and for the methine in compound 53 were a result of deshielding due to the spatially adjacent carbomethoxy group. The NOE difference spectrum of compound 52 exhibited an NOE of the vinyl proton at $\delta 5.74$ upon irradiation of the methine proton at $\delta 4.58$. Similarly, irradiation of the methylene protons at $\delta 2.40$ of compound 53 produced an NOE of the vinyl proton at $\delta 5.82$.

The reaction in Entry 3 was performed using the same procedure described for Entry 4 in Table V. After 6 hours, GC analysis indicated that only a trace of the starting material remained and a 54% yield of 52 and 53 in a 43:57 ratio.

Unlike the 5-membered rings, cyclization to the 6-membered rings displayed little or no selectivity. Attempts to enhance the selectivity using triethylborane/air to initiate reaction at lower temperatures proved unproductive. Reactions performed at 80 °C proceeded with limited product formation, but at or below 25 °C the reactions failed to proceed to any appreciable extent, even after multiple initiations.

Each of the reactions in Table VI produced small amounts of the acyclic reduction product 54. This side product was isolated in 7% yield from the reaction in Entry 4 and was estimated by GC analysis to be present in similar quantities in the other reactions. The measured mass for 54 was consistent with the molecular formula $\text{C}_{10}\text{H}_{14}\text{O}_5$. The IR showed a $\text{C}==\text{C}$ band at 2237 cm$^{-1}$. The $^1$H NMR included a two-proton singlet at $\delta 4.03$ for the methylene between O and CO$_2$Me.
The opportunity to use the reducing agent and reaction conditions to control the stereoselectivity of E- or Z-exocyclic alkene formation from substrates 36 and 37 showed only limited success. For compound 36, modest selectivity for the E-isomer 49 resulted from tri(n-butyl)tin hydride, while tris(trimethylsilyl)silane favoured formation of the Z-isomer 50. For compound 37, tris(trimethylsilyl)silane produced a slight excess of the Z-isomer 53, while no selectivity was observed using tri(n-butyl)tin hydride.

Lowinger's substrates, page 23 of the Introduction, cyclized with higher selectivity than did substrates 36 and 37. Recall that the rationale offered for understanding the selectivity in Lowinger's substrates involved an examination of the steric interactions between the reducing agent and the radical intermediate.

Figure 11. An abbreviated version of Lowinger's rationale for reaction selectivity.

Tris(trimethylsilyl)silane favoured cyclization followed by reduction to give the Z-product. This suggested that non-bonded interactions between the methyl substituent and the tris(trimethylsilyl)silane resulted in a higher energy transition state A for reduction to produce the E-product. Thus non-bonded interactions between the methyl substituent and the carbomethoxy group are less severe than the methyl substituent and the tris(trimethylsilyl)silane reducing agent (see B).

On the other hand, tri(n-butyl)tin hydride favoured formation of the E-product. Isomerization of Z-alkene to E-alkene was believe to be the main influence on the high selectivity of the tri(n-butyl)tin hydride mediated reactions. However it is not clear what influence on the selectivity can be attributed to tri(n-butyl)tin hydride being a less sterically demanding reducing agent than tris(trimethylsilyl)silane. Non-bonded
interactions between the methyl substituent and the tri(n-butyl)tin hydride in A may be less severe than between the methyl substituent and the carbomethoxy group in B. Thus, a lower energy transition state for reduction to the E-product may result.

One suggestion to account for the poorer selectivity for reactions of substrates 36 and 37 is the size of the ring substituent. The ring substituted carbomethoxy group may provide less steric impediment to an approaching reducing agent than does the ring substituted methyl group. Such a suggestion is supported by the conformational free energies (A values) of cyclohexanes substituted by carbomethoxy, 1.2-1.3 kcal/mol, and by methyl, 1.74 kcal/mol. The larger A value for the methyl substituted cyclohexane suggests that it is a more sterically demanding substituent than the carbomethoxy group.

In addition to the steric bulk of the ring substituents, one must also consider the effects of the conformation on the selectivity (Figure 12). Hydrogen-transfer transition states in which the cyclic radical intermediate is in a conformation that has the ring substituent equatorial would be expected to promote exocyclic alkene selectivity. A1,3 strain between the ring substituent and an approaching reducing agent would likely be more severe for an equatorial compared to an axial ring substituent. An equatorial substituent would be situated closer to the forming C=H bond and thus, would have a greater influence on the relative H-transfer transition state energies. The lower selectivity for reduction of the 2-carbomethoxy tetrahydrofuran and tetrahydropyran systems may result from H-transfer transition states having the 2-carbomethoxy substituent in an axial-like conformation. The less severe non-bonded interactions between the axial ring substituent and the approaching reducing agent may reduce the relative H-transfer transitions state energies for formation of the E- and Z-alkenes.
Figure 12. Analysis of potential ring conformation effects on the reaction selectivity.

An experiment was designed to test the above hypothesis. The conformational free energy for 2-carbomethoxy substituted tetrahydropyran is 1.38 kcal/mol while that for 2-hydroxymethyl substituted tetrahydropyran is 2.89 kcal/mol. Replacement of the 2-carbomethoxy by 2-hydroxymethyl is expected to increase the preference for the allylic ring substituent to occupy an equatorial conformation and thus, may exhibit improved selectivity.

2.1.4 Synthesis of Methyl 8-Hydroxy-6-oxa-7-(phenylthio)-2-octynoate (59)

Following the procedure described in Section 2.1.1, 3-butyn-1-ol and 48 were coupled using zinc acetate to produce methyl 3-oxa-2-(phenylthio)-6-heptynoate (55). Compound 55 was reduced with lithium aluminum hydride to 3-oxa-2-(phenylthio)-6-heptyn-1-ol (56). The hydroxyl group of 56 was protected as its t-butyldimethylsilyl ether and the acetylene 57 was then acylated with methyl chloroformate as described in Section 2.1.1. Treatment of methyl 6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-2-nonynoate (58) with standard conditions for cleaving TBDMS ethers, tetrabutylammonium fluoride in tetrahydrofuran, resulted in immediate decomposition of the substrate to a black tar. Lower temperatures only delayed the decomposition.
Treatment of 58 with 2,4,6-trimethylpyridinium fluoride cleanly removed the silyl ether to provide near quantitative yield of compound 59.

\[
\begin{align*}
\text{38} & \quad + \quad \text{48} \quad \xrightarrow{i} \quad \text{55} \\
\text{56} & \quad \xrightarrow{iii} \quad \text{57} \\
\text{58} & \quad \xrightarrow{v} \quad \text{59}
\end{align*}
\]

**Scheme III.** i. Zn(OAc)$_2$·2H$_2$O, PhH, Δ, 60%; ii. LiAlH$_4$, THF, 0 °C, 90%; iii. TBDMSI, imidazole, DMF, 95%; iv. MeLi, CICO$_2$Me, THF, -20 °C, 79%; v. 2,4,6-trimethylpyridinium fluoride, CH$_2$Cl$_2$, 97%.

The IR of 59 showed a C=C stretch at 2242 cm$^{-1}$ as well as a broad OH absorption centered at 3448 cm$^{-1}$. The measured mass was consistent with C$_{14}$H$_{16}$O$_4$S formula. An interesting observation in the 400 MHz $^1$H NMR spectrum of 59 is that the methylene hydrogens at position 8 are not diastereotopic by NMR at this field. On the other hand, the methylene hydrogens at position 5 are each found at significantly different chemical shifts and are geminal coupled.

2.1.5 Cyclization of Compounds 58 and 59

During the synthesis of compound 59, several procedures to cleave the TBDMS ether, were investigated. Substrate 58 might react similarly to the free alcohol,
therefore it was treated under the radical cyclization conditions. The reaction was initiated by the addition of triethylborane and air to a solution of 58 and tris(trimethylsilyl)silane in refluxing benzene. The product 60 was isolated in 48% yield along with 14% of the starting substrate. No products resulting from abstraction of the phenylthio group were isolated.

The addition product 60 was presumed to have been produced through the following radical chain reaction. Tris(trimethylsilyl)silyl radical could add to the activated acetylene in substrate 58 to afford the vinyl radical intermediate 61. Abstraction of hydrogen from tris(trimethylsilyl)silane would produce compound 60 and tris(trimethylsilyl)silyl radical which would continue the chain reaction process.

Treatment of the alcohol 58 under the same conditions resulted in complete consumption of starting material and addition product 62 was isolated in 64% yield. The Z stereochemistry of 60 and 62 was assigned by the chemical shift of the vinyl protons. A trace of the E-isomer of 62 was isolated from reaction of 58. Deshielding
due to the cis carbomethoxy group resulted in a 0.2 ppm downfield shift of the vinyl protons in the E-isomer relative to those in 60 and 62.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{(TMS)}_3\text{SiH, PhH} \quad \rightarrow \\
\text{O} & \quad \text{Et}_3\text{B/air, } \Delta \quad \rightarrow \\
\text{OH} & \quad \text{MeO}_2\text{C} - \quad \text{Si(SiMe}_3)_3 \quad \text{SPh} \\
\text{59} & \quad \text{62 (64%)} \\
\end{align*}
\]

Reaction of 59 with tri(n-butyl)tin hydride afforded a 34% yield of the Z-addition product 63. All of the starting substrate was consumed in the reaction. The Z stereochemistry of the alkene was assigned by the vinyl hydrogen to tin coupling constant of 105 Hz.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{Bu}_3\text{SnH, PhH} \quad \rightarrow \\
\text{O} & \quad \text{Et}_3\text{B/air, } \Delta \quad \rightarrow \\
\text{OH} & \quad \text{MeO}_2\text{C} - \quad \text{SnBu}_3 \quad \text{SPh} \\
\text{59} & \quad \text{63 (34%)} \\
\end{align*}
\]

In each of the reactions, no products resulting from abstraction of the phenylthio group were isolated. These results show that tri(n-butyl)tin and tris(trimethylsilyl)silyl radicals add to the triple bond of these propargyl esters at a faster rate than they abstract the phenylthio group. Although this result was a little surprising based on the results with 36 and 37, it has literature precedent. Arya et al. have shown that in the reaction of 64 with tris(trimethylsilyl)silane, addition to give 65 can predominate over abstraction.\(^{56}\)

\[
\begin{align*}
\text{S} & \quad \text{(TMS)}_3\text{SiH, AIBN} \quad \rightarrow \\
\text{S} & \quad \text{PhMe, 80 °C} \quad \rightarrow \\
\text{Si(SiMe}_3)_3 & \quad \text{65 (72%)} \\
\text{64} & \\
\end{align*}
\]
In contrast, Yadav and Fallis did not report any competitive addition in the tri(n-butyl)tin hydride cyclization of 66.\(^{57}\)

Burke and Jung found that the stereoselectivity in the synthesis of 2,3-substituted tetrahydrofurans was improved when the 2-position was substituted by both an ester group and a methyl group.\(^{58}\) This selectivity has been rationalized by the lower energy of the chair-like transition state 68, with the methyl group in a pseudo-equatorial position. The nonbonded interactions with the pseudo-axial hydrogens and a t-butylerster group are less than for a methyl group and the pseudo-axial hydrogens. These results suggested that incorporation of methyl and ester substituents in a similar fashion in our systems might provide a means to test this proposal.
2.1.6 Synthesis of Dimethyl 7-Methyl-6-oxa-7-(phenylthio)-2-octynedioate (71) and Dimethyl 8-Methyl-7-oxa-8-(phenylthio)-2-nonynedioate (72)

Ester 48 was alkylated with methyl iodide to provide the intermediate 70 which was used immediately. The best yields of 71 and 72 were obtained when crude 70 was used in the zinc acetate promoted coupling reactions with the alcohols 44 and 45.
Scheme IV. i. LDA, MeI, THF, -78 °C; ii. 44, Zn(OAc)$_2$·2H$_2$O, PhH, Δ, 20% of 71; 45, Zn(OAc)$_2$·2H$_2$O, PhH, Δ, 19% of 72.

2.1.7 Cyclization of Compounds 71 and 72

Treatment of a solution of 71 and tris(trimethylsilyl)silane in refluxing benzene with triethylborane and air produced compounds 73 and 74 in 1:2.4 ratio as indicated by GC analysis. Compound 73 was isolated in 22% yield and compound 74 was isolated in 47% yield, which confirmed the ratio of isomers as determined by GC. Reaction of 71 under the same conditions but using tri(n-butyl)tin hydride in place of tris(trimethylsilyl)silane produced compounds 73 and 74 in 2.4:1 ratio as indicated by GC analysis. Compound 73 was isolated in 42% yield and compound 74 was isolated in 18% yield. Both of these cyclizations proceeded in good yield and, as expected, reaction with tris(trimethylsilyl)silane favoured formation of the Z-isomer 74 and reaction with tri(n-butyl)tin hydride favoured formation of the E-isomer 73. The low selectivity of the reactions was a surprise.
The stereochemistry of the exocyclic alkenes was assigned by analysis of their \(^1\)H and NOE NMR spectral data. The \(^1\)H NMR spectrum of compound 73 exhibited one-proton multiplets at \(\delta 3.06\) and at \(\delta 3.16\) assigned to the allylic methylene hydrogens. The analogous signal in the \(^1\)H NMR spectrum of compound 74 was a two-proton multiplet at \(\delta 2.73-2.93\). Comparison of these signals suggested that the lower field resonance for the methylene protons in compound 73 was a result of deshielding by the spatially adjacent carbomethoxy group. The NOE difference spectrum of compound 73 showed an NOE of the vinyl proton at \(\delta 5.97\) upon irradiation of the methyl protons at \(\delta 1.55\). In addition, irradiation of the vinyl proton at \(\delta 5.97\) produced an NOE of the methyl protons at \(\delta 1.55\). Similarly, irradiation of the methylene protons at \(\delta 2.73-2.93\) of compound 74 produced an NOE of the vinyl proton at \(\delta 5.92\). Here also, irradiation of the vinyl proton at \(\delta 5.92\) produced an NOE of the methylene protons at \(\delta 2.73-2.93\).

After 3 hours in refluxing benzene with tri(n-butyl)tin hydride and AIBN, heterocycle 74 was converted to a 96:4 mixture of 73 and 74. Heterocycle 73 was unchanged after treatment for 2 hours under these isomerizing conditions. This suggested that 73 was the thermodynamically more stable isomer and, that given enough time under the radical isomerizing conditions, all of the Z-isomer would be converted to the E-isomer.
Substrate 72 was exposed to the same conditions as compound 71. Reaction with tris(trimethylsilyl)silane produced a 44% yield of heterocycles 75 and 76. GC and $^1$H NMR analyses indicated a 5:95 ratio of 75 and 76. Compounds 75 and 76 could not be separated by chromatography.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} \\
\text{PhS Me} & \quad \text{CO}_2\text{Me} \\
\text{72} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} \\
\text{CO}_2\text{Me} & \quad \text{Me} \\
\text{75} & \quad \text{76}
\end{align*}
\]

Reaction with tri($n$-butyl)tin hydride produced a 6% yield of 75 and 76 in 64:36 ratio as indicated by GC analysis. One of the major products, isolated in 18% yield, was compound 77. This product resulted from addition of tri($n$-butyl)tin hydride across the triple bond of the propargyl ester and from reduction of the phenylthio substituent. The slow rate of cyclization to this 6-membered ring seems to have allowed reduction by tri($n$-butyl)tin hydride to compete with cyclization.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Me} \\
\text{SnBu}_3 & \quad \text{CO}_2\text{Me} \\
\text{77}
\end{align*}
\]

A 5:95 mixture of 75 and 76, tri($n$-butyl)tin hydride and AIBN was converted to a 95:5 mixture of 75 and 76 after refluxing in benzene for 1 hour.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} \\
\text{76} & \quad \text{CO}_2\text{Me} \\
\text{Bu}_3\text{SnH} & \quad \text{Me} \\
\text{PhH, } & \quad \text{75}
\end{align*}
\]

The stereochemistry of these exocyclic alkenes was again assigned from an analysis of their $^1$H and NOE NMR spectral data. The $^1$H NMR spectrum of compound
75 had a one-proton doublet of triplets at δ 3.79 and a one-proton multiplet at δ 2.10 assigned to the allylic methylene hydrogens and a three-proton singlet at δ 1.51 assigned to the methyl hydrogens. The 1H NMR spectrum of compound 76 exhibited one-proton multiplets at δ 1.78, 2.03, 2.30 and 2.52 and a three-proton singlet at δ 1.62. The lower field resonance of one of the allylic methylene hydrogens in compound 75 and the methyl hydrogens in compound 76 are a result of deshielding by the cis carbomethoxy group. The NOE difference spectrum of compound 75 exhibited an NOE of the vinyl proton at δ 5.87 upon irradiation of the methyl protons at δ 1.51. In addition, irradiation of the vinyl proton at δ 5.87 produced an NOE of the methyl protons at δ 1.51.

The selectivity of the tris(trimethylsilyl)silane mediated radical reaction of substrate 72 to the tetrahydropyran 76 was similar to that reported by Lowinger and Weiler for the formation of the Z-carbocycle shown on page 23 of the Introduction. It seems likely that in both cases the lowest energy transition state for hydrogen transfer to the cyclic radical intermediate was such that the allylic methyl substituent adopted an equatorial position. The methyl group acted to block one side of the double bond, which resulted in hydrogen transfer to the opposite side of the double bond to afford the Z-product.

The selectivity for formation of the tetrahydrofurans 73 and 74 from substrate 71 were lower than for the carbocycles of Lowinger and Weiler. The tri(n-butyl)tin hydride mediated cyclization of 71 was expected to be selective for the E-product 73, mainly due to isomerization of 74 to 73. The isomerization appears to have been slowed, perhaps due to the use of Et3B/air as initiator. We have observed that reactions initiated by Et3B/air tend to generate a quick burst of reactivity which diminishes over time, presumably dependent on the efficiency of the radical chain
reaction. On the other hand, Lowinger and Weiler used AIBN as initiator and afforded high $E$-isomer selectivity. The slow thermal degradation of AIBN to initiator radicals appears to be better suited to maintain the tri($n$-butyl)tin hydride mediated isomerization reaction.

The tris(trimethylsilyl)silane mediated cyclization of 71 would be expected to exhibit improved selectivity for the $Z$-isomer 74 if the reaction could be run at lower temperature. Lowinger and Weiler observed high $Z$-isomer selectivity for cyclizations run at -78 °C. However, our experiences with the slower reactivity of 36 at low temperatures suggested that 71 also would not react well at lower temperatures.

2.2 Photochemical Cyclization

Huval and Singleton have reported a method of coupling alkyl halides and vinyl or allyl halides.\textsuperscript{59} Irradiation of a solution of hexa($n$-butyl)ditin, the alkyl bromide 78, and the vinyl bromide 79 in benzene, afforded the coupled product 80. The coupling reaction is suggested to proceed through an addition-elimination mechanism, affording the coupled product in high yield and moderate stereoselectivity.

Earlier studies in our group have shown that an addition-elimination sequence may also be involved in the stereoselective production of exocyclic alkenes.\textsuperscript{44} The yield of desired exocyclic alkene was occasionally diminished by the formation of acyclic reduction products. This complication occurred in the reactions promoted by either tri($n$-butyl)tin hydride or tris(trimethylsilyl)silane (eq. 10).
The fact that in the photochemical method the radical chain carrier is derived from hexa(n-butyl)ditin rather than from tri(n-butyl)tin hydride suggested that the yield of cyclic products could be improved by eliminating a pathway to acyclic reduction products. Curran and Chang\textsuperscript{60} had shown that reaction of iodide 81 with tri(n-butyl)tin hydride provided only the reduced ester 82. In this case, radical cyclization could not compete with hydrogen transfer from tri(n-butyl)tin hydride. However, the hexa(n-butyl)ditin mediated cyclization of the iodide, followed by tri(n-butyl)tin hydride reduction gave the lactone 83. Thus elimination of the hydrogen atom source allowed the cyclization step to proceed. Application of Curran's procedure to effect the addition-elimination reaction proved unsatisfactory due to the large amount of by-products formed.\textsuperscript{44} However, the success of the Huval and Singleton method for effecting the addition-elimination reaction suggested the following study of the application of the photochemical radical reaction in radical cyclizations.
2.2.1 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3,7-Dibromo-2-heptenoate (90) and (91).

To test whether this method was applicable to radical cyclization, methyl (E)- and (Z)-3,7-dibromo-2-heptenoate (90) and (91) were prepared. This synthesis began with commercially available 5-butyn-1-ol (84). The hydroxyl group was protected by conversion to 5-(2-tetrahydropyranyloxy)-1-pentyne (85).

\[
\begin{align*}
\text{MeO}_2C &= \text{MeO}_2C \\
\text{O} &\rightarrow \text{O} \\
\text{THP} &\rightarrow \text{THP} \\
\text{84} &\rightarrow \text{85}
\end{align*}
\]

The alkyne was deprotonated and acylated with methyl chloroformate to afford methyl 7-(2-tetrahydropyranyloxy)-2-heptenoate (86). The hydroxy group was deprotected by hydrolysis of the acetal using acidic methanol to afford methyl 7-hydroxy-2-heptenoate (87). The alkyne function was hydrobrominated with hydrogen bromide in diethyl ether to afford methyl (E)- and (Z)-3-bromo-7-hydroxy-2-heptenoate (88) and (89), which were separated by chromatography. That the reaction had occurred was easily seen by the loss of the C=C in the IR and by the appearance of...

\[
\begin{align*}
\text{MeO}_2C &= \text{MeO}_2C \\
\text{O} &\rightarrow \text{O} \\
\text{THP} &\rightarrow \text{THP} \\
\text{84} &\rightarrow \text{85} \\
\text{86} &\rightarrow \text{87} \\
\text{88} &\rightarrow \text{89} \\
\text{90} &\rightarrow \text{91}
\end{align*}
\]
new vinyl signals in the $^1$H NMR at $\delta$ 6.31 for 88 and at $\delta$ 6.29 for 89. The stereochemistry of 88 and 89 was assigned by comparing the chemical shifts of the allylic protons. The allylic protons at $\delta$ 3.09 are deshielded by the cis ester group in 88. This deshielding is not experienced by the allylic protons of 89 which are at $\delta$ 2.60 due to their trans relationship to the ester group. The synthesis was completed by conversion of the hydroxy group to the bromide using triphenylphosphine and carbon tetrabromide to afford the cyclization substrates 90 and 91.

The photochemical cyclization was performed as follows. A 0.02 M solution of equimolar amounts of substrate 90 and hexa(n-butyl)ditin in benzene was added to a Pyrex tube. The reaction mixture was deoxygenated by bubbling nitrogen through the solution for 30 minutes and the reaction mixture was irradiated in a Rayonet reactor equipped with 300 nm lamps. The reaction was stopped after 8 hours of irradiation at which time GC and TLC analyses indicated little or no starting material remained. The reaction mixture was worked up according to the method of Curran and Chang. To the reaction mixture was added 2 equiv. of DBU followed by a solution of iodine in diethyl ether just until the iodine colour persisted. The solution was stirred for 10 minutes and then filtered through silica gel. Purification by radial chromatography afforded a 54% yield of methyl (cyclopentylidene)acetate (92). The results for the photochemical radical reactions of 90 and 91 are presented in Table VII. The higher yield for Entry 2 is likely due to improvements in the isolation and purification techniques. The measured mass of the photochemical product is C$_8$H$_{12}$O$_2$ which is consistent with structure 92. The $^1$H NMR spectrum of 92 shows a pair of two-proton broad triplets at $\delta$ 2.41 and $\delta$ 2.75, assigned to the allylic protons. The lower field signal at $\delta$ 2.75 is due to deshielding by the cis ester group. The remaining four ring hydrogens make up the multiplet centered at $\delta$ 1.68.
Having confirmed that this method is effective at promoting cyclizations, substrates were prepared in which the stereoselectivity of the method could be studied. Methyl (E)- and (Z)-(2-methylcyclopentylidene)acetate (93) and (94) had been synthesized previously in the group. These compounds had been fully characterized and had been shown to be separable on GC and TLC.

2.2.2 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3,7-Dibromo-2-octenoate (106) and (107)

Methyl (E)- and (Z)-3,7-dibromo-2-octenoate (106) and (107) were synthesized as outlined in Scheme VI. 2-Acetyl-γ-butyrolactone was converted to 5-bromo-2-pentanone (96) and then to 5-bromo-2-pentanone ethylene acetal (97) following the procedures of Cornish and Warren. Addition of compound 97 to a solution of lithium acetylide in dimethyl sulfoxide afforded 1-heptyn-6-one ethylene acetal (98).
Scheme VI. i. HBr, H₂O, Δ, 50%; ii. (HOCH₂)₂, p-TsOH-H₂O, PhMe, Δ, 82%; iii. LiCCH-EDA, DMSO, 78%; iv. PPTs, acetone, Δ, 77%; v. LiAlH₄, THF, 0 °C, 90%; vi. DHP, p-TsOH-H₂O, CH₂Cl₂, 92%; vii. MeLi, ClCO₂Me, THF, -20 °C, 94%; viii. p-TsOH-H₂O, MeOH, 89%; ix. HBr, Et₂O, 0 °C, 104 (34%), 105 (52%); x. CBr₄, P(Ph)₃, CH₂Cl₂, 106 (63%), 107 (48%).

The ketal 98 was hydrolyzed to 99 and reduced to 1-heptyn-6-ol (100). The hydroxyl group was protected as its tetrahydropyranly ether. The THP protecting group
introduced a second chiral center in the molecule, thus 101 is a mixture of two diastereomers. The $^1$H NMR of 101 shows a methyl doublet at $\delta$ 1.09 and at $\delta$ 1.20, both of which integrate to 1.5 hydrogens indicating equal amounts of the diastereomers. The acetylene in 101 was deprotonated and then acylated with methyl chloroformate to afford methyl 7-(2-tetrahydropyranoyloxy)-2-octynoate (102). The tetrahydropyranyl ether in 102 was hydrolyzed to give 103. Bubbling hydrogen bromide through a solution of 103 in diethyl ether afforded methyl (E)- and (Z)-3-bromo-7-hydroxy-2-octenoate (104) and (105), which were separated by chromatography. The stereochemistry of 104 and 105 was assigned by comparing the chemical shifts of the allylic protons. For 104, the allylic protons signal is centered at $\delta$ 3.07 due to deshielding by the cis ester group. The allylic protons in 105 at $\delta$ 2.55 do not experience this deshielding due to their trans relationship to the ester group. The synthesis of each of the dibromides 106 and 107 was completed by reacting each of the substrates 104 and 105 with carbon tetrabromide and triphenylphosphine.

Compounds 106 and 107 were subjected to the photochemical cyclization conditions and the results are presented in Table VIII.

**Table VIII.** Photochemical Cyclization of Compounds 106 and 107.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>$E:Z$ Ratio ($93:94)^a$</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="106" /></td>
<td>89:11</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="107" /></td>
<td>34:66</td>
<td>NA</td>
</tr>
</tbody>
</table>

$^a$ Isomer ratios were determined by GC analysis.

In each case the reaction was found to be incomplete after 8 hours of irradiation. Compound 106 exhibited reasonable stereoselectivity. Compound 107 afforded 93 and 94 with slightly poorer stereoselectivity. Interestingly, after only 5 hours of irradiation of
the $E:Z$ ratio was 28:72. GC analysis also indicated that compound 106 was produced from the reaction of substrate 107, which suggested that isomerization of the starting material was occurring under the reaction conditions. It was unclear whether the change in selectivity over time was a result of isomerization of the starting material, or of the products, or of both.

Tin radicals are known to abstract iodine faster than bromine from alkyl halides. Thus the Br was replaced with I in an effort to overcome the slow reactivity of substrates 106 and 107.

2.2.3 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3-Bromo-7-iodo-2-octenoate (108) and (109)

The iodides 108 and 109 were prepared by adding iodine to solutions of each of the alcoholic substrates 104 and 105 with triphenylphosphine and imidazole, as shown below.

\[
\text{Scheme VII. } \text{i. I}_2, \text{P(Ph)}_3, \text{imidazole, Et}_2\text{O, MeCN, 108 (82%), 109 (84%)}.\]

The photochemical cyclization of approximately 100 mg of iodide 108 or 109 was complete after 20 minutes of irradiation. Smaller scale reactions required less irradiation time. For example, reactions on approximately 10 mg required 5 minutes irradiation for completion. The results of the photochemical cyclization of 108 and 109 are presented in Table IX. Reaction of each substrate was highly stereoselective and the overall reaction was stereospecific, and provided good yield of the cyclic products.
Table IX. Photochemical Cyclization of Compounds 108 and 109.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>E:Z Ratio (93:94)\textsuperscript{a}</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="108" /></td>
<td>96:4</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="109" /></td>
<td>7:93</td>
<td>76</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isomer ratios were determined by GC analysis.

2.2.4 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3-Bromo-7-iodo-2-heptenoate (110) and (111)

For completeness, the primary iodide analogues of 90 and 91 were prepared as outlined in Scheme VIII. Each of the iodides 110 and 111 was prepared from the alcohols 88 and 89 as shown below.\textsuperscript{64}

![Scheme VIII](image)

\textsuperscript{64} I\textsubscript{2}, P(Ph)\textsubscript{3}, imidazole, Et\textsubscript{2}O, MeCN, 110 (98%), 111 (81%).

Methyl (E)- and (Z)-3-bromo-7-iodo-2-heptenoate (110) and (111) underwent photochemical cyclization to 92 as outlined in Table X. The primary iodides required shorter irradiation times and provided greater yields of 92 than did the analogous primary bromides.
Table X. Photochemical Cyclization of Compounds 110 and 111.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image of Cyclization Substrate 110" /></td>
<td><img src="image" alt="Image of Product 92" /></td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image of Cyclization Substrate 111" /></td>
<td><img src="image" alt="Image of Product 92" /></td>
<td>68</td>
</tr>
</tbody>
</table>

Having shown that 5-membered ring exocyclic alkenes could be stereospecifically produced by this methodology, the extension to the synthesis of 6-membered ring analogues was studied.

2.2.5 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3-Bromo-8-iodo-2-octenoate (120) and (121)

Methyl (E)- and (Z)-3-bromo-8-iodo-2-octenoate (120) and (121) were prepared as outlined in Scheme IX. The synthesis started with commercially available 1,5-pentandiol (112) which was converted into 5-bromo-1-pentanol (113). The hydroxyl group was protected and the bromide of 114 was displaced with lithium acetylide to afford 7-(2-tetrahydropyranyloxy)-1-heptyne (115). The alkyne was acylated to give methyl 7-(2-tetrahydropyranyloxy)-2-heptynoate (116). The hydroxyl group was deprotected and the alkyne 117 was hydrobrominated to give methyl (E)- and (Z)-3-bromo-7-hydroxy-2-heptenoate (118) and (119), which were separated by chromatography. Once again the stereochemistry of 118 and 119 was assigned by comparing the chemical shifts of the allylic protons. The lower field signal for 118 at δ 3.08 is due to deshielding by the cis ester group. The hydroxyl group of 121 and 122 was converted to the iodide.
The primary iodides 120 and 121 were cyclized as outlined in Table XI. The cyclizations required approximately 40 minutes irradiation and proceeded in 60-70% yield. The longer reaction time required for the formation of the 6-membered ring is a result of their slower rate of cyclization. The $^1$H NMR spectrum of the photochemical product shows a pair of two-proton triplets at $\delta$ 2.17 and $\delta$ 2.80, assigned the allylic methylene hydrogens. The lower field signal at $\delta$ 2.80 is due to deshielding by the cis ester group. The remaining six ring hydrogens are in the methylene envelope at $\delta$ 1.59. The measured mass of C$_9$H$_{14}$O$_2$ is consistent with the proposed structure 122.
Table XI. Photochemical Cyclization of Compounds 120 and 121.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>Product</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="120" alt="Image" /></td>
<td><img src="122" alt="Image" /></td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td><img src="121" alt="Image" /></td>
<td><img src="122" alt="Image" /></td>
<td>60</td>
</tr>
</tbody>
</table>

Secure with the fact that this methodology could produce 6-membered ring exocyclic alkenes, precursors were prepared to study the cyclizations to methyl (E)- and methyl (Z)-(2-methylcyclohexylidene)acetate (123) and (124). Here again, these compounds had been synthesized previously in the group, and had been separated and fully characterized.44

2.2.6 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3-Bromo-8-iodo-2-nonenoate (134) and (135)

Methyl (E)- and (Z)-3-bromo-8-iodo-2-nonenoate (134) and (135) were synthesized as outlined in Scheme X. The synthesis started with the conversion of 5-hexynol (125) to 6-bromo-1-hexene (126). Oxymercuration of the double bond followed by reductive cleavage of the oxymercurial afforded 6-bromo-2-hexanol (127).66
Scheme X.  i. Br₂, P(Ph)₃, CH₂Cl₂, 0 °C; ii. Hg(OAc)₂, NaOH, NaBH₄, THF, H₂O; iii. DHP, p-TsOH·H₂O, CH₂Cl₂, (46% for 3 steps); iv. LiCCH·EDA, DMSO, 74%; v. MeLi, ClCO₂Me, THF, -20 °C, 95%; vi. p-TsOH·H₂O, MeOH, 98%; vii. HBr, Et₂O, 0 °C, 132 (32%), 133 (53%); viii. I₂, P(Ph)₃, imidazole, Et₂O, MeCN, 0 °C, 134 (67%), 135 (75%).

The hydroxyl group of 127 was protected and the halide 128 was treated with a solution of lithium acetylide in dimethyl sulfoxide to afford (2-tetrahydropyranyloxy)-1-octyne (129) which was acylated to give methyl 8-(2-tetrahydropyranyloxy)-2-nonynoate (130). The tetrahydropyranyl ether was hydrolyzed to afford methyl 8-hydroxy-2-nonynoate (131). Bubbling hydrogen bromide through a solution of 131 in cold diethyl ether afforded a mixture of methyl (E)- and (Z)-3-bromo-8-hydroxy-2-nonynoate (132)
and (133), which were separated by chromatography. Compound 132 was assigned the E-isomer because the chemical shift of its allylic protons at δ 3.06 are deshielded by the cis ester group. The hydroxyl group was converted to the iodide by adding iodine to solutions of each of the substrates 132 and 133 with triphenylphosphine, thus completing the synthesis of compounds 134 and 135.

Results of the photochemical cyclization of 134 and 135 are presented in Table XII. Both substrates afforded good yields of cyclic products. Compound 134 displayed high stereoselectivity for the E-isomer. However, iodide 135 was unexpectedly selective for the E-isomer rather than for the Z-isomer.

Table XII. Photochemical Cyclization of Compounds 134 and 135.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>E:Z Ratio</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(123:124)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td><img src="image" alt="" /></td>
<td>99:1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="" /></td>
<td>75:25</td>
<td>84</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isomer ratios were determined by GC analysis.

Investigations were carried out to determine if isomerization of the starting substrate or products was effecting the stereoselectivity of the reaction. Table XIII shows the results of these isomerization studies. Reactions were run using the standard photochemical cyclization conditions and were monitored at the specified intervals using GC analysis. In each case, after 1 minute of irradiation, considerable starting substrate remained and no isomerized starting material was detected. After 5 minutes of irradiation, no starting material remained in either of the cases. It is significant to note that little, if any, change in the E:Z ratio occurred over the time
required to complete the conversion of each of the starting materials into product. In addition little change in the isomer ratios after 4 hours of irradiation suggested that product isomerization was not significantly effecting the results.

**Table XIII.** Photochemical Cyclization Isomerization Study.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>123:124 at Irradiation Time$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td><img src="image" alt="134" /></td>
<td>100:0</td>
</tr>
<tr>
<td><img src="image" alt="135" /></td>
<td>76:24</td>
</tr>
</tbody>
</table>

$^a$ Isomer ratios were determined by GC analysis.

$^b$ Time at which GC analysis indicated no starting material remained.

Having concluded that isomerization was not responsible for the reverse stereoselectivity in the photochemical cyclization of compound 135, additional investigations were carried out to understand this puzzling reactivity. Figure 13 shows a possible addition-elimination reaction mechanism for the stereoselective radical cyclization of 109 to 94. Iodine abstraction by tri(n-butyl)tin radical would generate the acyclic radical intermediate 136. Cyclization in a 5-exo fashion could produce the cyclic radical intermediate 137. It is likely that 136 also cyclizes through a transition state having the exocyclic alkene in a pseudoaxial position. Neither axial nor equatorial disposition of the radical center in 137 is expected to effect the stereoselectivity of the transformation. Structure 138 is the Newman projection of 137 viewed in the direction of the arrow in 140. Elimination of bromine is facilitated by C-C rotation such that the C-Br bond and the singly occupied molecular orbital are coplanar. The shortest C-C bond rotation to achieve this coplanarity is the 60° rotation to structure 139. Bromine elimination from 139 would afford the Z-product 94. This reaction mechanism suggests
that the stereoselectivity of the reactions is dependent on the rate of elimination of the bromine substituent. The faster a substituent eliminates, the less time there would be for free bond rotation and the higher the stereoselectivity.

Figure 13. Rationale for retention of stereochemistry in addition-elimination mechanism to rationalize the retention of stereochemistry in the radical cyclization of 109.

As described in the Introduction, Russell and coworkers\(^42\) had shown that iodine and tri(n-butyl)tin substituents can provide good stereoselectivity in intermolecular addition-elimination radical reactions. Therefore, both the vinyl iodide and vinyl tri(n-butyl)tin analogues of the vinyl bromides were prepared. The vinyl tri(n-butyl)tin analogues had been prepared previously in our group.\(^44\) These substrates were cyclized under different radical reaction conditions and it was of interest to compare these earlier results to those of the photochemical radical reaction.
2.2.7 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-7-lodo-3-tri(n-butyl)stannyl-2-octenoate (144) and (148) and Methyl (E)- and (Z)-8-lodo-3-tri(n-butyl)stannyl-2-nonenoate (145) and (149)

The vinyl stannanes were prepared as outlined in Scheme XI. The synthesis of compounds 102 and 130 was outlined earlier in Schemes VII and X. Following the method of Piers et al., the acetylenic esters 102 and 130 were selectively transformed into the E-vinyl stannanes 140 and 141. The E-stereochemistry was confirmed by a vinyl proton doublet with $J_{H,Sn} = 65$ Hz due to coupling to the cis tin. The tetrahydropyranyl ethers were hydrolyzed to afford the alcohols 142 and 143. The hydroxyl group was converted to the iodide of 144 and 145.

Scheme XI. i. $(Bu_3Sn)_2$, BuLi, CuBr-SMe$_2$, THF, $-78$ °C, 140 (90%), 141 (93%); ii. $p$-TsOH·2H$_2$O, MeOH, 142 (94%), 143 (94%); iii. I$_2$, P(Ph)$_3$, imidazole, Et$_2$O, MeCN, 0 °C, 144 (86%), 145 (89%), 148 (91%), 149 (75%); iv. Bu$_3$SnH, AIBN, PhH, $\Delta$, 146 (92%), 147 (93%).

Synthesis of the Z-vinyl stannanes was accomplished by treating each of the alcohols 142 and 143 with tri(n-butyl)tin hydride and AIBN. This resulted in
isomerization of the $E$-vinyl stannanes to the $Z$-vinyl stannanes 146 and 147. The
$Z$ stereochemistry was confirmed by a vinyl proton doublet $J_{H,Sn}=108$ Hz due to
coupling to the $trans$ tin. The hydroxyl group was converted to the iodide of 148 and
149.

The results of the photochemical cyclization of 144 and 148 are presented in
Table XIV. Both compounds afforded good yields of the cyclic products. Reaction of
the $E$-vinyl stannane 144 was stereoselective, but the stereoselectivity was not as high
as for the analogous $E$-vinyl bromide 108 (96:4). Reaction of the $Z$-vinyl stannane 148
displayed essentially no selectivity, which was in marked contrast to the analogous
$Z$-vinyl bromide 109 (7:93).

A noteworthy feature of the photochemical cyclization of the vinyl tin compounds
is that only 0.2 equiv of hexa($n$-butyl)ditin was required. Thus, these reactions must be
chain reactions. Chain-carrying tri($n$-butyl)tin radicals are liberated on formation of the
cyclic product. In the case of the vinyl halides, 1.0 equiv of hexa($n$-butyl)ditin was
required. Presumably the other products in these reactions are 2 equiv of the
corresponding tri($n$-butyl)tin halides.

Table XIV. Photochemical Cyclization of Compounds 144 and 148.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>$E:Z$ Ratio (93:94)$^a$</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="144" /></td>
<td>89:11</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="148" /></td>
<td>54:46</td>
<td>91</td>
</tr>
</tbody>
</table>

$^a$ Isomer ratios were determined by GC analysis.
The stereoselectivity of the photochemical cyclization of compounds 144 and 148 was similar to the selectivity reported by Lowinger using other radical reaction conditions. The results of these cyclizations of compound 144 are presented in Table XV. Essentially the same stereoselectivity was obtained for reactions mediated by hexa(n-butyl)ditin and by tris(trimethylsilyl)silane.

Table XV. Comparison of Cyclizations of Compound 144.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chain Transfer Reagent</th>
<th>Initiator</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>E:Z Ratio&lt;sup&gt;a&lt;/sup&gt; (93:94)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Bu&lt;sub&gt;3&lt;/sub&gt;Sn)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>h&lt;sub&gt;v&lt;/sub&gt;</td>
<td>25</td>
<td>PhH</td>
<td>89:11</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>25</td>
<td>PhH</td>
<td>88:12</td>
<td>91&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>-78</td>
<td>THF</td>
<td>88:12</td>
<td>90&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC analysis.
<sup>b</sup> Isolated yield.
<sup>c</sup> From reference 44.

The results of the cyclization of compound 148 under different conditions are presented in Table XVI. None of the conditions was effective at selectively producing the Z-exocyclic alkene 94. It is not clear why there was a small difference in selectivity between the hexa(n-butyl)ditin and tris(trimethylsilyl)silane mediated reactions.

Table XVI. Comparison of Cyclizations of Compound 148.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chain Transfer Reagent</th>
<th>Initiator</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>E:Z Ratio&lt;sup&gt;a&lt;/sup&gt; (93:94)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Bu&lt;sub&gt;3&lt;/sub&gt;Sn)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>h&lt;sub&gt;v&lt;/sub&gt;</td>
<td>25</td>
<td>PhH</td>
<td>54:46</td>
<td>91&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>25</td>
<td>PhH</td>
<td>42:58</td>
<td>86&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>-78</td>
<td>THF</td>
<td>46:54</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC analysis.
<sup>b</sup> Isolated yield.
<sup>c</sup> From reference 44.
The results of the photochemical cyclizations of compounds 145 and 149 are presented in Table XVII. Cyclization of compound 145 was stereoselective, and the selectivity was slightly lower than that of the analogous E-vinyl bromide 134 (99:1). Cyclization of compound 149 had poorer stereoselectivity and, as was the case for the analogous Z-vinyl bromide 135 (75:25), was selective for the E-exocyclic alkene 123.

Table XVII. Photochemical Cyclization of Compounds 145 and 149.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>E:Z Ratio</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(123:124)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td><img src="145.png" alt="" /></td>
<td>97:3</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td><img src="149.png" alt="" /></td>
<td>72:28</td>
<td>66</td>
</tr>
</tbody>
</table>

Once again, the photochemical cyclization provided stereoselectivity similar to that obtained by Lowinger using different reaction conditions for cyclization of compounds 145 and 149. The results for compound 145 are presented in Table XVIII. The selectivity is similar for reactions mediated by tris(trimethylsilyl)silane, tri((n-butyl)tin hydride and hexa((n-butyl)d)itin.
Table XVIII. Comparison of Cyclizations of Compounds 145.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chain Transfer Reagent</th>
<th>Initiator</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>E:Z Ratio&lt;sup&gt;a&lt;/sup&gt; (123:124)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Bu&lt;sub&gt;3&lt;/sub&gt;Sn)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>h&lt;sub&gt;v&lt;/sub&gt;</td>
<td>25</td>
<td>PhH</td>
<td>97:3</td>
<td>62&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>25</td>
<td>PhH</td>
<td>100:0</td>
<td>82&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>25</td>
<td>PhH</td>
<td>100:0</td>
<td>70&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC analysis.
<sup>b</sup> Isolated yield.
<sup>c</sup> From reference 44.

The results for compound 149 are presented in Table XIX. Once again, similar stereoselectivity was obtained from reactions mediated by each of the chain transfer reagents.

Table XIX. Comparison of Cyclizations of Compound 149.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chain Transfer Reagent</th>
<th>Initiator</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>E:Z Ratio&lt;sup&gt;a&lt;/sup&gt; (123:124)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Bu&lt;sub&gt;3&lt;/sub&gt;Sn)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>h&lt;sub&gt;v&lt;/sub&gt;</td>
<td>25</td>
<td>PhH</td>
<td>72:28</td>
<td>66&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(TMS)&lt;sub&gt;3&lt;/sub&gt;SiH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>25</td>
<td>PhH</td>
<td>77:23</td>
<td>81&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Bu&lt;sub&gt;3&lt;/sub&gt;SnH</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;B/air</td>
<td>25</td>
<td>PhH</td>
<td>75:25</td>
<td>73&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by GC analysis.
<sup>b</sup> Isolated yield.
<sup>c</sup> From reference 44.

2.2.8 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3,7-Diiodo-2-octenoate (150) and (154) and Methyl (E)- and (Z)-3,8-Diiodo-2-nonenoate (151) and (155)

The synthesis of the E-vinyl iodides 150 and 151 is outlined in Scheme XII. Treatment of each of the E-vinyl stannanes 144 and 145 with iodine afforded the E-vinyl iodides 150 and 151. The analogous E-vinyl bromides 108 and 125, whose syntheses were described in Schemes VII and X, respectively, could alternatively be prepared from the E-vinyl stannanes 144 and 145 by reaction with bromine in methylene chloride.
The synthesis of the Z-vinyl iodides is outlined in Scheme XIII. Synthesis of the acetylenic esters 103 and 131 was outlined in Schemes VI and X. The hydroxyl group was converted to the iodide by adding iodine to solutions of each of the substrates 103 and 131 with triphenylphosphine and imidazole. The acetylenic esters 152 and 153 were then treated with sodium iodide in acetic acid to complete the synthesis of the Z-vinyl iodides 154 and 155.

The results of the photochemical cyclizations of compounds 150 and 154 are presented in Table XX. Reaction of the E-vinyl iodide 150 was stereoselective but was not as selective as the analogous E-vinyl bromide 108 (96:4). Reaction of the Z-vinyl iodide 154 also was stereoselective, however it too was less selective than was the analogous Z-vinyl bromide 109 (7:93).
The results of the photochemical cyclizations of compounds 151 and 155 are presented in Table XXI. Reaction of the E-vinyl iodide 151 was stereoselective, but the selectivity was considerably lower than for the analogous E-vinyl bromide 134 (99:1). Reaction of the Z-vinyl iodide 155 displayed high stereoselectivity unlike either the Z-vinyl bromide 135 (75:25) or the Z-vinyl stannane 149 (72:28).
Table XXI. Photochemical Cyclization of Compounds 151 and 155.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>E:Z Ratio</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(123:124)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="" /></td>
<td>66:34</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="" /></td>
<td>8:92</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isomer ratios determined by GC analysis.

The results of the photochemical cyclization of the bromo, iodo and stannyl compounds are summarized in Tables XXII and XXIII. The reactions have been arranged in order of decreasing stereoselectivity with each of the types of vinyl substituent.
Table XXII. Photochemical Cyclization of Cyclopentyl Precursors

\[
\text{MeO}_2\text{C-CH=CH}X \xrightarrow{(\text{Bu}_3\text{Sn})_2} \text{h}\nu \xrightarrow{} \text{CHCO}_2\text{Me} \\
\text{93/94}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Vinyl Substituent (X)</th>
<th>Substrate Stereochemistry</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108</td>
<td>Br</td>
<td>E</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>I</td>
<td>E</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>144</td>
<td>Bu\textsubscript{3}Sn</td>
<td>E</td>
<td>89:11</td>
</tr>
<tr>
<td>4</td>
<td>109</td>
<td>Br</td>
<td>Z</td>
<td>7:93</td>
</tr>
<tr>
<td>5</td>
<td>154</td>
<td>I</td>
<td>Z</td>
<td>15:85</td>
</tr>
<tr>
<td>6</td>
<td>148</td>
<td>Bu\textsubscript{3}Sn</td>
<td>Z</td>
<td>54:46</td>
</tr>
</tbody>
</table>
Table XXIII. Photochemical Cyclization of Cyclohexyl Precursors

Each of the exocyclic alkenes 93, 94, 123 and 124 could be stereoselectively produced with 84-98% diastereomeric selectivity. No one vinyl substituent was suitable for the selective synthesis of all of the exocyclic alkenes. The vinyl bromides 108, 109 and 125 were the most selective at producing compounds 93, 94 and 123, respectively. Only the vinyl iodide 155 was selective at producing compound 124. No rationale has been found to adequately account for why the selectivity varied so greatly for the substituents in the different substrates.

Further experiments were performed in an attempt to understand how to control the stereochemistry of this cyclization. As was mentioned earlier, the stereoselectivity of the reaction was thought to result from elimination of the "vinyl" substituent at a rate that exceeds the rate of rotation of the exocyclic carbon-carbon bond in the cyclic radical intermediate. In this way, the stereochemistry of the double bond is retained in the product. The above results obtained by changing the vinyl substituent in an effort to increase the rate of elimination prompted us to consider another tactic. It was thought that the rate of elimination would be increased if the radical intermediate was
destabilized. A carbon radical adjacent to a carbonyl is more stable than is one adjacent to a methylene. Therefore, substrates were prepared in which the ester group was converted to hydroxymethylene and to acetoxyethylene groups. Their synthesis is outlined in Scheme XIV.

2.2.9 Synthesis and Photochemical Cyclization of (E)- and (Z)-3-Bromo-7-iodo-2-octen-1-ol (156) and (158) and (E)- and (Z)-1-Acetoxy-3-bromo-7-iodo-2-octene (157) and (159)

The ester group in the vinyl bromides 108 and 109 and in the vinyl stannanes 144 and 148 was reduced with diisobutylaluminum hydride to afford the corresponding allylic alcohols. Treatment of each of the alcohols with acetic anhydride and pyridine produced the allylic acetates 157, 159, 161 and 164. Conversion of the vinyl stannanes 161 and 164 to the vinyl iodides 162 and 165 was accomplished by reaction with iodine.
Scheme XIV.  i. DIBAL, CH₂Cl₂, -78 °C, 84-97%; ii. Ac₂O, py, CH₂Cl₂, 86-97% iii. I₂, CH₂Cl₂, 86-96%.
The results of the photochemical cyclizations of the allylic alcohols to the exocyclic alkenes \(166\) and \(167\) are presented in Table XXIV. Included in the Table are the results of the cyclization of the analogous ester substrates for comparison. The cyclic products were purified by chromatography but could not be separated. Isomer ratios were determined by integration of the methyl proton doublets in the \(\text{\textsuperscript{1}}\text{H}\) NMR spectra. Structural assignment of the exocyclic alkenes was made by comparison with the \(\text{\textsuperscript{1}}\text{H}\) NMR spectrum of a pure sample of each of compounds \(166\) and \(167\) which were obtained by the lithium aluminum hydride reduction of the esters \(93\) and \(94\).

In general the yields of the cyclizations were lower for the alcohols than for the esters, with the exception of the \(E\)-vinyl stannane \(160\). Reactions of the \(E\)-substrates \(156\) and \(160\) were highly stereoselective. Compound \(163\) showed a modest preference for the \(Z\)-product \(167\), while reaction of compound \(158\) was nonselective. Comparison of the product \(E:Z\) ratios revealed that the vinyl bromide substituent provided greater selectivity in the ester substrates than in the alcohol substrates. Conversely, the vinyl stannane substituent provided greater selectivity in the alcohol substrates than in the ester substrates.
Table XXIV. Photochemical Cyclization of Allylic Alcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>E:Z (166:167)(^a) Isolated Yield</th>
<th>Analogous Ester E:Z (93:94)(^a) Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="156.png" alt="Image" /></td>
<td>92:8</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>96:4</td>
</tr>
<tr>
<td></td>
<td><img src="158.png" alt="Image" /></td>
<td>50:50</td>
<td>7:93</td>
</tr>
<tr>
<td>2</td>
<td><img src="160.png" alt="Image" /></td>
<td>94:6</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td><img src="160.png" alt="Image" /></td>
<td>94:6</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td><img src="163.png" alt="Image" /></td>
<td>33:67</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>91%</td>
</tr>
</tbody>
</table>

\(^a\) Isomer ratios determined by NMR analysis.

The results of the photochemical cyclization of the allylic acetates to the exocyclic alkenes 168 and 169 are presented in Table XXV. Once again, the cyclization results of the analogous esters have been included for comparison. Here again, the cyclic products 168 and 169 could not be separated by chromatography, and isomer ratios were determined by integration of the methyl proton doublets in the \(^1\)H NMR spectra. Structural assignment of the exocyclic alkenes was made by comparison
with the $^1$H NMR spectrum of a pure sample of each of 168 and 169 which were obtained by acetylation of compounds 166 and 167.

In general the yields of cyclic products were similar for the acetate and the ester substrates, with the only difference being about a 10% decrease in yield for reaction of the Z-acetates. As was the case with the allylic alcohols, comparison of the product $E$:Z ratios revealed that the vinyl bromide substituent provided greater selectivity in the ester substrates than in the allylic acetates. However, similar selectivity was exhibited by reaction of the allylic acetate and ester substrates bearing the vinyl iodide substituent.

**Table XXV.** Photochemical Cyclization of Allylic Acetates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization Substrate</th>
<th>$E$:Z (168:169)$^a$ Isolated Yield</th>
<th>Analogous Ester $E$:Z (93:94)$^a$ Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="157" /></td>
<td>91:9</td>
<td>96:4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77%</td>
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$^a$ Isomer ratios determined by NMR analysis.
2.3 Conclusions

Radical cyclization of an α,β-alkynyl ester led to the formation of exocyclic alkenes. The alkene stereochemistry was controlled by the choice of radical reducing agent and by the substituents α to the exocyclic double bond. In general, tris(trimethylsilyl)silane reactions were stereoselective for the Z-isomer whereas tri(n-butyl)tin hydride favoured the E-isomer. Each of the tetrahydrofuran derivatives, 49, 50, 75 and 76 were produced with moderate stereoselectivity. The tetrahydropyran derivatives 52 and 53 were synthesized with little or no selectivity. The doubly substituted heterocycles 77 and 78 were produced stereoselectively, although 77 was synthesized by tri(n-butyl)tin hydride promoted isomerization of 78. A rationalization based on ring conformation was provided to understand the substituent effects on the reaction stereoselectivity.

Radical cyclizations to (E)- and (Z)-bromo, iodo, and tri(n-butyl)stannyl substituted alkenes afforded exocyclic alkenes, in some cases with high stereoselectivity. In general, the bromine substituted compounds gave the highest stereoselectivity with the exception of cyclization to the Z-cyclohexane derivative (124), for which the iodine substituent was required.
CHAPTER 3
EXPERIMENTAL

3.1 General

Elevated temperature reactions were performed in a silicone oil bath heated to the desired temperature. Cold temperature baths were prepared as follows: -78 °C (dry ice, acetone), -20 °C (27 g of CaCl₂/100 mL of water, dry ice), 0 °C (ice, water).

Anhydrous reaction solvents were obtained by distillation. Diethyl ether and tetrahydrofuran (THF) were distilled either from sodium or from lithium aluminum hydride. Benzene was distilled from sodium. Methylene chloride was distilled from calcium hydride. Dimethyl sulfoxide was distilled at reduced pressure from calcium hydride. A reaction solvent that was treated as described above prior to use has been denoted a dry solvent, otherwise the solvent was used as received from the supplier. The low boiling fraction (35-60 °C) of petroleum ether (pet. ether) was used. Benzene was deoxygenated by bubbling nitrogen through the solvent for 30 min. All reactions that used dry solvent were performed under a nitrogen atmosphere using oven-dried or flame-dried glassware.

Reagents were purified according to the procedure given in the literature. Unless otherwise noted, reagents were purchased from the Aldrich Chemical Co. Alkylithium reagents were standardized by titration against diphenylacetic acid in THF at 0 °C. Tri(n-butyl)tin hydride was either purchased from the Aldrich Chemical Co. or was prepared following the procedure of Kuivila and Beumel. Tri(n-butyl)tin hydride and hexa(n-butyl)ditin were periodically redistilled when they had become cloudy white. Copper(I) bromide-dimethyl sulfide complex was prepared following the procedure of House et al.

Photochemical radical reactions were performed in a Rayonet Reactor equipped with 16 bulbs having an emitted wavelength of >300 nm.

Analytical gas-liquid chromatography (GC) was performed on a Hewlett-Packard model 5880A gas chromatograph, equipped with a split mode capillary injection system and a flame ionization detector. The stationary phase consisted of either an OV-101 or a DB-210 capillary column of dimensions 0.22 mm x 12 m. Helium was used as the
carrier gas. GC analyses were performed either isothermally, or with the following temperature program: 100 °C for 2 min., then a temperature increase to 200 °C at a rate of 20 °C per min., and a final time of 6 min at 200 °C.

Solutions of reaction mixture in solvent were dried by the addition of anhydrous magnesium sulfate. The concentration or evaporation of solvents under reduced pressure refers to the use of a Buchi rotary evaporator. A brine solution refers to a saturated NaCl solution.

Flash chromatography was performed using silica gel 60, 230-400 mesh, supplied by E. Merck Co. In most cases, a solvent system was chosen such that the desired product had an Rf of approximately 0.30-0.35 on TLC. Radial chromatography was performed using a Harrison Chromatotron™ model 8924. The adsorbent used was silica gel 60, PF254 with gypsum binder, supplied by EM Science. In most cases, a solvent system was chosen such that the desired product had an Rf of approximately 0.20-0.25 on TLC.

In most cases, the Kugelrohr distillation oven temperatures are not representative of the boiling point of the compound due to the method of distillation. Since many of the compounds would be unstable to prolonged heating, the following technique was employed. The pressure on the compound was reduced in a Kugelrohr tube and the system was held at room temperature for at least 15 min. The compound was then introduced into a preheated Kugelrohr oven and rapidly distilled into an ice cooled receiver.

Infrared (IR) spectra were recorded on a Bomem Michelson 100 FT-IR spectrometer using internal calibration. IR spectra were taken on either a neat liquid or a deuteriochloroform solution, between two 3 mm NaCl plates.

Proton nuclear magnetic resonance (1H NMR) spectra were recorded in deuteriochloroform solutions on a Bruker AC-200 (200 MHz), or a Bruker WH-400 (400 MHz). Chemical shifts are given in parts per million (ppm) on the δ scale, using chloroform (δ 7.24 ppm) as internal standard. Signal multiplicity, coupling constants, and integration ratios are indicated in parentheses. The reported signal multiplicity has been simplified for equivalent J couplings involving diastereotopic hydrogens. For example, a (dd, J = 6.2 & 6.2 Hz) has been assigned as a (t, J = 6.2 Hz). The tin-
proton coupling constants ($J_{\text{Sn-H}}$) are given as an average of the coupling constants for the $^{117}\text{Sn}$ and the $^{119}\text{Sn}$ isotopes, and are not included in determining the multiplicity of a signal.

Low resolution mass spectra (LRMS) in electron ionization (EI) mode were recorded on a Kratos-AEI model MS 50 spectrometer. LRMS in chemical ionization (Cl) mode were recorded on either a Kratos MS 80 spectrometer or a Kratos Concept II HQ spectrometer. LRMS in desorption chemical ionization (DCI) mode were recorded on a Delsi Nermag R10-10 C spectrometer. Only peaks with greater than 20% relative intensity or those which were analytically useful were reported. For molecules and fragments containing a tin atom, only the $^{120}\text{Sn}$, $^{118}\text{Sn}$ and $^{116}\text{Sn}$ isotopes have been reported.

High resolution mass spectra (HRMS) in EI mode were recorded on a Kratos-AEI model MS 50 spectrometer. HRMS in CI mode were recorded on either a Kratos MS 80 spectrometer or a Kratos Concept II HQ spectrometer.

Ultraviolet spectra were recorded on a Perkin Elmer Lambda-4B UV/vis spectrometer.

Microanalyses were done at the microanalytical laboratory at the University of British Columbia on either a Carlo Erba Elemental Analyzer Model 1106 or a Fisons CHN-O Elemental Analyzer Model 1108.
3.2 Dimethyl 6-oxa-7-(phenylthio)-2-octynedioate (36)

![Chemical Structure]

A solution of methyl 5-hydroxy-2-pentynoate (44) (0.51 g, 4.0 mmol), methyl chloro(phenylthio)acetate (48) (0.43 g, 2.0 mmol) and zinc acetate dihydrate (0.53 g, 2.4 mmol) in 10 mL of dry, deoxygenated benzene was refluxed for 6 hours through a Dean Stark apparatus containing anhydrous CaSO₄. The reaction mixture was cooled to room temperature, filtered and concentrated to a yellow oil which was purified by flash chromatography, eluting with 15% ethyl acetate / pet. ether to afford 0.34 g (56%) of 36 as a yellow oil.

IR (CDCl₃): 2942, 2240, 1748, 1714, 1436, 1266, 1075 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 2.67 (t, J = 6.7 Hz, 2 H), 3.64 (s, 3 H), 3.72 (s, 3 H), 3.74 (m, 1 H), 4.04 (dt, J = 9.2 & 7.0 Hz, 1 H), 5.24 (s, 1 H), 7.30 (m, 3 H), 7.47 (m, 2 H);

¹³C NMR (50 MHz, CDCl₃) δ: 19.78, 52.50, 52.62, 65.24, 73.96, 85.10, 85.42, 128.79, 129.07, 131.00, 133.94, 153.84, 167.49;

LRMS (El) m/z (relative intensity): 249 (M⁺-CO₂CH₃, 39), 109 (28), 53 (100);
(DCI(+), ammonia) m/z (relative intensity): 326 (M⁺+NH₄, 24), 88 (100);
HRMS (El) m/z calcd for C₁₅H₁₆O₅S: 308.0718, found: 308.0712;


3.3 Dimethyl 7-oxa-8-(phenylthio)-2-nonynedioate (37)

![Chemical Structure]

Methyl 6-hydroxy-2-hexynoate (45) (0.57 g, 4.0 mmol) was converted to 37 following the procedure outlined in Section 3.2. The crude yellow oil was purified by
flash chromatography, eluting with 17% ethyl acetate / pet. ether to afford 0.28 g (44%) of 37 as a colourless oil.

IR (neat): 2934, 2237, 1754, 1715, 1437, 1261, 1195, 1167, 1112, 1077, 749 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.89 (qn, J = 6.1 Hz, 2H), 2.43 (t, J = 6.1 Hz, 2H), 3.60 (dt, J = 9.6 & 6.1 Hz, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 3.97 (dt, J = 9.6 & 6.1 Hz, 1H), 5.19 (s, 1H), 7.31 (m, 3H), 7.47 (m, 2H);

¹³C NMR (50 MHz, CDCl₃) δ: 15.55, 27.28, 52.44, 52.57, 66.81, 73.30, 85.21, 88.60, 128.70, 129.03, 131.27, 133.94, 154.08, 167.83;

LRMS (El) m/z (relative intensity): 322 (M⁺, 26), 263 (82), 84 (100);

(DCI(+), ammonia) m/z (relative intensity): 340 (M⁺+NH₄⁺, 100), 323 (M⁺+1· 33), 88(100);

HRMS (El) m/z calcd for C₁₆H₁₈O₅S: 322.0875, found: 322.0871;


3.4 4-(2-Tetrahydropyranloxy)-1-butyne (40)

\[
\text{==\text{O}}_{\text{O}}\]

Dihydropyran (7.80 mL, 85.5 mmol) was added dropwise to a solution of 3-butyne-1-ol (38) (5.00 g, 71.3 mmol) and p-toluenesulfonic acid monohydrate (0.68 g, 3.6 mmol) in 350 mL of dry methylene chloride. The reaction mixture was stirred overnight and then worked up by washing with saturated NaHCO₃ solution and with brine. The organic layer was dried, filtered and concentrated by rotary evaporation to afford a brown oil which was purified by flash chromatography, eluting with 6% ethyl acetate / pet. ether, to afford 9.73 g (88%) of 40 as a colourless oil.

IR (CDCl₃): 3308, 2945, 2876, 2242, 1201, 1128, 1070, 1032 cm⁻¹;
1H NMR (200 MHz, CDCl₃) δ: 1.46-1.88 (m, 6H), 1.96 (t, J = 2.7 Hz, 1H), 2.48 (dt, J = 2.7 & 7.1 Hz, 2H), 3.52 (m, 2H), 3.86 (m, 2H), 4.63 (m, 1H);
13C NMR (50 MHz, CDCl₃) δ: 19.36, 19.91, 25.38, 30.51, 62.18, 65.49, 69.15, 81.40, 98.74;
LRMS (EI) m/z (relative intensity): 153 (M⁺-1, 13), 125 (20), 85 (100), 67 (23), 53 (48), 41 (39);
HRMS (EI) m/z calcd for C₉H₁₃O₂ (M⁺-1): 153.0916, found 153.0912;

3.5  5-(2-Tetrahydropyranloxy)-1-pentyne (41)

![Structure of 5-(2-Tetrahydropyranloxy)-1-pentyne (41)](image)

4-Pentyn-1-ol (39) (4.00 g, 47.6 mmol) was converted to 41 following the procedure outlined in Section 3.4. The crude brown oil was purified by flash chromatography, eluting with 7% ethyl acetate / pet. ether to afford 7.14 g (89%) of 41 as a colourless oil.

IR (CDCl₃): 3308, 2945, 2873, 2242, 1136, 1068, 1032 cm⁻¹;
1H NMR (400 MHz, CDCl₃) δ: 1.45-1.70 (m, 6H), 1.80 (qn, J = 7.0 Hz, 2H), 1.91 (t, J = 2.6 Hz, 1H), 2.28 (dt, J = 2.7 & 7.0 Hz, 2H), 3.47 (m, 2H), 3.81 (m, 2H), 4.57 (m, 1H);
13C NMR (50 MHz, CDCl₃) δ: 15.29, 19.46, 25.43, 28.66, 30.61, 62.11, 65.72, 68.41, 83.91, 98.73;
LRMS (EI) m/z (relative intensity): 167 (M⁺-1, 4), 85 (100), 67 (57), 41 (75);
HRMS (EI) m/z calcd for C₁₀H₁₅O₂ (M⁺-1): 167.1072, found: 167.1072;
3.6 Methyl 5-(2-tetrahydropyranyloxy)-2-pentynoate (42)

A solution of 4-(2-tetrahydropyranyloxy)-1-butyne (40) (4.05 g, 26.3 mmol) in 200 mL of dry THF was cooled to -78 °C and methyllithium (22.5 mL of 1.4 M in hexanes, 31.5 mmol) was added dropwise. The resulting solution was stirred at -78 °C for 10 min., methyl chloroformate (2.43 mL, 31.5 mmol) was added dropwise and stirring was continued for 1 hour. The reaction mixture was warmed to room temperature and concentrated by rotary evaporation. The crude material was dissolved in 400 mL of diethyl ether and washed consecutively with water, saturated KHCO₃ solution and brine, and then dried. The solution was filtered and concentrated to a yellow oil which was purified by flash chromatography, eluting with 12% ethyl acetate / pet. ether to afford 4.87 g (87%) of 42 as a colourless oil.

IR (CDCl₃): 2949, 2878, 2238, 1711, 1436, 1265, 1129, 1074, 1033 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.46-1.86 (m, 6H), 2.62 (t, J = 7.0 Hz, 2H), 3.55 (m, 2H), 3.52 (m, 2H), 3.74 (s, 3H), 3.85 (m, 2H), 4.60 (m, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 19.26, 20.28, 25.36, 30.44, 52.58, 62.20, 64.37, 73.51, 86.65, 98.82, 154.04;

LRMS (El) m/z (relative intensity): 211 (M⁺-1, 8), 125 (20), 85 (100), 41 (20);

HRMS (El) m/z calcd for C₁₁H₁₅O₄ (M⁺-1): 211.0970, found: 211.0974;


3.7 Methyl 6-(2-tetrahydropyranyloxy)-2-hexynoate (43)

5-(2-Tetrahydropyranyloxy)-1-pentyne (41) (6.37 g, 37.9 mmol) was converted to 43 following the procedure outlined in Section 3.7. The crude yellow oil was purified by
flash chromatography, eluting with 12% ethyl acetate / pet. ether to afford 6.75 g (79%) of 43 as a colourless oil.

IR (CDCl₃): 2948, 2874, 2237, 1710, 1436, 1265, 1033 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.45-1.75 (m, 6H), 1.83 (qn, J = 7.5 Hz, 2H), 2.46 (t, J = 7.5 Hz, 2H), 3.47 (m, 2H), 3.74 (s, 3H), 3.83 (m, 2H), 4.57 (m, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 15.68, 19.48, 25.42, 27.82, 30.60, 52.53, 62.26, 65.52, 72.99, 89.23, 98.85, 154.19;

LRMS (El) m/z (relative intensity): 225 (M⁺-1, 0.3), 167 (6), 111 (25), 85 (100), 41 (42);

HRMS (El) m/z calcld for C₁₂H₁₇O₄ (M⁺-1): 225.1127, found: 225.1135;

Anal. Calcd for C₁₂H₁₈O₄: C, 63.68; H, 8.02. Found: C, 63.59; H, 7.89.

3.8 Methyl 5-hydroxy-2-pentynoate (44)

Methyl 5-(2-tetrahydropyranyloxy)-2-pentynoate (42) (3.54 g, 16.7 mmol) was dissolved in 250 mL of methanol and p-toluenesulfonic acid monohydrate (0.16 g, 0.84 mmol) was added. The reaction mixture was stirred for 2 hours and then concentrated by rotary evaporation. The crude material was dissolved in 500 mL of diethyl ether, washed with saturated KHCO₃ solution and then dried. The solution was filtered and concentrated to a colourless oil which was purified by flash chromatography, eluting with 33% ethyl acetate / pet. ether to afford 1.78 g (83%) of 44 as a colourless oil.

IR (CDCl₃): 3615, 2955, 2239, 1712, 1436, 1266, 1077, 1048 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 2.56 (t, J = 6.2 Hz, 2 H), 2.67 (s, 1H), 3.72 (s, 3H), 3.75 (t, J = 6.2 Hz, 2 H);

¹³C NMR (50 MHz, CDCl₃) δ: 22.92, 52.70, 59.91, 73.94, 86.86, 154.18;

LRMS (El) m/z (relative intensity): 128 (M⁺, 3), 110 (22), 98 (60), 79 (100), 66 (38), 44 (36);
HRMS (El) m/z calcd for C₆H₈O₃: 128.0473, found: 128.0474;

3.9 **Methyl 6-hydroxy-2-hexynoate (45)**

![Chemical structure of Methyl 6-hydroxy-2-hexynoate](image)

Methyl 6-(2-tetrahydropyranoyloxy)-2-hexynoate (43) (6.75 g, 29.8 mmol) was converted to 45 following the procedure outlined in Section 3.9. The crude colourless oil was purified by flash chromatography, eluting with 30% diethyl ether / pet. ether to afford 3.56 g (84%) of 45 as a colourless oil.

IR (CDCl₃): 3624, 2952, 2236, 1710, 1436, 1265, 1063 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.79 (s, 1H), 1.80 (qn, J = 7.0 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 3.72 (s, 3H), 3.72 (s, 3H),

¹³C NMR (50 MHz, CDCl₃) δ: 15.09, 30.15, 52.59, 60.77, 72.95, 89.29, 154.27;

LRMS (El) m/z (relative intensity): 142 (M⁺ 27), 111 (84), 84 (38), 69 (100);

HRMS (El) m/z calcd for C₇H₁₀O₃: 142.0630, found: 142.0631;

3.10 **Methyl (phenylthio)acetate (47)**

![Chemical structure of Methyl (phenylthio)acetate](image)

Hydrogen chloride was bubbled for 30 seconds through a room temperature solution of (phenylthio)acetic acid (5.04 g, 30.0 mmol) in 125 mL of dry methanol. The reaction vessel was fitted with a drying tube and stirred overnight at room temperature. The methanol was evaporated under reduced pressure and the residue was diluted to 200 mL with diethyl ether. The ether solution was washed with saturated KHCO₃ solution and then dried. Filtration, followed by evaporation under reduced pressure afforded a colourless oil. The crude material was purified by flash chromatography, eluting with 6% ethyl acetate / pet. ether to afford 4.68 g (86%) of 47 as a colourless oil.
IR (neat): 2954, 1736, 1438, 1284, 1013 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 3.62 (s, 2H), 3.72 (s, 3H), 7.32 (m, 3H), 7.48 (m, 2H);
LRMS (El) m/z (relative intensity): 182 (M⁺, 48), 123 (100).

3.11 Methyl chloro(phenylthio)acetate (48)

\[
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{PhS} \quad \text{Cl}
\]

A solution of methyl (phenylthio)acetate (47) (5.66 g, 31.0 mmol) and
N-chlorosuccinimide (4.56 g, 34.1 mmol) in 150 mL of dry CCl₄ was stirred at 0 °C and
allowed to warm to room temperature overnight. The mixture was filtered and
concentrated under reduced pressure. The crude material was purified by distillation
(105-115 °C / 0.2 mm Hg) to afford 5.14 g (76%) of 48 as a yellow oil.

IR (neat): 3059, 2955, 1741, 1580, 1477, 1437, 1283, 1155, 1007, 745 cm⁻¹;
¹H NMR (200 MHz, CDCl₃) δ: 3.80 (s, 3H), 5.52 (s, 1H), 7.32 (m, 3H), 7.48 (m, 2H);
LRMS (El) m/z (relative intensity): 218 (³⁷Cl, M⁺, 24), 216 (³⁵Cl, M⁺, 45), 159 (39), 157
(100), 121 (99), 109 (63);
HRMS (El) m/z calcd for C₉H₉O₂³⁷CIS: 217.9982, found: 217.9974
m/z calcd for C₉H₉O₂³⁵CIS: 216.0011, found: 216.0011.

3.12 Methyl (E)-(2-carbomethoxy-3-oxacyclopentylidene)acetate (49)

\[
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} \quad \text{CO}_2\text{Me} \\
\text{O}
\]

A solution of dimethyl 6-oxa-7-(phenylthio)-2-octynedioate (36) (34.3 mg,
0.111 mmol), tri(n-butyl)tin hydride (45 μL, 0.22 mmol), and AIBN (1.8 mg, 0.011 mmol)
in 1.1 mL of dry benzene was heated in an 82 °C oil bath. After 1 hour the reaction
mixture was cooled to room temperature and then concentrated. The crude oil was
purified by radial chromatography, eluting with 2% diethyl ether / methylene chloride to afford 10.7 mg (48%) of 49, 50 and 51 in a 1.4:1.4:1 ratio. Pure samples of 49, 50 and 51 were obtained by radial chromatography, eluting with a solution of 30% diethyl ether / pet. ether and formic acid, 2 drops per 5 mL of eluent.

IR (CDCl$_3$): 2949, 1745, 1717, 1670, 1437, 1339, 1214, 1130, 1048, 840 cm$^{-1}$;

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.02-3.20 (m, 2 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 4.13 (dt, $J = 5.3 \& 8.3$ Hz, 1 H), 4.23 (m, 1 H), 4.95 (m, 1H), 6.10 (q, $J = 2$ Hz, 1 H);

LRMS (El) m/z (relative intensity): 200 (M$^+$, 3), 168 (6), 141 (100), 109 (37), 84 (89), 53 (38);

HRMS (El) m/z calcd for C$_9$H$_{12}$O$_5$: 200.0685, found: 200.0679;


3.13 Methyl (Z)-(2-carbomethoxy-3-oxacyclopentylidene)acetate (50)

A solution of dimethyl 6-oxa-7-(phenylthio)-2-octynedioate (36) (20.4 mg, 0.066 mmol) and tris(trimethylsilyl)silane (41 $\mu$L, 0.13 mmol) in 0.3 mL of dry benzene was heated in an 82 °C oil bath. A 0.5 mL portion of air was bubbled through the solution followed by addition of triethylborane (17 $\mu$L of 1.0 M solution in hexanes, 0.017 mmol). After 10 minutes the reaction mixture was cooled to room temperature and then concentrated. The crude oil was purified by radial chromatography, eluting with 2% diethyl ether / methylene chloride to afford 9.0 mg (68%) of 50, 49 and 51 in a 17:6:1 ratio.

IR (CDCl$_3$): 2954, 1745, 1718, 1674, 1438, 1340, 1235, 1134, 1063, 1022, 842 cm$^{-1}$;

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.78 (m, 1H), 2.86 (m, 1H), 3.68 (s, 3H), 3.73 (s, 3H), 4.03 (dd, $J = 7.7 \& 6.2$ Hz, 2H), 5.42 (t, $J = 2$ Hz, 1H), 6.02 (q, $J = 2$ Hz, 1H);
$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 34.02, 51.53, 52.36, 67.06, 79.97, 114.50, 158.53, 166.10, 169.41;

LRMS (El) $m/z$ (relative intensity): 200 (M$^+$, 5), 168 (28), 141 (100), 113 (62), 81 (25);

HRMS (El) $m/z$ calcd for C$_9$H$_{12}$O$_5$: 200.0685, found: 200.0691;


3.14 Methyl (2-carbomethoxy-3-oxa-1-cyclopentenyl)acetate (51)

See to Section 3.12.

IR (CDCl$_3$): 2927, 1731, 1439, 1146 cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 2.70 (t, J = 9.8 Hz, 2 H), 3.47 (s, 2H), 3.55 (s, 3 H), 3.62 (s, 3 H), 4.23 (t, J = 9.8 Hz, 2H);

LRMS (El) $m/z$ (relative intensity): 200 (M$^+$, 32), 168 (53), 141 (74), 140 (50), 81 (100);

HRMS (El) $m/z$ calcd for C$_9$H$_{12}$O$_5$: 200.0685, found: 200.0684;

3.15 Methyl (E)-(2-carbomethoxy-3-oxacyclohexylidene)acetate (52)

See Section 3.16.

IR (CDCl$_3$): 2946, 1747, 1723, 1659, 1601, 1438, 1246, 1202 cm$^{-1}$;
1H NMR (400 MHz, CDCl3) δ: 1.79 (m, 2H), 2.61 (m, 1H), 3.39 (dt, J = 14.7 & 5.0 Hz, 1H), 3.70 (s, 3H), 3.77 (s, 3H), 3.80 (dt, J = 14.7 & 4.8 Hz, 1H), 4.06 (m, 1H), 4.58 (s, 1H), 5.74 (s, 1H);

13C NMR (50 MHz, CDCl3) δ: 25.05, 26.45, 51.30, 52.43, 65.36, 79.09, 117.50, 152.67, 170.50, 197.23;

LRMS (El) m/z (relative intensity): 214 (M+, 4), 182 (4), 155 (100), 123 (33), 95 (25), 84 (22), 67 (25);

HRMS (El) m/z calcd for C10H14O5: 214.0841, found: 214.0835;


3.16 Methyl (Z)-(2-carbomethoxy-3-oxacyclohexylidene)acetate (53)

A solution of dimethyl 7-oxa-8-(phenylthio)-2-nonynedioate (37) (30.8 mg, 0.096 mmol) and tris(trimethylsilyl)silane (59 µL, 0.19 mmol) in 0.5 mL of benzene was heated in an 82 °C oil bath. A 0.5 mL portion of air was bubbled through the solution followed by addition of 24 µL triethylborane. A second 24 µL of triethylborane was added after 10 minutes. After a total reaction time of 20 minutes the reaction was allowed to cool to room temperature and then was concentrated. The crude oil was purified by radial chromatography, eluting first with 2% diethyl ether / methylene chloride and second with 30% diethyl ether / pet. ether to afford 9.0 mg (44%) of 53 and 52 in a 1.2:1 ratio, as a colourless oil. Compounds 53 and 52 were separated and obtained analytically pure by radial chromatography, eluting with 2% diethyl ether / pet. ether followed by concentration to constant weight over anhydrous CaSO4.

IR (CDCl3): 2948, 1740, 1716, 1659, 1602, 1437, 1235, 1206, 1152 cm⁻¹;
\[ \text{MeO}_2\text{C} \equiv \text{O} \text{C}_2\text{Me} \]

Compound 54 is a side product that was produced in the reaction described in Section 3.16. Purification by radial chromatography, eluting with 30% diethyl ether / pet. ether afforded 1.4 mg (7%) of 54 as a colourless film.

IR \((\text{CDCl}_3)\): 2956, 2855, 2237, 1748, 1711, 1437, 1264 cm\(^{-1}\);  
\[ ^1\text{H NMR (200 MHz, CDCl}_3\) \delta: 1.83 (qn, J = 7.0 Hz, 2H), 2.40 (t, J = 7.0 Hz, 2H), 3.52 (t, J = 7.0 Hz, 2H), 3.71 (s, 3H), 4.03 (s, 2H); \]
LRMS (EI) \(m/z\) (relative intensity): 214 (M\(^+\), 1.6), 183 (12), 155 (82), 141 (50), 123 (40), 109 (73), 95 (100);  
HRMS (EI) \(m/z\) calcd for C\(_{10}\)H\(_{14}\)O\(_5\): 214.0841, found: 214.0838.

3.18 Methyl 3-oxa-2-(phenylthio)-6-heptynoate (55)

\[ \equiv \text{O} \text{C}_2\text{Me} \quad \text{SPh} \]

3-Butyn-1-ol (38) (2.42 g, 34.5 mmol) was converted to 55 following the procedure outlined in Section 3.2. The procedure was amended such that 3 equiv. of
the alcohol and 1 equiv. of the chloride 48 were used. The crude yellow oil was purified by flash chromatography, eluting with 15% ethyl acetate / pet. ether to afford 2.20 g (77%) of 55 as a colourless oil. Kugelrohr distillation (170 °C / 0.1 mm Hg) afforded analytically pure 55.

IR (neat): 3288, 2951, 1747, 1476, 1438, 1268, 1104, 1024, 748 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.97 (t, J = 2.6 Hz, 1H), 2.54 (dt, J = 2.6 & 7.3 Hz, 2H), 3.66 (s, 3H), 3.73 (dt, J = 9.5 & 7.3 Hz, 1H), 4.02 ( dt, J = 9.5 & 7.3 Hz, 1H), 5.28 (s, 1H), 7.31 (m, 3H), 7.50 (m, 2H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 268 (M⁺+NH₄⁺, 100);

HRMS (Cl(+), isobutane) m/z calcd for C₁₃H₁₄O₃S: 250.0663, found: 250.0663;


3.19 3-Oxa-2-(phenylthio)-6-heptyn-1-ol (56)

![Structure of 3-Oxa-2-(phenylthio)-6-heptyn-1-ol (56)]

A solution of methyl 3-oxa-2-(phenylthio)-6-hepynoate (55) (2.15 g, 8.60 mmol) in 10 mL of dry THF was added to an ice cooled suspension of lithium aluminum hydride (0.69 g, 17 mmol) in 40 mL of dry THF. The ice bath was removed and the reaction was stirred at room temperature for 1 hour. The reaction was then cooled in ice and the reaction was quenched by the slow addition of 20 mL of saturated Na₂SO₄. The resulting white precipitate was removed by suction filtration and rinsed with ethyl acetate. The organic layer was separated and washed consecutively with NaHCO₃, water and brine, and then dried. The solution was filtered and concentrated to afford 1.81 g (95%) of 56 as a colourless oil which was pure by TLC and ¹H NMR. Approximately 100 mg was purified by radial chromatography, eluting with 25% ethyl acetate / pet. ether followed by Kugelrohr distillation (170 °C / 0.1 mm Hg) to afford analytically pure 56.

IR (neat): 3423, 3293, 2929, 2877, 1476, 1439, 1104, 744 cm⁻¹;
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.99 (t, $J = 2.6$ Hz, 1H), 2.13 (br s, 1H), 2.50 (dt, $J = 2.6$ & 6.7 Hz, 2H), 3.60 (dt, $J = 9.2$ & 6.7 Hz, 1H), 3.67 (d, $J = 6.4$ Hz, 2H), 4.12 (dt, $J = 9.2$ & 6.7 Hz, 1H), 4.75 (t, $J = 6.4$ Hz, 1H), 7.29 (m, 3H), 7.48 (m, 2H);

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 240 (M$^+$NH$_4^+$, 100);

HRMS (Cl(+), isobutane) $m/z$ calcd for C$_{12}$H$_{14}$O$_2$S: 222.0714, found: 222.0714;

Anal. Calcd for C$_{12}$H$_{14}$O$_2$S: C, 64.84; H, 6.35. Found: C, 64.81; H, 6.40.

3.20 5-Oxa-6-(phenylthio)-7-(t-butyldimethylsilyloxy)-1-heptyne (57)

\[
\begin{align*}
\text{OTBDMS} & \\
\text{SPh} & \\
\end{align*}
\]

A solution of 3-oxa-2-(phenylthio)-6-heptyn-1-ol (56) (1.75 g, 7.88 mmol), t-butyldimethylsilyl chloride (1.43 g, 9.46 mmol), and imidazole (1.34 g, 19.2 mmol) in 5 mL of dimethylformamide was stirred at room temperature for 3 hours. The reaction mixture was poured into 100 mL of saturated NH$_4$Cl and extracted with four 50 mL portions of 1:1 diethyl ether / pet. ether. The combined organics were washed with water and then dried. The solution was filtered and concentrated to afford 2.65 g (100%) of 57 as a colourless oil which was a single spot by TLC analysis. Approximately 100 mg was purified by radial chromatography, eluting with 2% diethyl ether / pet. ether followed by Kugelrohr distillation (170 °C / 0.1 mm Hg) to afford analytically pure 57.

IR (neat): 3303, 2939, 2858, 1472, 1254, 1133, 1094, 842, 778, 746 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.01 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.95 (t, $J = 2.7$ Hz, 1H), 2.47 (dt, $J = 2.7$ & 7.0 Hz, 2H), 3.63 (dt, $J = 9.2$ & 7.0 Hz, 1H), 3.75 (m, 2H), 4.03 (dt, $J = 9.2$ & 7.0 Hz, 1H), 4.73 (dd, $J = 6.7$ & 4.9 Hz, 1H), 7.25 (m, 3H), 7.48 (m, 2H);

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 354 (M$^+$NH$_4^+$, 100), 284 (39);

HRMS (Cl(+), isobutane)

\[
\begin{align*}
\text{m/z calcd for C}_{18}\text{H}_{29}\text{O}_2\text{SSi (M}^+1\text{): 337.1657, found: 337.1652;}
\end{align*}
\]
3.21 Methyl 6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-2-nonynoate (58)

\[
\text{MeO}_2\text{C} = \equiv \text{O} \quad \text{OTBDMS} \quad \text{SPh}
\]

5-Oxa-6-(phenylthio)-7-(t-butyldimethylsilyloxy)-1-heptyne (57) (2.65 g, 7.89 mmol) in 40 mL of dry THF was cooled to -78 °C. Methyllithium (11.1 mL of 1.07 M in hexanes, 11.8 mmol) was added to this dropwise and the mixture was stirred at -78 °C for 20 minutes, after which the reaction mixture was stirred in -20 °C bath for 30 minutes. Methyl chloroformate (0.90 mL, 12 mmol) was added rapidly to the reaction mixture and stirring at -20 °C was continued for 1 hour, followed by 1.5 hours at room temperature, after which, TLC analysis indicated the reaction was completed. The reaction was cooled in an ice bath and quenched by the addition of 25 mL of half-saturated NaHCO₃ solution and then warmed to room temperature. The reaction mixture was diluted to 200 mL with ethyl acetate and washed with saturated NaHCO₃ solution and then dried. The ethyl acetate solution was filtered and concentrated to a yellow oil which was purified by flash chromatography, eluting with 10% ethyl acetate / pet. ether to afford 2.45 g (79%) of 58 as a slightly yellow oil. Approximately 100 mg was purified by radial chromatography, eluting with 7% ethyl acetate / pet. ether followed by Kugelrohr distillation (170 °C / 0.05 mm Hg) to afford analytically pure 58 as a colourless oil.

IR (neat): 2953, 2858, 2244, 1718, 1471, 1436, 1259, 1133, 1081, 842, 779, 750 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.00 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H) 2.62 (t, J = 6.7 Hz, 2H), 3.65 (dt, J = 9.2 & 6.7 Hz, 1H), 3.74 (s, 3H) 3.77 (m, 2H), 4.07 (dt, J = 9.2 & 6.7 Hz, 1H), 4.71 (dd, J = 7.0 & 4.6 Hz, 1H), 7.26 (m, 3H), 7.47 (m, 2H);

LRMS (Cl(+), ammonia) m/z (relative intensity): 412 (M⁺+NH₄⁺, 100), 395 (M⁺+1, 1), 287 (30), 192 (35);

HRMS (Cl(+), ammonia/methane)

\[ m/z \text{ calcd for C}_{20}\text{H}_{34}\text{NO}_{4}\text{SSi} (M⁺+NH₄⁺): 412.1978, \text{ found: 412.1976}; \]

Anal. Calcd for C₁₈H₂₈O₂SSi: C, 64.24; H, 8.39. Found: C, 64.37; H, 8.37.
Anal. Calcd for C$_{20}$H$_{30}$O$_4$SSi: C, 60.88; H, 7.66. Found: C, 61.00; H, 7.70.

3.22 Methyl 8-hydroxy-6-oxa-7-(phenylthio)-2-octynoate (59)

\[
\text{MeO}_2\text{C} === \text{O} \quad \text{SPh}
\]

2,4,6-Trimethylpyridinium fluoride (0.12 g, 0.83 mmol) was added to an ice cooled solution of methyl 6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-2-nonynoate (58) (0.31 g, 0.79 mmol) in 8 mL of methylene chloride. The reaction vessel was loosely stoppered so as to allow the mixture to slowly concentrate while stirring at room temperature overnight. The reaction mixture was diluted with diethyl ether and washed consecutively with 1 M HCl, NaHCO$_3$ and brine, and then dried. The solution was filtered and concentrated followed by purification by flash chromatography, eluting with 40% ethyl acetate / pet. ether to afford 0.20 g (91%) of 59 as a slightly yellow oil. Approximately 100 mg was purified by radial chromatography, eluting with 40% ethyl acetate / pet. ether followed by Kugelrohr distillation (170 °C / 0.05 mm Hg) to afford analytically pure 59 as a colourless oil.

IR (neat): 3448, 2949, 2878, 2242, 1711, 1476, 1266, 1079, 747 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 2.08 (br s, 1H), 2.66 (t, $J = 6.6$ Hz, 2H), 3.63 (dt, $J = 9.2$ & 6.6 Hz, 1H), 3.67 (d, $J = 6.4$ Hz, 2H), 3.75 (s, 3H), 4.17 (dt, $J = 9.2$ & 6.6 Hz, 1H), 4.73 (t, $J = 6.4$ Hz, 1H), 7.29 (m, 3H), 7.47 (m, 2H);

LRMS (El) m/z (relative intensity): 280 (M$^+$, 2), 249 (20), 171 (73), 139 (100), 109 (45);

HRMS (El) m/z calcd for C$_{14}$H$_{16}$O$_4$S: 280.0769, found: 280.0764;

Anal. Calcd for C$_{14}$H$_{16}$O$_4$S: C, 59.98; H, 5.75. Found: C, 59.60; H, 5.85.

3.23 Methyl (Z)-6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-3-tris(trimethylsilyl)silyl-2-octenoate (60)

\[
\text{MeO}_2\text{C} \quad \text{Si(SiMe$_3$)$_3$} \quad \text{SPh}
\]
A solution of methyl 6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-2-nonynoate (58) (94.6 mg, 0.240 mmol), tris(trimethylsilyl)silane (148 µL, 0.480 mmol) in 1.2 mL of dry benzene was heated in an 78 °C oil bath. The reaction was initiated by adding 0.5 mL of air followed by triethylborane (60 µL of 1.0 M solution in hexanes, 0.060 mmol). TLC and GC analysis suggested little or no starting material remained after 20 minutes at which time heating was stopped. The reaction mixture was cooled and concentrated. The crude material was purified by radial chromatography, eluting with 5% then 10% diethyl ether / pet. ether to afford 74.3 mg (48%) of 60 as a colourless oil.

IR (neat): 2948, 2893, 2112, 1715, 1591, 1471, 1248, 1104, 841 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.01 (s, 6H), 0.17 (s, 27H), 0.86 (s, 9H), 2.49 (q, J = 6.7 Hz, 2H), 3.46 (dt, J = 9.2 & 6.7 Hz, 1H), 3.65 (s, 3H), 3.75 (t, J = 6.4 Hz, 2H), 3.95 (dt, J = 9.2 & 6.7 Hz, 1H), 4.69 (t, J = 6.4 Hz, 1H), 6.08 (t, J = 7.0 Hz, 1H), 7.24 (m, 3H), 7.46 (m, 2H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 660 (M⁺+NH₄⁺, 100);

HRMS (El) m/z calcd for C₂₅H₆₂NO₄SSi₅ (M⁺+NH₄⁺): 660.3245, found: 660.3256.

3.24 Methyl (Z)-8-hydroxy-6-oxa-7-(phenylthio)-3-tris(trimethylsilyl)silyl-2-octenoate (62)

\[
\text{MeO}_2\text{C}-\text{Si}((\text{SiMe}_3)_3\text{SPh})-\text{OH}
\]

A solution methyl 8-hydroxy-6-oxa-7-(phenylthio)-2-octynoate (59) (61.9 mg, 0.221 mmol), tris(trimethylsilyl)silane (136 µL, 0.442 mmol) in 1.1 mL of dry benzene was heated in an 78 °C oil bath. The reaction was initiated by adding 0.5 mL of air followed by triethylborane (55 µL of 1.0 M solution in hexanes, 0.055 mmol). TLC analysis after 20 minutes suggested considerable starting material remained so the reaction was reinitiated. A third initiation was administered 20 minutes later. After a further 20 minutes, TLC analysis showed little starting material remained so heating was stopped. The reaction mixture was cooled and concentrated. The crude material
was purified by radial chromatography, eluting with 20% ethyl acetate / pet. ether to afford 72.1 mg (64%) of 62 as a colourless oil.

IR (neat): 3461, 2952, 2893, 2113, 1708, 1590, 1435, 1245, 1203, 1078, 841, 744 cm⁻¹;
1H NMR (400 MHz, CDCl₃) δ: 0.16 (s, 27H), 2.49 (q, J = 6.4 Hz, 2H), 3.42 (dt, J = 9.5 & 6.4 Hz, 1H), 3.65 (s, 3H), 3.64-3.66 (m, 2H), 4.07 (dt, J = 9.5 & 6.4 Hz, 1H), 4.69 (t, J = 6.1 Hz, 1H), 6.05 (t, J = 6.4 Hz, 1H), 7.27 (m, 3H), 7.44 (m, 2H);
LRMS (DCI(+), ammonia) m/z (relative intensity): 546 (M⁺+NH₄, 45), 527 (M⁺+1, 12);
HRMS (El) m/z calcd for C₂₃H₄₈NO₄SSi₄ (M⁺+NH₄): 546.2381, found: 546.2367.

3.25 Methyl (Z)-8-hydroxy-6-oxa-7-(phenylthio)-3-tri(n-butyl)stannyl-2-octenoate (63)

\[
\text{MeO}_2\text{C} - \text{SnBu}_3 - \text{SPh}
\]

A solution methyl 8-hydroxy-6-oxa-7-(phenylthio)-2-octynoate (59) (59.0 mg, 0.211 mmol), tri(n-butyl)tin hydride (85 μL, 0.32 mmol) in 1.1 mL of dry benzene was heated in a 78 °C oil bath. The reaction was initiated by adding triethylborane (53 μL of 1.0 M solution in hexanes, 0.053 mmol) followed by 5.3 mL of air. TLC and GC analysis showed no starting material remained after 25 minutes at which time heating was stopped. The reaction mixture was cooled and concentrated. The crude material was purified by radial chromatography, eluting with 10% then 20% ethyl acetate / pet. ether to afford 40.4 mg (34%) of 63 as a colourless oil.

IR (CDCl₃): 3596, 2957, 2924, 1707, 1599, 1437, 1332, 1201, 1110 cm⁻¹;
1H NMR (400 MHz, CDCl₃) δ: 0.85 (t, J = 8.5 Hz, 9H), 0.94 (m, 6H), 1.28 (sextet, J = 8.5 Hz, 6H), 1.44 (m, 6H), 1.83 (br s, 1H), 2.70 (t, J = 6.9 Hz, 2H), 3.48 (dt, J = 9.5 & 6.7 Hz, 1H), 3.64 (d, J = 5.8 Hz, 2H), 3.71 (s, 3H), 4.08 (9.5 & 7.0 Hz, 1H), 4.69 (dd, J = 5.8 & 5.8 Hz, 1H), 6.43 (s, J Sn-H=105 Hz, 1H), 7.28 (m, 3H), 7.44 (m, 2H);
LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 590 ($^{120}$Sn, M$^+$+NH$_4$, 30), 588 ($^{118}$Sn, M$^+$+NH$_4$, 25), 586 ($^{116}$Sn, M$^+$+NH$_4$, 15), 573 ($^{120}$Sn, M$^+$+1, 20), 571 ($^{118}$Sn, M$^+$+1, 17), 569 ($^{116}$Sn, M$^+$+1, 9);

HRMS (DCI(+), isobutane)

$m/z$ calcd for C$_{26}$H$_{45}$O$_4$S$^{120}$Sn (M$^+$+1): 573.2060, found: 573.2050;
$m/z$ calcd for C$_{26}$H$_{45}$O$_4$S$^{118}$Sn (M$^+$+1): 571.2054, found: 571.2036;
$m/z$ calcd for C$_{26}$H$_{45}$O$_4$S$^{116}$Sn (M$^+$+1): 569.2056, found: 569.2063.

3.26 Dimethyl 6-oxa-7-methyl-7-(phenylthio)-2-octynedioate (71)

\[ \text{MeO}_2\text{C} \equiv \text{O} \quad \text{CO}_2\text{Me} \]
\[ \text{PhS} \quad \text{Me} \]

Methyl chloro(thiophenoxy)acetate (48) (0.50 g, 2.3 mmol) in 2 mL of dry THF was added over four minutes to a -78 °C solution of lithium diisopropylamide (4.6 mmol) in 12 mL of dry THF. The lithium diisopropylamine was prepared by adding n-BuLi (3.5 mL of 1.3 M in hexanes, 4.6 mmol) to a -78 °C solution of diisopropylamine (0.60 mL, 4.6 mmol) in 12 mL of dry THF. To facilitate formation of the lithium diisopropylamide, the solution was stirred at -78 °C for 5 minutes, at room temperature for 15 minutes, and then cooled to -78 °C for 5 minutes prior to addition of 48. During the addition of the 48 solution, the reaction mixture became dark green. The reaction mixture was stirred for 10 minutes at -78 °C and then for 15 minutes at 0 °C, followed by rapid addition of methyl iodide (0.29 mL, 4.6 mmol) resulting in the solution turning brown. TLC analysis showed no starting material remained after 5 minutes and the reaction mixture was poured into 20 mL of 0.1 M HCl and then this solution was diluted to 100 mL with diethyl ether. The organic layer was separated and washed with brine and then dried. The solution was filtered and concentrated to afford 0.52 g of crude methyl 2-chloro-2-(thiophenoxy)propanoate (70) as a dark brown oil. Following the procedure outlined in Section 3.2, methyl 5-hydroxy-2-pentynoate (44) (0.29 g, 2.3 mmol) and the crude 70 was converted to 74. The crude material was purified by radial chromatography, first by eluting with 15% ethyl acetate / pet. ether and second by
eluting with 2% ethyl acetate / benzene to afford 0.15 g (20% for 2 steps) of 71 as a yellow oil.

IR (neat): 2952, 2243, 1740, 1715, 1438, 1261, 1137, 1080, 752 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.68 (s, 3H), 2.67 (t, J = 7.2 Hz, 2H), 3.64 (s, 3H), 3.75 (s, 3H), 3.92 (t, J = 7.0 Hz, 1H), 3.93 (t, J = 7.0 Hz, 1H), 7.32 (m, 3H), 7.45 (m, 2H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 340 (M⁺+NH₄, 100), 195 (30);

HRMS (Cl(+), isobutane) m/z calcd for C₁₆H₁₉O₅S (M⁺+1): 323.0953, found: 323.0951.

3.27 Dimethyl 7-oxa-8-methyl-8-(phenylthio)-2-nonynedioate (72)

Methyl 6-hydroxy-2-hexynoate (45) (0.29 g, 2.3 mmol) was converted to 72 following the procedure outlined in Section 3.26. The crude material was purified by radial chromatography, first by eluting with 10% ethyl acetate / pet. ether and second by eluting with 2% ethyl acetate / benzene to afford 0.14 g (18% for 2 steps) of 72 as a yellow oil.

IR (neat): 2949, 2237, 1739, 1715, 1437, 1262, 1136, 752 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.68 (s, 3H), 1.89 (qn, J = 7.0 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 3.64 (s, 3H), 3.73 (s, 3H), 3.79 (m, 2H), 7.31 (m, 3H), 7.44 (m, 2H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 354 (M⁺+NH₄, 100);

HRMS (Cl(+), isobutane) m/z calcd for C₁₇H₂₁O₅S (M⁺+1): 337.1110, found: 337.1110.
3.28 Methyl (E)-(2-carbomethoxy-2-methyl-3-oxacyclopentylidene)acetate (73)

A solution of dimethyl 6-oxa-7-methyl-7-(phenylthio)-2-octynedioate (71) (115 mg, 0.357 mmol) and tri(n-butyl)tin hydride (144 µL, 0.536 mmol) in 1.8 mL of dry benzene was heated in an 83 °C oil bath. The reaction was initiated by adding triethylborane (89 µL of 1.0 M solution in hexanes, 0.89 mmol) followed by 1 mL of air. TLC and GC analyses suggested little or no starting material remained after 15 minutes at which time heating was stopped, and the reaction mixture was cooled and then concentrated. The crude material was purified by radial chromatography, eluting with 15% ethyl acetate / pet. ether to afford 32.5 mg (42%) of 73, as well as 13.4 mg (18%) of 74 as colourless oils. Kugelrohr distillation (150 °C / 3 mm Hg) afforded analytically pure 73.

IR (neat): 2954, 1739, 1720, 1666, 1439, 1241, 1179, 1122, 1033 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.55 (s, 3H), 3.06 (m, 1H), 3.19 (m, 1H), 3.71 (s; 3H), 3.72 (s, 3H), 4.09 (q, J = 8.6 Hz, 1H), 4.16 (dt, J = 4.1 & 8.6 Hz, 1H), 5.97 (t, J = 2.4 Hz, 1H);

LRMS (El) m/z (relative intensity): 214 (M⁺, 2), 183 (4), 155 (100), 123 (11), 113 (46), 43 (70);

HRMS (El) m/z calcd for C₁₀H₁₄O₅: 214.0841, found: 214.0843;


3.29 Methyl (Z)-(2-carbomethoxy-2-methyl-3-oxacyclopentylidene)acetate (74)
A solution of dimethyl 6-oxa-7-methyl-7-(phenylthio)-2-octynedioate (71) (87.6 mg, 0.272 mmol) tris(trimethylsilyl)silane (168 µL, 0.544 mmol) in 1.4 mL of dry benzene was heated in an 83 °C oil bath. The reaction was initiated by adding triethylborane (68 µL of 1.0 M solution in hexanes, 0.68 mmol). TLC and GC analysis suggested little or no starting material remained after 10 minutes at which time heating was stopped, and the reaction mixture was cooled and then concentrated. The crude material was purified by radial chromatography, eluting with 15% ethyl acetate / pet. ether to afford 27.3 mg (47%) of 74, as well as 12.6 mg (22%) of 73 as colourless oils. Kugelrohr distillation (150 °C / 3 mm Hg) afforded analytically pure 74.

IR (neat): 2953, 1749, 1715, 1667, 1442, 1248, 1168, 1129, 1014 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.58 (s, 3H), 2.73-2.93 (m, 2H), 3.65 (s, 3H), 3.70 (s, 3H), 3.93 (dt, J = 6.4 & 8.3 Hz, 1H), 4.05 (dt, J = 3.7 & 8.3 Hz, 1H), 5.92 (t, J = 2.1 Hz, 1H);

LRMS (EI) m/z (relative intensity): 214 (M⁺, 3), 183 (0.5), 155 (100), 123 (51), 95 (22), 43 (24);

HRMS (EI) m/z calcd for C₁₀H₁₄O₅: 214.0841, found: 214.0844;


3.30 Methyl (E)-(2-carbomethoxy-2-methyl-3-oxacyclohexylidene)acetate (75)

Method A. Via cyclization of compound 72.

A solution dimethyl 7-oxa-8-methyl-8-(phenylthio)-2-nonynedioate (72) (88.6 mg, 0.264 mmol), tri(n-butyl)tin hydride (106 µL, 0.396 mmol) in 1.3 mL of dry benzene was heated in an 78 °C oil bath. The reaction was initiated by adding triethylborane (66 µL of 1.0 M solution in hexanes, 0.66 mmol) followed by 1 mL of air. GC analysis after 15 minutes suggested considerable starting material and tri(n-butyl)tin hydride
remained so the reaction was reinitiated, with 55 \( \mu \text{L} \) triethylborane and 5 mL of air. After a further 30 minutes, GC analysis showed no tri(n-butyl)tin hydride remained but starting material did remain, so 50 \( \mu \text{L} \) of tri(n-butyl)tin hydride was added and the reaction was reinitiated. After a further 30 minutes, TLC and GC analysis showed little starting material remained so heating was stopped. The reaction mixture was cooled and concentrated. The crude material was purified by radial chromatography, eluting with 25% ethyl acetate / pet. ether to afford 3.7 mg (6.2%) of 75 and 76 in 64:36 ratio as a colourless oil. Compound 77 was also isolated from this reaction.

**Method B. Via isomerization of compound 76.**

A solution of compounds 76 and 75 in 95:5 ratio (23 mg, 0.10 mmol), tri(n-butyl)tin hydride (39 \( \mu \text{L}, 0.15 \text{ mmol} \)), and a catalytic amount of AIBN in 2 mL of dry benzene was heated in an 82 °C oil bath 1 hour. The reaction mixture was cooled to room temperature and 20 \( \mu \text{L} \) of DBU was added followed by a solution of iodine in diethyl ether just until the yellow colour remained. The solution was stirred for 10 minutes and then filtered through silica gel, eluting with diethyl ether and concentrated to a yellow oil. The crude material was purified by radial chromatography, eluting with 15% ethyl acetate / pet. ether followed by Kugelrohr distillation (120 °C / 10 mm Hg for 15 minutes to remove AIBN then 1 mm Hg) to afford 20.7 mg (90%) of 75 and 76 in 95:5 ratio, as a colourless oil.

IR (neat): 2953, 1728, 1654, 1436, 1257, 1190, 1015 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 1.51 (s, 3H), 1.60-1.82 (m, 2H), 2.10 (m, 1H), 3.70 (s, 3H), 3.73 (s, 3H), 3.79 (dt, \( J = 12.6 \) & 3.8 Hz, 1H), 3.88 (m, 2H), 5.87 (s, 1H);

LRMS (EI) \( m/z \) (relative intensity): 228 (M\(^+\), 4), 197 (6), 169 (100), 137 (8);

HRMS (EI) \( m/z \) calcd for C\(_{11}\)H\(_{16}\)O\(_5\): 228.0998, found: 228.0999;
3.31 Methyl (Z)-(2-carbomethoxy-2-methyl-3-oxacyclohexylidene)acetate (76)

\[
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me} \\
\text{Me} \\
\text{O} \\
\text{Me}
\]

Dimethyl 7-oxa-8-methyl-8-(phenylthio)-2-nonynedioate (72) (102.0 mg, 0.304 mmol) was converted to 76 following the procedure outlined in Section 3.29. The crude material was purified by radial chromatography, eluting with 15% ethyl acetate / pet. ether to afford 30.2 mg (44%) of 76 and 75 in 94:6 ratio, as a colourless oil. The mixture was further purified by Kugelrohr distillation (170 °C / 3 mm Hg).

IR (neat): 2957, 1732, 1647, 1442, 1246, 1171, 1013 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.62 (s, 3H), 1.78 (m, 1H), 2.03 (m, 1H), 2.30 (m, 1H), 2.52 (m, 1H), 3.61 (s, 3H), 3.70 (s, 3H), 3.77 (m, 2H), 5.77 (d, J = 1.2 Hz, 1H);

LRMS (El) \(m/z\) (relative intensity): 228 (M\(^+\), 1.0), 169 (100), 137 (54), 109 (24), 81 (28), 43 (43);

HRMS (El) \(m/z\) calcd for C\(_{11}\)H\(_{16}\)O\(_5\): 228.0998, found: 228.0997.

3.32 Dimethyl (Z)-7-oxa-8-methyl-8-(phenylthio)-3-tri(n-butyl)stanny1-2-nonenedioate (77)

\[
\text{MeO}_2\text{C} \\
\text{SnBu}_3 \\
\text{O} \\
\text{Me} \\
\text{CO}_2\text{Me}
\]

Compound 77 was produced in the reaction described in Section 3.30, Method A. Purification by radial chromatography, eluting with 7% ethyl acetate / pet. ether afforded 25.0 mg (18.0%) of 77 as a colourless oil.

IR (neat): 2954, 1756, 1740, 1708, 1597, 1447, 1329, 1204, 1145 cm\(^{-1}\);
$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 0.81-0.97 (m, 15H), 1.18-1.52 (m, 15H), 1.67 (qn, $J = 7.0$ Hz, 2H), 3.32 (dt, $J = 9.0 \& 7.0$ Hz, 1H), 3.53 (dt, $J = 9.0 \& 7.0$ Hz, 1H), 3.69 (t, $J = 1.3$ Hz, $J_{\text{Sn-H}} = 107$ Hz, 1H);

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 521 ($^{120}\text{Sn}$, $M^+$+1, 2.3), 519 ($^{118}\text{Sn}$, $M^+$+1, 1.7), 517 ($^{116}\text{Sn}$, $M^+$+1, 1.1), 463 (100), 461 (77), 459 (41);

HRMS (Cl(+), ammonia/methane) $m/z$ calcd for C$_{23}$H$_{45}$O$_5$$^{120}\text{Sn}$ ($M^+$+1): 521.2292, found: 521.2284.

3.33 6-(2-Tetrahydropyranyloxy)-1-hexyne (85)

1-Hexyn-6-ol (84) (1.00 g, 10.2 mmol) was converted to 85 following the procedure outlined in Section 3.4. The crude brown oil was purified by flash chromatography, eluting with 15% diethyl ether / pet. ether to afford 1.64 g (89%) of 85 as a colourless oil.

IR (neat): 3287, 2938, 2869, 1201, 1137, 1121, 1071, 1031, 989 cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 1.40-1.80 (m, 10H), 1.92 (t, $J = 2.6$ Hz, 1H), 2.20 (dt, $J = 2.6 \& 6.8$ Hz, 2H), 3.44 (m, 2H), 3.76 (m, 2H), 4.56 (m, 1H);

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 200 ($M^+$+NH$_4$, 100), 183 ($M^+$+1, 48), 169 (41);

HRMS (Cl(+), isobutane) $m/z$ calcd for C$_{11}$H$_{19}$O$_2$ ($M^+$+1): 183.1385, found: 183.1384;

Anal. Calcd for C$_{11}$H$_{18}$O$_2$: C, 72.49; H, 9.95. Found: C, 72.81; H, 9.82.

3.34 Methyl 7-(2-tetrahydropyranyloxy)-2-heptynoate (86)

$\text{MeO}_2\text{C}$-\begin{align*}
\begin{array}{c}
\text{O} \\
\text{O} \\
\end{array}
\end{align*}
6-(2-Tetrahydropyranloxy)-1-hexyne (85) (1.27 g, 6.98 mmol) was converted to 86 following the procedure outlined in Section 3.21. The crude yellow oil was purified by flash chromatography, eluting with 15% ethyl acetate / pet. ether followed by Kugelrohr distillation (130 °C / 0.05 mm Hg) from K₂CO₃ to afford 1.54 g (92%) of 86 as a colourless oil.

IR (neat): 2941, 2870, 2237, 1716, 1440, 1260, 1136, 1121, 1074, 1031, 753 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) δ: 1.51 (m, 4H), 1.68 (m, 5H), 1.78 (m, 1H), 2.36 (m, 2H), 3.38 (m, 1H), 3.47 (m, 1H), 3.73 (s, 3H), 3.82 (m, 1H), 4.54 (m, 1H);
LRMS (DCI(+), ammonia) m/z (relative intensity): 258 (M⁺+NH₄, 2), 241 (M⁺+1, 2), 174 (100), 157 (53);
HRMS (Cl(+), isobutane) m/z calcd for C₁₃H₂₀O₄ (M⁺+1): 241.1440, found: 241.1440;
Anal. Calcd for C₁₃H₂₀O₄: C, 64.98; H, 8.39. Found: C, 64.92; H, 8.19.

3.35 Methyl 7-hydroxy-2-heptynoate (87)

Methyl 7-(2-tetrahydropyranloxy)-2-heptynoate (86) (1.38 g, 5.75 mmol) was converted to 87 following the procedure outlined in Section 3.9. The crude material was purified by flash chromatography, eluting with 50% diethyl ether / pet. ether followed by Kugelrohr distillation (120 °C / 0.1 mm Hg) to afford 0.88 g (98%) of 87 as a colourless oil.

IR (neat): 3400, 2945, 2872, 2237, 1708, 1438, 1266, 1068, 753 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) δ: 1.43 (s, 1H), 1.66 (m, 4H), 2.37 (t, J = 6.0 Hz, 2H), 3.65 (t, J = 6.2 Hz, 2H), 3.73 (s, 3H);
LRMS (El) m/z (relative intensity): 156 (M⁺, 10), 124 (100), 98 (37), 79 (37), 69 (72);
HRMS (El) m/z calcd for C₈H₁₂O₃: 156.0786, found: 156.0781;
3.36  Methyl \((E)\)-3-bromo-7-hydroxy-2-heptenoate (88)

![Chemical Structure](image)

A solution of methyl 7-hydroxy-2-heptynoate (87) (0.68 g, 4.4 mmol) in 22 mL of dry diethyl ether was stirred in an ice bath. Hydrogen bromide was bubbled through the stirred solution for 1 minute and the flask was stoppered and sealed with parafilm. The hydrogen bromide addition was repeated twice at 5 hour intervals and stirred at room temperature overnight. The reaction mixture was diluted to 200 mL with ethyl acetate, was washed successively with saturated NaHCO₃ and brine and then dried. This was filtered and concentrated to a yellow oil which was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (120 °C / 0.05 mm Hg) to afford 0.22 g (21%) of 88 as a colourless oil. This reaction also afforded after Kugelrohr distillation (130 °C / 0.05 mm Hg) 0.35 g (34%) of 89 as a colourless oil.

IR (neat) 3382, 2942, 2869, 1719, 1624, 1434, 1347, 1203, 1167 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ: 1.59 (m, 2H), 1.70 (m, 2H), 1.74 (s, 1H), 3.09 (t, J = 7.3 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 3.67 (s, 3H), 6.31 (s, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 24.52, 31.29, 37.26, 51.58, 62.24, 122.89, 150.21, 164.80;

LRMS (DCI(+), ammonia) m/z (relative intensity): 256 (³¹Br, M⁺+NH₄⁺, 100), 254 (⁷⁹Br, M⁺+NH₄⁺, 93), 239 (³¹Br, M⁺+1, 21), 237 (⁷⁹Br, M⁺+1, 9);

HRMS (Cl(+), methane) m/z calcd for C₈H₁₄O₃⁺³¹Br(M⁺+1): 239.0107, found: 239.0111;

m/z calcd for C₈H₁₄O₃⁺⁷⁹Br(M⁺+1): 237.0127, found: 237.0126;

3.37 Methyl (Z)-3-bromo-7-hydroxy-2-heptenoate (89)

\[ \text{MeO}_2\text{C} = \text{Br} \]

See Section 3.36.

IR (neat): 3622, 2947, 2878, 1726, 1634, 1435, 1308, 1198, 1181, 1061 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.48 (s, 1H), 1.55 (m, 2H), 1.70 (m, 2H), 2.60 (t, \(J = 6.7\) Hz, 2H), 3.65 (t, \(J = 6.7\) Hz, 2H), 3.72 (s, 3H), 6.29 (s, 1H);

\(^{13}\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\): 24.31, 31.28, 43.18, 51.53, 62.32, 119.25, 142.14, 164.63;

LRMS (Cl(+), ammonia) \(m/z\) (relative intensity): 256 (\(^{81}\)Br, M\(^{+}\)+NH\(_4\), 6), 254 (\(^{79}\)Br, M\(^{+}\)+NH\(_4\), 6), 239 (\(^{81}\)Br, M\(^{+}\)+1, 27), 237 (\(^{79}\)Br, M\(^{+}\)+1, 28), 207 (22), 205 (25), 157 (87), 125 (100), 111 (23), 107 (27), 97 (73), 81 (82), 79 (88), 67 (55), 59 (51), 55 (57);

HRMS (Cl(+), methane) \(m/z\) calcd for C\(_8\)H\(_{14}\)O\(_3\)\(^{81}\)Br (M\(^{+}\)+1): 239.0107 found: 239.0096;

\(m/z\) calcd for C\(_8\)H\(_{14}\)O\(_3\)\(^{79}\)Br (M\(^{+}\)+1): 237.0127, found: 237.0126;


3.38 Methyl (E)-3,7-dibromo-2-heptenoate (90)

\[ \text{CO}_2\text{Me} \]

Carbon tetrabromide (0.09 g, 0.3 mmol) was added to an ice cooled solution of methyl (E)-3-bromo-7-hydroxy-2-heptenoate (88) (0.05 g, 0.2 mmol) and triphenylphosphine (0.07 g, 0.3 mmol) in 1.1 mL of dry methylene chloride. The ice bath was removed and the reaction mixture was stirred for 2.5 hours. The solution was concentrated and filtered through silica gel, eluting with 300 mL of 5% diethyl ether / pet. ether. After concentration material was purified by radial chromatography, eluting
with 5% diethyl ether / pet. ether followed by Kugelrohr distillation (135 °C / 0.05 mm Hg) to afford 0.05 g (80%) of 90 as a colourless oil.

IR (neat): 2954, 1721, 1625, 1437, 1347, 1189, 1135 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.77 (qn, J = 7.0 Hz, 2H), 1.89 (qn, J = 7.0 Hz, 2H), 3.12 (t, J = 7.0 Hz, 2H), 3.41 (t, J = 7.0 Hz, 2H), 3.69 (s, 3H), 6.34 (s, 1H);

LRMS (EI) m/z (relative intensity): 302 (2⁸¹Br, M⁺, 2), 300 (²⁹Br²¹Br, M⁺, 3), 298 (²⁷⁹Br, M⁺, 2), 271 (8), 269 (16), 267 (9), 221 (99), 219 (100), 161 (21), 159 (19), 111 (33), 107 (59), 99 (28), 81 (63), 80 (54), 79 (98), 77 (44), 71 (43), 67 (45);

HRMS (EI) m/z calcd for C₈H₁₂O₂²¹Br₂: 301.9163 found: 301.9160;

m/z calcd for C₈H₁₂O₂²¹Br²⁷⁹Br: 299.9184 found: 299.9191;

m/z calcd for C₈H₁₂O₂²⁷⁹Br²: 297.9204 found: 297.9210;

Anal. Calcd for C₈H₁₂O₂Br₂: C, 32.03; H, 4.03. Found: C, 32.31; H, 3.95.

3.39 Methyl (Z)-3,7-dibromo-2-heptenoate (91)

Methyl (Z)-3-bromo-7-hydroxy-2-heptenoate (89) was converted to 91 following the procedure outlined in Section 3.31. The crude material was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (120 °C / 0.05 mm Hg) to afford 0.07 g (50%) of 91 as a colourless oil.

IR (neat): 2944, 1727, 1637, 1439, 1293, 1184 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.72-1.90 (m, 4H), 2.60 (t, J = 6.7 Hz, 2H), 3.39 (t, J = 6.4 Hz, 2H), 3.73 (s, 3H), 6.30 (s, 1H);

LRMS (EI) m/z (relative intensity): 302 (2⁸¹Br, M⁺, 2), 300 (²⁹Br²¹Br, M⁺, 3), 298 (²⁷⁹Br, M⁺, 2), 271 (17), 269 (36), 267 (19), 221 (99), 219 (100), 161 (27), 159 (26), 121 (21), 119 (24), 111 (36), 107 (65), 99 (43), 81 (66), 80 (60), 79 (95), 77 (40), 71 (40), 63 (43);
HRMS (El) m/z calcd for C₈H₁₂O₂⁸¹Br₂: 301.9163, found: 301.9167;
m/z calcd for C₈H₁₂O₂⁸¹Br⁷⁹Br: 299.9184, found: 299.9181;
m/z calcd for C₈H₁₂O₂⁷⁹Br₂: 297.9204, found: 297.9201;

Anal. Calcd for C₈H₁₂O₂Br₂: C, 32.03; H, 4.03. Found: C, 32.24; H, 4.21.

3.40 Methyl (cyclopentylidene)acetate (92)

\[
\text{CO}_2\text{Me}
\]

Methyl (E)-3-bromo-7-iodo-2-heptenoate (110) (88.6 mg, 0.255 mmol), hexa(n-butyl)ditin (129 µl, 0.255 mmol) was dissolved in 12.8 mL of benzene in a Pyrex tube. Nitrogen was bubbled through the mixture for 30 min. and then the vessel was capped with a septum and sealed with parafilm. This solution was irradiated in a Rayonet Reactor equipped with 16 X 300 nm lamps. After 20 minutes, GC and TLC analyses indicated that all the starting substrate was consumed. The reaction mixture was diluted in diethyl ether and 98 µl DBU was added followed by a solution of iodine in diethyl ether until the iodine colour persisted. This was stirred 10 minutes and then filtered through silica gel, eluting with diethyl ether. The concentrated crude material was purified by radial chromatography, eluting with 4% diethyl ether / pet. ether to afford 26.8 mg (75%) of 92 as a colourless oil.

IR (neat): 2956, 1705, 1654, 1436, 1208, 1124 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.68 (m, 4H), 2.41 (br t, J = 6.1 Hz, 2H), 2.75 (br t, J = 7.6 Hz, 2H), 3.66 (s, 3H), 5.79 (qn, J = 2.2 Hz, 1H);

LRMS (El) m/z (relative intensity): 140 (M⁺, 100), 139 (26), 109 (57), 108 (39), 107 (28), 86 (45), 84 (69), 81 (39), 80 (35), 79 (45);

HRMS (El) m/z calcd for C₈H₁₂O₂: 140.0837, found: 140.0835.
3.41 Methyl (\(E\))-\(\text{2-methylcyclopentylidene}\)acetate (93)

Methyl (\(E\))-3-bromo-7-iodo-2-octenoate (108) (59.0 mg, 0.163 mmol) was converted to 93 following the procedure outlined in Section 3.40. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl ether / pet. ether to afford 19.2 mg (76%) of 93 and 94 which GC analysis showed to be of 97:3, respectively. The IR and \(^1\)H NMR data for compound 93 were consistent with those reported in the literature.\(^{44}\)

IR (neat): 2956, 2872, 1717, 1653, 1438, 1357, 1202, 1136 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.09 (d, \(J = 6.7\) Hz, 3H), 1.22 (m, 1H), 1.58 (m, 1H), 1.81 (m, 1H), 1.89 (m, 1H), 2.50 (m, 1H), 2.72 (m, 1H), 2.90 (m, 1H), 3.67 (s, 3H), 5.67 (m, 1H).

3.42 Methyl (\(Z\))-\(\text{2-methylcyclopentylidene}\)acetate (94)

Methyl (\(Z\))-3-bromo-7-iodo-2-octenoate (109) (79.6 mg, 0.220 mmol) was converted to 94 following the procedure outlined in Section 3.40. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl ether / pet. ether to afford 25.7 mg (76%) of 94 and 93 which GC analysis showed to be of 95:5, respectively. The IR and \(^1\)H NMR data for compound 94 were consistent with those reported in the literature.\(^{44}\)

IR (neat): 2955, 2871, 1718, 1655, 1433, 1354, 1206, 1162, 1130 cm\(^{-1}\);
$^1$H NMR (400 MHz, CDCl$_3$) δ: 1.06 (d, J = 7.0 Hz, 3H), 1.51 (m, 1H), 1.61 (m, 1H), 1.66-1.86 (m, 2H), 2.36 (m, 1H), 2.52 (m, 1H), 3.43 (m, 1H), 3.66 (s, 3H), 5.70 (d, J = 1.8 Hz, 1H).

3.43 1-Heptyn-6-one ethylene acetal (98)

![Chemical Structure](image)

2-Acetylbutyrolactone (20.0 g, 0.160 mmol), hydrobromic acid (40 mL, 0.23 mmol) and 25 mL of water were combined in flask fitted with distillation apparatus. The reaction flask was immersed in an oil bath and the oil bath temperature was increased to 120 °C. Distillation began after about 50 minutes and the receiver was cooled in an ice bath. A second 25 mL portion of water was added to the stillpot 30 minutes after distillation began. The distillation was stopped after approximately 80 mL of distillate had been collected. The distillate was set aside and the reaction was repeated a second time using the identical reagent quantities and reaction conditions. The distillates were combined and the layers were separated. The aqueous layer was extracted with 3 X 50 mL of diethyl ether. The organic layers were combined, washed with 2 mL of saturated NaHCO$_3$ solution and 10 mL of brine and then dried. The solution was filtered, concentrated and purified by distillation (70-73 °C / 9 mm Hg) to afford 26.5 (51%) of 96 as a colourless oil. A solution of 96 (26.5 g, 0.160 mmol), ethylene glycol (13.1 g, 0.21 mmol) and $p$-TsOH·H$_2$O (0.15 g, 0.80 mmol) in 320 mL of toluene was heated at 120 °C for 45 hours. The reaction mixture was washed with 40 mL of saturated NaHCO$_3$ solution and this aqueous solution was extracted with diethyl ether. The organic layers were combined, washed with 10 mL of water and dried. The ether solution was filtered, concentrated under reduced pressure and purified by distillation (77-81 °C / 5 mm Hg) to afford 27.73 g (83%) of 97 as a colourless oil. Lithium acetylide-ethylenediamine complex (9.8 g of 90% purity, 96 mmol) was suspended in 32 mL of dry dimethyl sulfoxide, and the suspension was stirred in a cool water bath. To this was added 97 (13.3 g, 63.7 mmol). The cooling bath was removed and the reaction was stirred at room temperature for 2 hours. The
reaction mixture was cooled in an ice bath and quenched by the slow addition of 100 mL of water. This was extracted seven times with 100 mL portions of 1:1 diethyl ether / pet. ether, and the combined extracts were washed with 50 mL of water and dried. The solution was filtered and concentrated to a yellow oil which was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (94-97 °C / 11 mm Hg) to afford 7.67 g (78%) of 98 as a colourless oil.

IR (neat): 3287, 2954, 2881, 1378, 1227, 1134, 1105, 1057 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.28 (s, 3H), 1.50-1.75 (m, 4H), 1.92 (t, J = 2.7 Hz, 1H), 2.18 (dt, J = 2.7 & 6.7 Hz, 2H), 3.90 (m, 4H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 155 (M⁺+1, 49), 139 (38), 87 (100);

HRMS (Cl(+), methane) m/z calcd for C₉H₁₅O₂ (M⁺+1): 155.1072, found: 155.1068;


3.44 1-Heptyn-6-one (99)

![1-Heptyn-6-one](image)

A solution of 1-heptyn-6-one ethylene acetal (98) (7.67 g, 49.8 mmol) and pyridinium p-toluenesulfonate (3.75 g, 14.9 mmol) in 400 mL of acetone was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. The crude material was dissolved in 400 mL of diethyl ether, and was washed consecutively with saturated NaHCO₃ solution and brine, and then dried. The ether solution was filtered and concentrated to a colourless oil which was purified by flash chromatography, eluting with 20% diethyl ether / pet. ether followed by fractional vacuum distillation (86-90 °C / 19 mm Hg) to afford 4.08 g (75%) of 99 as a colourless oil.

IR (CDCl₃): 3285, 2937, 2116, 1714, 1436, 1413, 1365, 1161 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.68 (qn, J = 7.0 Hz, 2H), 1.88 (t, J = 2.7 Hz, 1H), 2.06 (s, 3H), 2.12 (dt, J = 2.7 & 7.0 Hz, 2H), 2.49 (t, J = 7.0 Hz, 2H);
LRMS (DCI(+), ammonia) m/z (relative intensity): 128 (M⁺+NH₄, 100), 111 (M⁺+1, 22);
HRMS (Cl(+), methane) m/z calcd for C₇H₁₁O (M⁺+1): 111.0810, found: 111.0810;

3.45 1-Heptyn-6-ol (100)

Lithium aluminum hydride (1.74 g, 43.4 mmol) was suspended in 180 mL of dry THF and stirred in an ice bath. To this suspension was added dropwise a solution of 1-heptyn-6-one (99) (3.98 g, 36.2 mmol) in 25 mL of dry THF. The cooling bath was removed and stirring was continued for 2.5 hours. The reaction mixture was cooled in an ice bath and quenched by the slow addition of 20 mL of saturated Na₂SO₄ solution, resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was washed with ethyl acetate. The filtrate was washed consecutively with 25 mL portions of 5% NaHCO₃ solution, water and brine, and dried. This was filtered and concentrated to a colourless oil which was purified by filtering through silica gel, eluting with diethyl ether followed by fractional vacuum distillation (97-99 °C / 18 mm Hg) to afford 3.66 g (90%) of 100 as a colourless oil.

IR (CDCl₃): 3367, 3298, 2967, 2932, 2870, 2116, 1457, 1433, 1375, 1128, 1086 cm⁻¹;
¹H NMR (200 MHz, CDCl₃) δ: 1.16 (d, J = 6.4 Hz, 3H), 1.45-1.73 (m, 5H), 1.92 (t, J = 2.6 Hz, 1H), 2.18 (dt, J = 2.6 & 6.8 Hz, 2H), 3.78 (m, 1H);
LRMS (DCI(+), ammonia) m/z (relative intensity): 130 (M⁺+NH₄, 100), 113 (M⁺+1, 13);
HRMS (Cl(+), methane) m/z calcd for C₇H₁₃O (M⁺+1): 113.0966, found: 113.0968;
Anal. Calcd for C₇H₁₂O: C, 74.95; H, 10.78. Found: C, 74.79; H, 10.70.
3.46 6-(2-Tetrahydropyranyloxy)-1-heptyne (101)

\[ \text{MeO}_2\text{C} \equiv \text{CH}_7\text{OH} \]

1-Heptyn-6-ol (100) (3.50 g, 31.3 mmol) was converted to 101 following the procedure outlined in Section 3.4. The crude brown oil was purified by flash chromatography, eluting with 10% diethyl ether / pet ether followed by Kugelrohr distillation (80-87 °C / 1 mm Hg) from K\(_2\)CO\(_3\) to afford 5.62 g (92%) of 101 as a colourless oil.

IR (neat): 3290, 2940, 2871, 1449, 1376, 1199, 1128, 1077, 1020, 870 cm\(^{-1}\);

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 1.09 (d, \(J = 6.1\) Hz, 1.5H), 1.20 (d, \(J = 6.3\) Hz, 1.5H), 1.48-1.83 (m, 10H), 1.91 (t, \(J = 2.6\) Hz, 1H), 2.18 (m, 2H), 3.45 (m, 1H), 3.81 (m, 2H), 4.61 (m, 0.5H), 4.66 (m, 0.5H);

LRMS (EI) m/z (relative intensity): 195 (M\(^+\)-1,0.1), 95 (20), 85 (100);

HRMS (EI) m/z calcd for C\(_{12}\)H\(_{20}\)O\(_2\) (M\(^+\)-1): 195.1385, found: 195.1381;

Anal. Calcd for C\(_{12}\)H\(_{20}\)O\(_2\): C, 73.43; H, 10.27. Found: C, 73.28; H, 10.40.

3.47 Methyl 7-(2-tetrahydropyranyloxy)-2-octynoate (102)

\[ \text{MeO}_2\text{C} \equiv \text{CH}_7\text{O} \]

6-(2-Tetrahydropyranyloxy)-1-heptyne (101) (5.51 g, 28.1 mmol) was converted to 102 following the procedure outlined in Section 3.21. The crude material was purified by flash chromatography, eluting with 10% ethyl acetate / pet. ether followed by Kugelrohr distillation (95-118 °C / 0.2 mm Hg) from K\(_2\)CO\(_3\) to afford 6.70 g (94%) of 102 as a colourless oil.

IR (neat): 2942, 2871, 2237, 1716, 1439, 1259, 1128, 1077, 1028, 1001, 753 cm\(^{-1}\);
1H NMR (200 MHz, CDCl3) δ: 1.08 (d, J = 6.1 Hz, 1.5H), 1.20 (d, J = 6.3 Hz, 1.5H), 1.50-1.82 (m, 10H), 2.33 (m, 2H), 3.44 (m, 1H), 3.71 (s, 3H), 3.65-3.92 (m, 2H), 4.55 (m, 0.5H), 4.63 (m, 0.5H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 272 (M+NH4, 100.), 255 (M+1, 12);

HRMS (Cl(+), methane) m/z calcd for C14H23O4 (M+1): 255.1596, found: 255.1598;


3.48 Methyl 7-hydroxy-2-octynoate (103)

Methyl 7-(2-tetrahydropyranyloxy)-2-octynoate (102) (6.75 g, 29.8 mmol) was converted to 103 following the procedure outlined in Section 3.9. The crude material was purified by flash chromatography, eluting with 35% diethyl ether / pet. ether followed by Kugelrohr distillation (112 °C / 0.1 mm Hg) to afford 1.34 g (89%) of 103 as a colourless oil.

IR (neat): 3404, 2939, 2237, 1709, 1437, 1268, 1080 cm⁻¹;

1H NMR (400 MHz, CDCl3) δ: 1.14 (d, J = 6.1 Hz, 3H), 1.47 (m, 2H), 1.61 (m, 1H), 1.71 (m, 1H), 1.77 (s, 1H), 2.32 (t, J = 7.0 Hz, 2H), 3.70 (s, 3H), 3.76 (sextet, J = 6.1 Hz, 1H);

LRMS (EI) m/z (relative intensity): 170 (M+, 4), 138 (19), 123 (22), 111 (11), 98 (100), 79 (23), 66 (35), 55 (30);

HRMS (EI) m/z calcd for C9H14O3: 170.0943, found: 170.0937;

3.49 Methyl (E)-3-bromo-7-hydroxy-2-octenoate (104)

Method A. Via hydrobromination of compound 103.
See Section 3.50.

Method B. Via bromo-destannylation of compound 142.

Bromine was added dropwise to a solution of methyl (E)-3-(tri(n-butyl)stannyl)-7-hydroxy-2-octenoate (142) (0.76 g, 1.6 mmol) in 5.4 mL of dry methylene chloride, until the solution remained orange. The reaction mixture was stirred for 45 minutes and then was filtered through silica gel, eluting with diethyl ether and concentrated in vacuo. The crude material was purified by radial chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (110 °C / 0.2 mm Hg) to afford 0.40 g (98%) of 104 as a colourless oil.

IR (neat): 3387, 2948, 2869, 1719, 1624, 1433, 1345, 1314, 1204, 1172, 1118 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.16 (d, J = 6.1 Hz, 3H), 1.43 (m, 2H), 1.53-1.80 (m, 2H), 1.85 (s, 1H), 2.90-3.20 (m, 2H), 3.66 (s, 3H), 3.80 (sextet, J = 6.1 Hz, 1H), 6.30 (s, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 270 (⁸¹Br, M⁺+NH₄, 68), 268 (⁷⁹Br, M⁺+NH₄, 100), 253 (⁸¹Br, M⁺+1, 7), 251 (⁷⁹Br, M⁺+1, 7);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₉H₁₅O₃⁸¹Br (M⁺+1): 253.0262, found: 253.0253;

m/z calcd for C₉H₁₆O₃⁷⁹Br (M⁺+1): 251.0283, found: 251.0280;

Anal. Calcd for C₉H₁₅O₃Br: C, 43.05; H, 6.02. Found: C, 43.07; H, 5.88.
3.50 Methyl (Z)-3-bromo-7-hydroxy-2-octenoate (105)

Methyl 7-hydroxy-2-octynoate (103) (0.71 g, 4.2 mmol) was converted to 105 following the procedure outlined in Section 3.36. The crude yellow oil was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (130 °C / 0.1 mm Hg) to afford 0.55 g (52%) of 105 as a colourless oil. This reaction also afforded after Kugelrohr distillation (120 °C / 0.1 mm Hg) 0.34 g (34%) of 104 as a colourless oil.

IR (neat): 3408, 2948, 2869, 1728, 1636, 1434, 1306, 1197, 1174, 1128 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.15 (d, J = 6.1 Hz, 3H), 1.43 (m, 2H), 1.50-1.80 (m, 2H), 1.72 (s, 1H), 2.55 (t, J = 7.2 Hz, 2H), 3.69 (s, 3H), 3.76 (sextet, J = 6.1 Hz, 1H), 6.26 (s, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 270 (⁸¹Br, M⁺+NH₄, 65), 268 (⁷⁹Br, M⁺+NH₄, 100);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₉H₁₉NO₃⁸¹Br (M⁺+NH₄): 270.0528, found: 270.0523;
m/z calcd for C₉H₁₉NO₃⁷⁹Br (M⁺+NH₄): 268.0548, found: 268.0558;

Anal. Calcd for C₉H₁₅O₃Br: C, 43.05; H, 6.02. Found: C, 42.61; H, 5.87.

3.51 Methyl (E)-3,7-dibromo-2-octenoate (106)

Methyl (E)-3-bromo-7-hydroxy-2-octenoate (104) was converted to 106 following the procedure outlined in Section 3.38. The crude material was purified by radial chromatography, eluting with 5% diethyl ether / pet. ether followed by Kugelrohr distillation (155 °C / 0.2 mm Hg) to afford 0.15 g (63%) 106 as a colourless oil.
IR (neat): 2947, 1722, 1625, 1439, 1346, 1315, 1187, 1123 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 1.69 (d, J = 6.4 Hz, 3H), 1.70-1.90 (m, 4 H), 3.10 (m, 2H), 3.69 (s, 3H), 4.12 (sextet, J = 6.4 Hz, 1H), 6.34 (s, 1H);

LRMS (El) m/z (relative intensity): 316 (2⁸¹Br, M⁺, 1), 314 (⁷⁹Br⁸¹Br, M⁺, 2), 312 (²⁷⁹Br, M⁺, 1), 285 (3), 283 (4), 281 (2), 235 (62), 233 (64), 153 (25), 121 (60), 93 (100), 67 (35), 55 (60);

HRMS (El) m/z calcd for C₉H₁₄O₂⁸¹Br₂: 315.9320, found: 315.9331;
m/z calcd for C₉H₁₄O₂⁷⁹⁸¹Br: 313.9340, found: 313.9341;
m/z calcd for C₉H₁₄O₂⁷⁹Br₂: 311.9361, found: 311.9358;


3.52 Methyl (Z)-3,7-dibromo-2-octenoate (107)

Methyl (Z)-3-bromo-7-hydroxy-2-octenoate (105) was converted to 107 following the procedure outlined in Section 3.38. The crude material was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (145 °C / 0.05 mm Hg) to afford 0.14 g (48%) of 107 as a colourless oil.

IR (neat): 2946, 1731, 1636, 1439, 1296, 1183 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 1.69 (d, J = 6.7 Hz, 3H), 1.70-1.90 (m, 4 H), 2.59 (m, 2H), 3.72 (s, 3H), 4.09 (sextet, 6.7 Hz, 1H), 6.29 (s, 1H);

LRMS (El) m/z (relative intensity): 316 (2⁸¹Br, M⁺, 0.8), 314 (⁷⁹Br⁸¹Br, M⁺, 2), 312 (²⁷⁹Br, M⁺, 0.9), 285 (3), 283 (7), 281 (3), 235 (45), 233 (45), 153 (25), 121 (40), 93 (100), 67 (30), 55 (90);

HRMS (El) m/z calcd for C₉H₁₄O₂⁸¹Br₂: 315.9320, found: 315.9322;
m/z calcd for C₉H₁₄O₂⁷⁹⁸¹Br: 313.9340, found: 313.9339;
m/z calcd for C₉H₁₄O₂⁷⁹Br₂: 311.9361, found: 311.9367;

3.53 Methyl (E)-3-bromo-7-iodo-2-octenoate (108)

Iodine (0.39 g, 1.6 mmol) was added in one portion to an ice cooled solution of methyl (E)-3-bromo-7-hydroxy-2-octenoate (104) (0.30 g, 1.2 mmol), triphenylphosphine (0.41 g, 1.6 mmol) and imidazole (0.11 g, 1.6 mmol) in 7.5 mL of diethyl ether and 4.5 mL of acetonitrile. After 4 hours, TLC analysis indicated that the reaction was completed. The reaction mixture was diluted to 100 mL with diethyl ether and was washed successively with saturated Na₂S₂O₃ solution, saturated CuSO₄ solution and water, and then dried. This was filtered and concentrated to a white solid and a colourless oil. The oily solid was triturated in pet. ether and filtered through silica gel, eluting with 5% diethyl ether / pet. ether. The eluant was concentrated to a colourless oil which was purified by radial chromatography, eluting with 4% diethy ether / pet. ether, followed by Kugelrohr distillation (170 °C / 0.1 mm Hg) to afford 0.35 g (85%) of 108 as a colourless oil.

IR (neat): 2944, 1721, 1624, 1438, 1349, 1314, 1205, 1175, 1141, 1120, 864 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.60-1.90 (m, 4H), 1.91 (d, J = 6.8 Hz, 3H), 3.11 (t, J = 6.2 Hz, 1 Hz, 2H), 3.70 (s, 3H), 4.16 (sextet, J = 6.8 Hz, 1H), 6.34 (s, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 28.36, 28.83, 29.12, 36.45, 41.33, 51.59, 123.32, 149.50, 164.65;

LRMS (Cl(+), ammonia) m/z (relative intensity): 380 (⁸¹Br, M⁺+NH₄⁺, 1), 378 (⁷⁹Br, M⁺+NH₄⁺, 1), 363 (⁸¹Br, M⁺+1, 3), 361 (⁷⁹Br, M⁺+1, 4), 331 (5), 329 (5), 235 (75), 233(74), 203 (29), 201 (31), 175 (26), 173 (28), 153 (31), 125 (67), 121 (75), 111 (28), 93 (100), 67 (84), 55 (92);
Methyl (Z)-3-bromo-7-iodo-2-octenoate (109)

Methyl (Z)-3-bromo-7-hydroxy-2-octenoate (105) (0.44 g, 1.75 mmol) was converted to 109 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 8% diethy ether / pet. ether, followed by Kugelrohr distillation (190 °C / 0.1 mm Hg) to afford 0.53 g (84%) of 109 as a colourless oil.

IR (neat): 2941, 2863, 1729, 1636, 1440, 1296, 1182, 1076 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.55-1.90 (m, 4H), 1.91 (d, J = 6.8 Hz, 3H), 2.59 (t, J = 6.8 Hz, 2H), 3.73 (s, 3H), 4.14 (sextet, J = 6.8 Hz, 1H), 6.30 (t, J = 1 Hz, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 28.10, 28.72, 28.85, 41.19, 42.42, 51.56, 119.50, 141.54, 164.49;

LRMS (Cl(+), ammonia) m/z (relative intensity): 363 (¹¹Br, M⁺+1, 23), 361 (¹⁷Br, M⁺+1, 24), 331 (7), 329 (7), 235 (20), 233 (20), 203 (10), 201 (10), 175 (28), 173 (29), 153 (35), 125 (80), 121 (81), 111 (24), 93 (100), 67 (95), 55 (93);

HRMS (Cl(+), ammonia)

m/z calcd for C₉H₁₅O₂⁺¹Br (M⁺+1): 362.9280, found: 362.9292;
m/z calcd for C₉H₁₅O₂⁺²Br (M⁺+1): 360.9300, found: 360.9304;

3.55 Methyl (E)-3-bromo-7-iodo-2-heptenoate (110)

Methyl (E)-3-bromo-7-hydroxy-2-heptenoate (88) (0.070 g, 0.30 mmol) was converted to 110 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 5% diethyl ether / pet. ether, followed by Kugelrohr distillation (125 °C / 0.05 mm Hg) to afford 0.10 g (100%) of 110 as a colourless oil.

IR (neat): 2941, 1720, 1624, 1435, 1346, 1192, 1129 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.73 (qn, J = 7.0 Hz, 2H), 1.86 (qn, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 3.19 (t, J = 7.0 Hz, 2H), 3.69 (s, 3H), 6.34 (s, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 5.89, 29.09, 32.13, 36.33, 51.61, 123.35, 149.38, 164.64;

LRMS (DCI(+), ammonia) m/z (relative intensity): 366 (⁸¹Br, M⁺+NH₄, 11), 364 (⁷⁹Br, M⁺+NH₄, 11), 349 (⁸¹Br, M⁺+1, 32), 348 (⁸¹Br, M⁺, 14), 347 (⁷⁹Br, M⁺+1, 33), 346 (⁷⁸Br, M⁺, 12), 317 (35), 315 (35), 267 (83), 221 (84), 219 (84), 189 (78), 187 (78), 161 (74), 159 (75), 141 (70), 140 (80), 139 (87), 112 (73), 111 (93), 109 (51), 108 (70), 107 (83), 99 (34), 98 (36), 97 (75), 81 (100), 67 (95), 59 (97);

HRMS (Cl(+), ammonia)

m/z calcd for C₈H₁₃O₂⁸¹Br (M⁺+1): 346.9144, found: 346.9127;

m/z calcd for C₈H₁₃O₂⁷⁹Br (M⁺+1): 348.9123, found: 348.9129;


3.56 Methyl (Z)-3-bromo-7-iodo-2-heptenoate (111)
Methyl (Z)-3-bromo-7-hydroxy-2-heptenoate (89) (0.11 g, 0.46 mmol) was converted to 111 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 7% diethy ether / pet. ether followed by Kugelrohr distillation (130 °C / 0.05 mm Hg) to afford 0.13 g (81%) of 111 as a colourless oil.

IR (neat): 2944, 2837, 1728, 1636, 1436, 1297, 1251, 1185, 850 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.73 (qn, J = 6.8 Hz, 2H), 1.82 (qn, J = 6.8 Hz, 2H), 2.58 (t, J = 6.8 Hz, 2H), 3.17 (t, J = 6.8 Hz, 2H), 3.73 (s, 3H), 6.29 (s, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 5.59, 28.78, 31.94, 42.28, 51.57, 119.53, 141.43, 164.47;

LRMS (Cl(+), ammonia) m/z (relative intensity): 366 (⁸¹Br, M⁺+NH₄, 26), 364 (⁷⁹Br, M⁺+NH₄, 27), 349 (⁸¹Br, M⁺+1, 91), 347 (⁷⁹Br, M⁺+1, 92), 317 (50), 315 (52), 267 (98), 221 (87), 219 (87), 189 (37), 187 (36), 161 (52), 159 (54), 141 (17), 140 (70), 139 (92), 112 (36), 111 (94), 109 (15), 108 (29), 107 (90), 81 (100) 67 (44), 59 (78);

HRMS (Cl(+), methane)

m/z calcd for C₈H₁₃O₂⁸¹BrL (M⁺+1): 346.9144, found: 346.9137;

m/z calcd for C₈H₁₃O₂⁷⁹BrL (M⁺+1): 348.9123, found: 348.9137;


3.57 5-Bromo-1-(tetrahydropyranloxy)pentane (114)

5-Bromopentan-1-ol (113) (6.15 g, 35.8 mmol) was converted to 114 following the procedure outlined in Section 3.4. The crude brown oil was purified by distillation (85-103 °C / 0.15 mm Hg) from K₂CO₃ to afford 7.91 g (86%) of 114 as a colourless oil.

IR (neat): 2907, 1453, 1440, 1354, 1201, 1128, 1074, 1031, 870 cm⁻¹;
$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 1.41-1.95 (m, 12H), 3.40 (t, $J = 6.8$ Hz, 2H), 3.42 (m, 2H), 3.78 (m, 2H), 4.55 (m, 1H);

LRMS (Cl(+), ammonia) $m/z$ (relative intensity): 270 ($^{81}$Br, M$^+$+NH$_4^+$, 51), 268 ($^{79}$Br, M$^+$+NH$_4^+$, 52), 251 (14), 249 (11), 119 (48), 102 (100), 85 (55);

HRMS (Cl(+), methane)

$m/z$ calcd for C$_{10}$H$_{20}$O$_2$$^{81}$Br (M$^+$+1): 253.0626, found: 253.0634;
$m/z$ calcd for C$_{10}$H$_{20}$O$_2$$^{79}$Br (M$^+$+1): 251.0647, found: 251.0638;

Anal. Calcd for C$_{10}$H$_{19}$O$_2$: C, 47.82; H, 7.62. Found: C, 47.95; H, 7.78.

3.58 7-(2-Tetrahydropyranyloxy)-1-heptyne (115)

5-Bromo-1-(2-tetrahydropyranyloxy)pentane (114) (7.00 g, 27.9 mmol) was converted to 115 following the procedure outlined in Section 3.43. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 3.60 g (66%) of 115 as a colourless oil. Kugelrohr distillation (95-100 °C / 1.0 mm Hg) afforded analytically pure 115 as a colourless oil.

IR (neat): 3286, 2906, 2116, 1449, 1354, 1201, 1129, 1073, 1030, 981, 871 cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 1.37-1.80 (m, 12H), 1.90 (t, $J = 2.7$ Hz, 1H), 2.16 (dt, $J = 2.7$ & 6.6 Hz, 2H), 3.40 (m, 2H), 3.77 (m, 2H), 4.54 (m, 1H);

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 18.34, 19.64, 25.42, 25.48, 28.31, 29.22, 30.74, 62.29, 67.34, 68.17, 84.48, 98.82;

LRMS (Cl(+), ammonia) $m/z$ (relative intensity): 214 (M$^+$+NH$_4^+$, 47), 197 (M$^+$+1, 4), 118 (30), 102 (80), 85 (25);

HRMS (Cl(+), methane) $m/z$ calcd for C$_{12}$H$_{21}$O$_2$ (M$^+$+1): 197.1542, found: 197.1545;

Anal. Calcd for C$_{12}$H$_{20}$O$_2$: C, 73.43; H, 10.27. Found: C, 73.47; H, 10.44.
3.59 Methyl 8-(2-tetrahydropyranyloxy)-2-octynoate (116)

\[
\text{MeO}_2\text{C} = \equiv \quad \text{O} \\
\text{O} \\
\text{MeO}_2\text{C} = \equiv \quad \text{O}
\]

7-(2-Tetrahydropyranyloxy)-1-heptyne (115) (0.37 g, 1.9 mmol) was converted to 116 following the procedure outlined in Section 3.21. The crude yellow oil was purified by flash chromatography, eluting with 12% ethyl acetate / pet. ether to afford 0.44 g (92%) of 116 as a colourless oil. Kugelrohr distillation (115-120 °C / 0.05 mm Hg) from K\textsubscript{2}CO\textsubscript{3} afforded analytically pure 116.

IR (neat): 2940, 2866, 2236, 1714, 1436, 1258, 1132, 1120, 1074, 1031 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \delta: 1.40-1.88 (m, 12H), 2.31 (t, J = 6.8 Hz, 2H), 3.40 (m, 2H), 3.71 (s, 3H), 3.63-3.88 (m, 2H), 4.53 (m, 1H);

LRMS (Cl(+), ammonia) m/z (relative intensity): 272 (M\textsuperscript{+}+NH\textsubscript{4}, 100), 255 (M\textsuperscript{+}+1, 10), 188 (30), 102 (30), 85 (20);

HRMS (Cl(+), methane) m/z calcd for C\textsubscript{14}H\textsubscript{23}O\textsubscript{4} (M\textsuperscript{+}+1): 255.1596, found: 255.1588;

Anal. Calcd for C\textsubscript{14}H\textsubscript{22}O\textsubscript{4}: C, 66.12; H, 8.72. Found: C, 66.10; H, 8.85.

3.60 Methyl 8-hydroxy-2-octynoate (117)

Methyl 8-(2-tetrahydropyranyloxy)-2-octynoate (116) (0.53 g, 2.1 mmol) was converted to 117 following the procedure outlined in Section 3.9. The crude colourless oil was purified by flash chromatography, eluting with 40% ethyl acetate / pet. ether to afford 0.33 g (94%) of 117 as a colourless oil. Kugelrohr distillation (100-120 °C / 0.2 mm Hg) afforded analytically pure 117.

IR (neat): 3387, 2939, 2865, 2236, 1709, 1436, 1264, 1068, 753 cm\textsuperscript{-1};

\textsuperscript{1}H NMR (200 MHz, CDCl\textsubscript{3}) \delta: 1.35-1.65 (m, 6H), 1.77 (br s, 1H), 2.31 (t, J = 6.8 Hz, 2H), 3.59 (t, J = 6.0 Hz, 2H), 3.70 (s, 3H);
LRMS (El) m/z (relative intensity): 170 (M+ , 7), 139 (51), 138 (54), 111 (59), 110 (41), 109 (43), 108 (31), 97 (28), 93 (47), 81 (55), 79 (100), 67 (43), 55 (48);

HRMS (El) m/z calcd for C9H14O3: 170.0943, found: 170.0942;


3.61 Methyl (E)-3-bromo-8-hydroxy-2-octenoate (118)

Methyl 8-hydroxy-2-octynoate (117) (0.26 g, 1.5 mmol) was converted to 118 following the procedure outlined in Section 3.36. The crude material was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (120 °C / 0.3 mm Hg) to afford 0.15 g (39%) 118 as a colourless oil. This reaction also afforded after Kugelrohr distillation (145 °C / 0.3 mm Hg) 0.18 g (47%) of 119 as a colourless oil.

IR (neat): 3378, 2937, 2863, 1718, 1624, 1437, 1339, 1187, 1049, 991 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.40 (qn, J = 7.3 Hz, 2H), 1.56 (s, 1H), 1.61 (m, 4H), 3.08 (t, J = 7.3 Hz, 2H), 3.61 (t, J = 6.6 Hz. 2H), 3.67 (s, 3H), 6.30 (s, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 24.71, 28.07, 32.37, 37.55, 51.52, 62.69, 122.83, 150.41, 164.75;

LRMS (Cl(+), ammonia) m/z (relative intensity): 270 (⁸¹Br, M⁺+NH₄, 100), 268 (⁷⁹Br, M⁺+NH₄, 98), 253 (⁸¹Br, M⁺+1, 26), 251 (⁷⁹Br, M⁺+1, 25), 190 (70), 173 (50);

HRMS (Cl(+), methane) m/z calcd for C₉H₁₆O₃⁸¹Br (M⁺+1): 253.0264, found: 253.0268; m/z calcd for C₉H₁₆O₃⁷⁹Br (M⁺+1): 253.0283, found: 251.0282;

Anal. Calcd for C₉H₁₅O₃Br: C, 43.05; H, 6.02. Found: C, 43.48; H, 6.25.
3.62 Methyl (Z)-3-bromo-8-hydroxy-2-octenoate (119)

\[
\text{MeO}_2\text{C}^\text{\(\text{\(-)}\)}\text{(CH}_2\text{)}_7\text{OH} \quad \text{Br}
\]

See Section 3.61.

IR (neat): 3400, 2937, 2862, 1724, 1635, 1438, 1308, 1186, 1047, 851 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.35 (qn, \(J = 6.4\) Hz, 2H), 1.55 (qn, \(J = 6.4\) Hz, 2H), 1.62 (qn, \(J = 6.4\) Hz, 2H), 1.64 (s, 1H), 2.55 (t, \(J = 6.4\) Hz, 2H), 3.60 (t, \(J = 6.4\) Hz, 2H), 3.70 (s, 3H), 6.26 (s, 1H);

\(^1^3\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\): 24.60, 27.74, 32.29, 43.43, 51.51, 62.59, 119.10, 142.36, 164.64;

LRMS (Cl(+), ammonia) \(m/z\) (relative intensity): 270 (\(^{81}\)Br, M\(^+\)+NH\(_4\), 18), 268 (\(^{79}\)Br, M\(^+\)+NH\(_4\), 19), 253 (\(^{81}\)Br, M\(^+\)+1, 1), 269 (\(^{79}\)Br, M\(^+\)+1, 1);

HRMS (Cl(+), methane) \(m/z\) calcd for C\(_9\)H\(_{16}\)O\(_3\)\(^{81}\)Br (M\(^+\)+1): 253.0264, found: 253.0274;

\(m/z\) calcd for C\(_9\)H\(_{16}\)O\(_3\)\(^{79}\)Br (M\(^+\)+1): 253.0283, found: 251.0287;

Anal. Calcd for C\(_9\)H\(_{15}\)O\(_3\)Br: C, 43.05; H, 6.02. Found: C, 43.09; H, 6.07.

3.63 Methyl (E)-3-bromo-8-iodo-2-octenoate (120)

Methyl (E)-3-bromo-8-hydroxy-2-octenoate (118) (0.08 g, 0.3 mmol) was converted to 120 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 5% diethyl ether / pet. ether followed by Kugelrohr distillation (150 °C / 0.2 mm Hg) to afford 0.09 g (80%) of 120 as a colourless oil.

IR (neat): 2937, 2859, 1721, 1624, 1434, 1343, 1267, 1190, 1128, 981, 863 cm\(^{-1}\);
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.44 (qn, J = 7.2 Hz, 2H), 1.64 (qn, J = 7.2 Hz, 2H), 1.84 (qn, J = 7.2 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 3.17 (t, J = 7.2 Hz, 2H), 3.69 (s, 3H), 6.32 (s, 1H);

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 6.53, 27.17, 29.37, 33.06, 37.32, 51.56, 123.02, 149.97, 164.67;

LRMS (Cl(+), ammonia) $m/z$ (relative intensity): 380 ($^{81}$Br, M$^+$+NH$_4^+$, 77), 378 ($^{79}$Br, M$^+$+NH$_4^+$, 79), 363 ($^{81}$Br, M$^+$+1, 38), 361 ($^{79}$Br, M$^+$+1, 40), 331 (40), 329 (42), 298 (45), 281 (90), 235 (85), 233 (85), 203 (80), 201 (80), 175 (70), 173 (70), 153 (90), 125 (95), 121 (94), 111 (55), 93 (100), 81 (60), 67 (75), 55 (97);

HRMS (Cl(+), methane)

$m/z$ calcd for C$_9$H$_{15}$O$_2$Br$_{81}$ (M$^+$+1): 362.9280, found: 362.9280;

$m/z$ calcd for C$_9$H$_{15}$O$_2$Br$_{79}$ (M$^+$+1): 360.9300, found: 360.9309;


3.64 Methyl (Z)-3-bromo-8-iodo-2-octenoate (121)

Methyl (Z)-3-bromo-8-hydroxy-2-octenoate (119) (0.09 g, 0.4 mmol) was converted to 121 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 7% diethyl ether / pet. ether followed by Kugelrohr distillation (150 °C / 0.05 mm Hg) to afford 0.11 g (90%) of 121 as a colourless oil.

IR (neat): 2936, 2858, 1731, 1635, 1434, 1300, 1179, 921, 849 cm$^{-1}$;

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 1.41 (qn, J = 7.3 Hz, 2H), 1.64 (qn, J = 7.3 Hz, 2H), 1.82 (qn, J = 7.3 Hz, 2H), 2.57 (t, J = 7.3 Hz, 2H), 3.16 (t, J = 7.3 Hz, 2H), 3.72 (s, 3H), 6.28 (s, 1H);

$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 6.30, 26.89, 29.22, 33.04, 43.21, 51.53, 119.28, 141.96, 164.55;
LRMS (Cl(+), ammonia) $m/z$ (relative intensity): 380 ($^{81}\text{Br}, M^+\text{+NH}_4, 4$), 378 ($^{79}\text{Br}, M^+\text{+NH}_4, 4$), 363 ($^{81}\text{Br}, M^+\text{+1}, 72$), 361 ($^{79}\text{Br}, M^+\text{+1}, 72$), 331 (25), 329 (25), 281 (65), 235 (30), 233 (30), 203 (20), 201 (20), 175 (30), 173 (35), 153 (80), 125 (75), 121 (85), 111 (30), 93 (95), 81 (45), 67 (70), 55 (100);

HRMS (Cl(+), methane)

$m/z$ calcd for C$_9$H$_{15}$O$_2^{81}\text{Br}$ (M$^+$+1): 362.9280, found: 362.9287;

$m/z$ calcd for C$_9$H$_{15}$O$_2^{79}\text{Br}$ (M$^+$+1): 360.9300, found: 360.9296;


3.65 Methyl (cyclohexylidene)acetate (122)

![Methyl (Z)-3-bromo-8-iodo-2-octenoate](image)

Methyl (Z)-3-bromo-8-iodo-2-octenoate (121) (60.4 mg, 0.167 mmol) was converted to 122 following the procedure outlined in Section 3.40. The procedure was amended by allowing 40 minutes of irradiation. The concentrated crude material was purified by radial chromatography, eluting with 4% diethyl ether / pet. ether to afford 15.6 mg (60%) of 122.

IR (neat): 2938, 1708, 1647, 1438, 1213, 1164 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.59 (m, 6H), 2.17 (t, $J = 6.4$ Hz, 2H), 2.80 (t, $J = 6.4$ Hz, 2H), 3.66 (s, 3H), 5.58 (s, 1H);

LRMS (El) $m/z$ (relative intensity): 154 (M$^+$, 100), 151 (26), 123 (33), 122 (20), 95 (40), 81 (21);

HRMS (El) $m/z$ calcd for C$_9$H$_{14}$O$_2$: 154.0994, found: 154.1001.
3.66  Methyl (E)-(2-methylcyclohexylidene)acetate (123)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{MeH} \\
\text{C} & \quad \text{H} \\
\end{align*}
\]

Methyl (E)-3-bromo-8-iodo-2-nonenoate (125) (108.6 mg, 0.290 mmol) was converted to 123 following the procedure outlined in Section 3.40. The procedure was amended by allowing 40 minutes of irradiation. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl ether / pet. ether to afford 47.3 mg (90%) of 123 and 124 which GC analysis showed to be of 99:1 ratio. The \(^1\)H NMR data for compound 123 was consistent with that reported in the literature.\(^{44}\)

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 1.02 (d, \(J = 7.0\) Hz, 3H), 1.23 (m, 1H), 1.42 (m, 2H), 1.68 (m, 3H), 2.16 (m, 2H), 3.44 (m, 1H), 3.62 (s, 3H), 5.52 (s, 1H).

3.67  Methyl (Z)-(2-methylcyclohexylidene)acetate (124)

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{MeH} \\
\text{C} & \quad \text{H} \\
\end{align*}
\]

Methyl (Z)-3,8-diiodo-2-nonenoate (155) (91.4 mg, 0.217 mmol) was converted to 124 following the procedure outlined in Section 3.40. The procedure was amended by allowing 40 minutes of irradiation. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl ether / pet. ether to afford 31.1 mg (85%) of 124 and 123 which GC analysis showed to be of 92:8 ratio. The \(^1\)H NMR data for compound 124 was consistent with that reported in the literature.\(^{44}\)

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 1.13 (d, \(J = 7.0\) Hz, 3H), 1.2-1.6 (m, 5H), 1.83 (m, 1H), 2.01 (m, 1H), 2.37 (ddt, \(J = 2.0, 5.0\) & 13.0 Hz, 1H), 3.67 (s, 3H), 4.00 (m, 1H), 5.52 (d, \(J = 2.0\) Hz, 1H).
3.68 1-Bromo-5-(2-tetrahydropyranloxy)hexane (128)

Bromine (3.1 mL, 60 mmol) was added to an ice cooled solution of triphenylphosphine (15.7 g, 60.0 mmol) in 170 mL of dry methylene chloride. To the resulting white precipitate was added 6-hydroxy-1-hexene (125) (5.00 g, 50.0 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted to 500 mL with methylene chloride, washed consecutively with water, 1 M NaOH, water and brine, and then dried. This was filtered and concentrated to a white solid which was triturated with pet. ether and filtered through silica gel, eluting with pet. ether. These filtrates were concentrated to a pale yellow oil, which was dissolved in 50 mL of THF and added to a solution of mercuric acetate (15.3 g, 47.9 mmol) in 50 mL of water. During the addition, the reaction mixture became bright yellow and after 30 seconds returned to colourless. This was stirred for 15 minutes and then 150 mL of 3 M NaOH was added, followed immediately by the addition of 150 mL of 0.5 M NaBH₄ solution in 3 M NaOH. The resulting dark gray mixture was stirred for 10 minutes, and allowed to settle. The supernatant was decanted and saturated with NaCl, and the layers were separated. The aqueous layer was extracted three times with 100 mL of diethyl ether and the combined organic extracts were washed with brine and dried. This was filtered and concentrated to give a cloudy oil which was filtered through silica gel, eluting with diethyl ether. The filtrate was concentrated to give a colourless oil, which was dissolved in 250 mL of dry methylene chloride, followed by addition of p-toluenesulfonic acid monohydrate (0.46 g, 2.4 mmol) and dihydropyran (5.3 mL, 58 mmol). The mixture was stirred overnight, diluted to 750 mL with diethyl ether, washed with saturated NaHCO₃ solution and brine, and dried. This was filtered and concentrated to brown oil, which was purified by flash chromatography, eluting with 5% diethyl ether/ pet. ether to afford 5.86 g (46%) of 128 as a colourless oil. Kugelrohr distillation (115 °C / 4 mm Hg) afforded analytically pure 128.

IR (neat): 2940, 2867, 1376, 1127, 1027 cm⁻¹;
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.08 (d, J = 6.1 Hz, 1.5H), 1.20 (d, J = 6.1 Hz, 1.5H), 1.33-1.60 (m, 8H), 1.67 (m, 1H), 1.74-1.92 (m, 3H), 3.38 (m, 2H), 3.43 (m, 1H), 3.69 (sextet, J = 6.1 Hz, 0.5H), 3.76 (sextet, J = 6.1 Hz, 0.5H), 3.80-3.92 (m, 1H), 4.60 (m, 0.5H), 4.66 (m, 0.5H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 284 ($^{81}$Br, M$^+$+NH$_4$, 58), 282 ($^{79}$Br, M$^+$+NH$_4$, 60), 267 ($^{81}$Br, M$^+$+1, 12), 265 ($^{79}$Br, M$^+$+1, 15), 186 (61), 169 (62), 165 (64), 163 (66), 102 (100), 85 (31);

HRMS (Cl(+), isobutane)

$m/z$ calcd for C$_{11}$H$_{22}$O$_2$$^{81}$Br (M$^+$+1): 267.0783, found: 267.0782;

$m/z$ calcd for C$_{11}$H$_{22}$O$_2$$^{79}$Br (M$^+$+1): 265.0803, found: 265.0798;

Anal. Calcd for C$_{11}$H$_{21}$O$_2$Br: C, 49.82; H, 7.98. Found: C, 49.77; H, 7.83.

3.69 7-(2-Tetrahydropyranloxy)-1-octyne (129)

1-Bromo-5-(2-tetrahydropyranloxy)hexane (128) (5.85 g, 22.1 mmol) was converted to 129 following the procedure outlined in Section 3.43. The crude material was purified by flash chromatography, eluting with 15% diethyl ether / pet. ether to afford 3.43 g (74%) of 129 as a colourless oil. Kugelrohr distillation (130 °C / 1.0 mm Hg) afforded analytically pure 129.

IR (neat): 3291, 2938, 2865, 2117, 1376, 1201, 1127, 1019 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.08 (d, J = 6.1 Hz, 1.5H), 1.19 (d, J = 6.1 Hz, 1.5H), 1.31-1.61 (m, 10H), 1.67 (m, 1H), 1.79 (m, 1H), 1.90 (t, J = 2.7 Hz, 1H), 2.16 (m, 2H), 3.47 (m, 1H), 3.69 (m, 0.5H), 3.74 (m, 0.5H), 3.86 (m, 1H), 4.61 (m, 0.5H), 4.67 (m, 0.5H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 228 (M$^+$+NH$_4$, 100), 211 (M$^+$+1, 43), 102 (60), 85 (41);
HRMS (Cl(+), isobutane) m/z calcd for C\textsubscript{13}H\textsubscript{23}O\textsubscript{2} (M\textsuperscript{++1}): 211.1698, found: 211.1698;

Anal. Calcd for C\textsubscript{13}H\textsubscript{22}O\textsubscript{2}: C, 74.24; H, 10.54. Found: C, 74.17; H, 10.77.

3.70 Methyl 8-(2-tetrahydropyranyloxy)-2-nonynoate (130)

\[
\text{MeO}_2\text{C} = \equiv \quad \text{O}\quad \text{O}
\]

7-(2-Tetrahydropyranyloxy)-1-octyne (129) (1.32 g, 62.9 mmol) was converted to 130 following the procedure outlined in Section 3.21. The crude material was purified by flash chromatography, eluting with 15% diethyl ether / pet. ether to afford 1.59 g (95%) of 130 as a colourless oil. Kugelrohr distillation (140 °C / 0.1 mm Hg) afforded analytically pure 130.

IR (neat): 2940, 2866, 2236, 1717, 1438, 1257, 1128, 1076, 1027 cm\textsuperscript{-1};

\(^1\)H NMR (200 MHz, CDCl\textsubscript{3}) \(\delta\): 1.08 (d, J = 6.1 Hz, 1.5H), 1.20 (d, J = 6.1 Hz, 1.5H), 1.32-1.88 (m, 12H), 2.32 (t, J = 6.8 Hz, 2H), 3.46 (m, 1H), 3.73 (s, 3H), 3.65-3.95 (m, 1H), 4.59 (m, 0.5H), 4.66 (m, 0.5H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 286 (M\textsuperscript{++NH\textsubscript{4}}, 100), 269 (M\textsuperscript{++1}, 8), 185 (22), 102 (21);

HRMS (Cl(+), isobutane) m/z calcd for C\textsubscript{15}H\textsubscript{25}O\textsubscript{4} (M\textsuperscript{++1}): 269.1753, found: 269.1754;

Anal. Calcd for C\textsubscript{15}H\textsubscript{24}O\textsubscript{4}: C, 67.14; H, 9.01. Found: C, 67.49; H, 9.11.

3.71 Methyl 8-hydroxy-2-nonynoate (131)

\[
\text{MeO}_2\text{C} = \equiv \quad \text{OH}
\]

Methyl 8-(2-tetrahydropyranyloxy)-2-nonynoate (130) (1.59 g, 6.26 mmol) was converted to 131 following the procedure outlined in Section 3.9. The crude material was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether to
afford 1.04 g (98%) of 131 as a colourless oil. Kugelrohr distillation (130 °C / 0.05 mm Hg) afforded analytically pure 131.

IR (neat): 3407, 2940, 2865, 2236, 1711, 1436, 1263, 1078, 754 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.17 (d, J = 6.1 Hz, 3H), 1.43 (m, 4H), 1.49-1.65 (m, 2H), 2.33 (t, J = 6.8 Hz, 2H), 3.73 (s, 3H), 3.80 (m, 1H);

LRMS (EI) m/z (relative intensity): 184 (M⁺, 0.5), 111 (48), 109 (33), 108 (57), 107 (34), 79 (100), 67 (43), 45 (100);

HRMS (EI) m/z calcd for C₁₀H₁₆O₃: 184.1099, found: 184.1103;


3.72 Methyl (E)-3-bromo-8-hydroxy-2-nonenoate (132)

Methyl 8-hydroxy-2-nynoate (131) (0.50 g, 2.9 mmol) was converted to 132 following the procedure outlined in Section 3.36. The crude yellow oil was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (160 °C / 0.2 mm Hg) to afford 0.25 g (32%) of 132 as a colourless oil. This reaction also afforded after Kugelrohr distillation (130 °C / 0.1 mm Hg) 0.41 g (53%) of 133 as a colourless oil.

IR (neat): 3393, 2940, 2862, 1718, 1624, 1440, 1345, 1200, 1170, 1126 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.14 (d, J = 6.1 Hz, 3H), 1.29-1.49 (m, 4H), 1.60 (m, 3H), 3.06 (t, J = 7.3 Hz, 2H), 3.66 (s, 3H), 3.75 (m, 1H), 6.29 (s, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 284 (⁸¹Br, M⁺+NH₄, 100), 282 (⁷⁹Br, M⁺+NH₄, 100), 267 (⁸¹Br, M⁺+1, 3), 265 (⁷⁹Br, M⁺+1, 3), 167 (43);
HRMS (Cl(+), isobutane)

\[ m/z \text{ calcd for } C_{10}H_{18}O_3^{81}Br (M^{+}+1): 267.0419, \text{ found: 267.0406}; \]

\[ m/z \text{ calcd for } C_{10}H_{18}O_3^{79}Br (M^{+}+1): 265.0440, \text{ found: 265.0430}; \]

Anal. Calcd for C_{10}H_{17}O_{3}Br: C, 45.30; H, 6.46. Found: C, 45.30; H, 6.60.

3.73 Methyl (Z)-3-bromo-8-hydroxy-2-nonenolate (133)

See Section 3.72.

IR (neat): 3411, 2938, 2861, 1725, 1635, 1440, 1305, 1185, 1130, 1077 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.14 (d, \(J = 6.4\ \text{ Hz}, 3\)H), 1.23-1.48 (m, 4H), 1.59 (m, 3H), 2.54 (t, \(J = 7.3\ \text{ Hz}, 2\)H), 3.69 (s, 3H), 3.75 (m, 1H), 6.25 (s, 1H);

LRMS (DCI(+), ammonia) \(m/z\) (relative intensity): 284 (\(^{81}\)Br, M\(^{+}\)+NH\(_4\), 100), 282 (\(^{79}\)Br, M\(^{+}\)+NH\(_4\), 90), 267 (\(^{81}\)Br, M\(^{+}\)+1, 5), 265 (\(^{79}\)Br, M\(^{+}\)+1, 5), 202 (76), 185 (79), 167 (85), 153 (70), 141 (37);

HRMS (Cl(+), isobutane)

\[ m/z \text{ calcd for } C_{10}H_{18}O_3^{81}Br (M^{+}+1): 267.0419, \text{ found: 267.0413}; \]

\[ m/z \text{ calcd for } C_{10}H_{18}O_3^{79}Br (M^{+}+1): 265.0440, \text{ found: 265.0430}; \]

Anal. Calcd for C_{10}H_{17}O_{3}Br: C, 45.30; H, 6.46. Found: C, 45.69; H, 6.66.

3.74 Methyl (E)-3-bromo-8-iodo-2-nonenolate (134)

Methyl (E)-3-bromo-8-hydroxy-2-nonenolate (132) (0.13 g, 0.49 mmol) was converted to 134 following the procedure outlined in Section 3.53. The crude
colourless oil was purified by radial chromatography, eluting with 3% diethy ether / pet. ether, followed by Kugelrohr distillation (130 °C / 0.2 mm Hg) to afford 0.12 g (67%) of 134 as a colourless oil.

IR (neat): 2935, 2860, 1722, 1623, 1436, 1343, 1199, 1173, 863 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.36-1.70 (m, 5H), 1.84 (m, 1H), 1.89 (d, J = 7.0 Hz, 3H), 3.09 (t, J = 7.3 Hz, 2H), 3.69 (s, 3H), 4.16 (sextet, J = 7.0 Hz, 1H), 6.32 (s, 1H);

LRMS (Cl(+), ammonia) m/z (relative intensity): 394 (⁸¹Br, M⁺+NH₄⁺, 15), 392 (⁷⁹Br, M⁺⁺NH₄⁺, 17), 377 (⁸¹Br, M⁺⁺⁺, 20), 375 (⁷⁹Br, M⁺⁺⁺, 21), 345 (12), 343 (13), 249 (87), 247 (87), 217 (75), 215 (76), 189 (71), 187 (72), 167 (85), 135 (90), 107 (100), 69 (94);

HRMS (Cl(+), methane)

m/z calcd for C₁₀H₁₇O₂⁸iBr (M⁺+1): 376.9437, found: 376.9432;

m/z calcd for C₁₀H₁₇O₂⁷⁹Br (M⁺+1): 374.9457, found: 374.9460;


3.75 Methyl (Z)-3-bromo-8-iodo-2-nonenoate (135)

Methyl (Z)-3-bromo-8-hydroxy-2-nonenoate (133) (0.14 g, 0.53 mmol) was converted to 135 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 4% diethy ether / pet. ether to afford 0.12 g (75%) of 135 as a colourless oil. Kugelrohr distillation (150 °C / 0.05 mm Hg) afforded analytically pure 135.

IR (neat): 2935, 2860, 1731, 1635, 1440, 1302, 1181, 1078, 847 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 1.32-1.72 (m, 5H), 1.81 (m, 1H), 1.89 (d, J = 7.0 Hz, 3H), 2.57 (t, J = 7.3 Hz, 2H), 3.72 (s, 3H), 4.14 (sextet, J = 7.0 Hz, 1H), 6.28 (s, 1H);
LRMS (Cl(+), ammonia) m/z (relative intensity): 394 (\(^{81}\)Br, M\(^{++}\)NH\(_4\), 7), 392 (\(^{79}\)Br, M\(^{++}\)NH\(_4\), 8), 377 (\(^{81}\)Br, M\(^{++}\)+1, 84), 375 (\(^{79}\)Br, M\(^{++}\)+1, 84), 345 (12), 343 (12), 249 (50), 247 (52), 217 (19), 215 (20), 189 (40), 187 (41), 167 (83), 135 (91), 107 (100), 69 (86);

HRMS (Cl(+), methane)

m/z calcd for C\(_{10}\)H\(_{17}\)O\(_2\)\(^{81}\)Br\(_{1}\) (M\(^{++}\)+1): 376.9437, found: 376.9430;
m/z calcd for C\(_{10}\)H\(_{17}\)O\(_2\)\(^{79}\)Br\(_{1}\) (M\(^{++}\)+1): 374.9457, found: 374.9449;

Anal. Calcd for C\(_{10}\)H\(_{16}\)O\(_2\)\(^{81}\)Br\(_{1\ r m s}\): C, 28.46; H, 3.82. Found: C, 28.50; H, 3.87.

### 3.76 Methyl (E)-7-(2-tetrahydropyranloxy)-3-(tri(n-butyl)stannyl)-2-octenoate (140)

A solution of hexa(n-butyl)ditin (1.97 g, 3.90 mmol) in 26 mL of dry THF was cooled in an ice bath and n-butyllithium (2.50 mL of 1.54 M in hexanes, 3.90 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 20 minutes, and then cooled to -78 °C. Copper bromide-dimethyl sulfide complex (0.80 g, 3.9 mmol) was added in one portion and the resulting reddish-brown reaction mixture was stirred for 30 minutes before methyl 7-(2-tetrahydropyranloxy)-2-octynoate (102) (0.66 g, 2.6 mmol) in 4 mL of dry THF was added. The reaction mixture was stirred for 3 hours, quenched by the addition of 1.5 mL of ethanol followed by 10 mL of 20:1 saturated NH\(_4\)Cl:NH\(_4\)OH solution, and then allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted twice with 20 mL of portions of diethyl ether. The combined organics were washed with 20 mL of 20:1 saturated NH\(_4\)Cl:NH\(_4\)OH solution and then dried. This was filtered and concentrated to a yellow oil which was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (190-205 °C / 0.1 mm Hg) from K\(_2\)CO\(_3\) to afford 1.28 g (90%) of 140 as a colourless oil.
IR (neat): 2936, 2853, 1720, 1592, 1451, 1376, 1348, 1166, 1135, 1026, 870, 665 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 0.80-0.97 (m, 15H), 1.08 (d, J = 6.1 Hz, 1.5H), 1.20 (d, J = 6.3 Hz, 1.5H), 1.23-1.83 (m, 22H), 2.86 (m, 2H), 3.45 (m, 1H), 3.67 (s, 3H), 3.70-3.96 (m, 2H), 4.61 (m, 0.5H), 4.70 (m, 0.5H), 5.92 (s, J₅₆₋H = 64 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 564 (¹²⁰Sn, M⁺+NH₄, 18), 562 (¹¹⁸Sn, M⁺⁺+NH₄, 13), 560 (¹¹⁶Sn, M⁺⁺+NH₄, 7), 405 (100), 403 (75) 401 (40);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₂₆H₅₄NO₄¹²⁰Sn (M⁺⁺+NH₄): 564.3075, found: 564.3066;


3.77 Methyl (E)-8-(2-tetrahydropyranloxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (141)

Methyl 8-(2-tetrahydropyranloxy)-2-nonynoate (132) (0.65 g, 2.4 mmol) was converted to 141 following the procedure outlined in Section 3.76. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 1.27 g (93%) of 141 as a colourless oil. Kugelrohr distillation (200 °C / 0.05 mm Hg) afforded analytically pure 141.

IR (neat): 2936, 2854, 1720, 1592, 1452, 1165, 1136, 1026 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.80-1.00 (m, 15H), 1.08 (d, J = 6.1 Hz, 1.5H), 1.19 (d, J = 6.1 Hz, 1.5H), 1.22-60 (m, 22H), 1.68 (m, 1H), 1.81 (m, 1H), 2.85 (m, 2H), 3.47 (m, 1H), 3.66 (s, 3H), 3.75 (m, 1H), 3.89 (m, 1H), 4.61 (m, 0.5H), 4.69 (m, 0.5H), 5.91 (s, J₅₆₋H = 65 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 578 (¹²⁰Sn, M⁺+NH₄, 100), 576 (¹¹⁸Sn, M⁺⁺+NH₄, 69), 574 (¹¹⁶Sn, M⁺⁺+NH₄, 34), 503 (43), 501 (31), 499 (18), 419 (91), 417 (65), 415 (36), 85 (27);
3.78 Methyl (E)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate (142)

A solution of methyl (E)-7-(2-tetrahydropyranyloxy)-3-(tri(n-butyl)stannyl)-2-octenoate (140) (1.17 g, 2.15 mmol) and p-toluenesulfonic acid monohydrate in 11 mL of methanol was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and purified by flash chromatography, eluting with 35% diethyl ether / pet. ether followed by Kugelrohr distillation (160-175 °C / 0.2 mm Hg) to afford 0.93 g (94%) of 142 as a colourless oil.

IR (neat): 3420, 2925, 2854, 1714, 1459, 1432, 1196, 1165, 665 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 0.80-0.96 (m, 15H), 1.15 (d, J = 6.1 Hz, 3H), 1.18-1.58 (m, 16H), 2.12 (d, J = 4.4 Hz, 1H), 2.66 (m, 1H), 2.98 (m, 1H), 3.65 (s, 3H), 3.84 (m, 1H), 5.92 (s, J_{Sn-H} = 64 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 463 (¹²⁰Sn, M⁺+1, 91), 461 (¹¹⁸Sn, M⁺+1, 65), 459 (¹¹⁶Sn, M⁺+1, 35), 405 (100), 403 (73), 401 (41);

HRMS (Cl(+), methane)

m/z calcd for C₂₁H₄₃O₃¹¹⁸Sn (M⁺+1): 461.2228, found: 461.2225;

3.79 Methyl (E)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenooate (143)

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{OH} \\
\text{SnBu}_3 & \\
\end{align*}
\]

Methyl (E)-8-(2-tetrahydropyranyloxy)-3-(tri(n-butyl)stannyl)-2-nonenooate (141) (1.30 g, 2.39 mmol) was converted to 143 following the procedure outlined in Section 3.9. The crude material was purified by radial chromatography, eluting with 35% diethyl ether / pet. ether to afford 1.06 g (94%) of 143 as a colourless oil. Kugelrohr distillation (200 °C / 0.05 mm Hg) from copper wire afforded analytically pure 143.

IR (neat): 3408, 2926, 2854, 1716, 1591, 1460, 1174 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 0.81-1.02 (m, 15H), 1.16 (d, J = 6.1 Hz, 3H), 1.25-1.57 (m, 18H), 2.86 (m, 2H), 3.67 (s, 3H), 3.77 (m, 1H), 5.93 (s, J\(_{\text{Sn-H}}\) = 65 Hz, 1H);

LRMS (DCI(+), ammonia) \(m/z\) (relative intensity): 494 (\(^{120}\)Sn, M\(^{+}\)+NH\(_4\), 18), 492 (\(^{118}\)Sn, M\(^{+}\)+NH\(_4\), 14), 490 (\(^{116}\)Sn, M\(^{+}\)+NH\(_4\), 7), 477 (\(^{120}\)Sn, M\(^{+}\)+1, 48), 475 (\(^{118}\)Sn, M\(^{+}\)+1, 39), 473 (\(^{116}\)Sn, M\(^{+}\)+1, 18), 419 (100), 417 (71), 415 (37);

HRMS (Cl(+), ammonia/methane)

\(m/z\) calcd for C\(_{22}\)H\(_{45}\)O\(_3\)\(^{120}\)Sn (M\(^{+}\)+1): 477.2391, found: 477.2398;


3.80 Methyl (E)-7-iodo-3-(tri(n-butyl)stannyl)-2-octenoate (144)

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{SnBu}_3 \\
\text{I} & \\
\end{align*}
\]

Methyl (E)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate (142) (0.30 g, 1.2 mmol) was converted to 144 following the procedure outlined in Section 3.53. The crude material was purified by radial chromatography, eluting with 2% diethyl ether / pet. ether...
followed by Kugelrohr distillation (180 °C / 0.05 mm Hg) to afford 0.42 g (98%) of 144 as a colourless oil.

IR (neat): 2956, 2924, 1718, 1592, 1449, 1377, 1348, 1174, 869 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.88 (t J = 7.3 Hz, 9H), 0.92-1.02 (m, 6H), 1.30 (sextet, J = 7.3 Hz, 6H), 1.40-1.85 (m, 10H), 1.90 (d, J = 7.0 Hz, 3H), 2.86 (m, 2H), 3.67 (s, 3H), 4.19 (m, 1H), 5.94 (s, J_{Sn-H} = 63 Hz, 1H);

LRMS (Cl(+), ammonia) m/z (relative intensity): 590 (¹²⁰Sn, M⁺+NH₄, 40), 588 (¹¹⁸Sn, M⁺⁺NH₄, 32), 586 (¹¹⁶Sn, M⁺⁺NH₄, 20) 573 (¹²⁰Sn, M⁺⁺1, 30), 571 (¹¹⁸Sn, M⁺⁺1, 22), 569 (¹¹⁶Sn, M⁺⁺1, 15), 515 (40), 513 (32), 511 (20), 445 (35), 443 (28), 441 (17), 378 (50), 376 (38), 374 (22), 172 (45), 155 (100);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₂₁H₄₂O₂¹²⁰Sn (M⁺+1): 573.1252, found: 573.1246.

3.81 Methyl (E)-8-iodo-3-(tri(n-butyl)stannyl)-2-nonenoate (145)

Methyl (E)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (143) (0.99 g, 2.1 mmol) was converted to 145 following the procedure outlined in Section 3.53. The crude material was purified by radial chromatography, eluting with 2% diethyl ether / pet. ether to afford 0.96 g (79%) of 145 as a colourless oil.

IR (neat): 2928, 2855, 1709, 1597, 1434, 1197, 1173 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.82-1.02 (m, 15H), 1.21-1.52 (m, 16H), 1.64 (m, 1H), 1.85 (m, 1H), 1.90 (d, J = 6.7 Hz, 3H), 2.86 (m, 2H), 3.67 (s, 3H), 4.16 (sextet, J = 6.7 Hz, 1H), 5.93 (s, J_{Sn-H} = 65 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 604 (¹²⁰Sn, M⁺+NH₄, 54), 602 (¹¹⁸Sn, M⁺⁺NH₄, 40), 600 (¹¹⁶Sn, M⁺⁺NH₄, 28), 587 (¹²⁰Sn, M⁺⁺1, 65), 585 (¹¹⁸Sn,
M^+1, 46), 583 (^{116}Sn, M^+1, 26), 529 (17), 527 (12), 525 (8), 378 (38), 376 (20), 374 (13), 186 (57), 169 (100);

HRMS (Cl(+), ammonia/methane)
\[ m/z \text{ calcd for } C_{22}H_{44}O_2^{120}Sn (M^+1): 587.1406, \text{ found: } 587.1405. \]

3.82 Methyl (Z)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate (146)

A solution of methyl (E)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate (142) (0.50 g, 1.1 mmol), tri(n-butyl)tin hydride (0.15 mL, 0.54 mmol) and AIBN (catalytic amount) in 7.2 mL of benzene was refluxed for 2 hours. The reaction mixture was concentrated in vacuo and purified by flash chromatography, eluting with 25% diethyl ether followed by Kugelrohr distillation (140-150 °C / 0.1 mm Hg) to afford 0.43 g (86%) of 146 as a colourless oil.

IR (neat): 3371, 2923, 1708, 1597, 1460, 1435, 1375, 1328, 1199, 1070, 667 cm\(^{-1}\);

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 0.80-0.96 (m, 15H), 1.16 (d, J = 6.1 Hz, 3H), 1.20-1.51 (m, 17H), 2.38 (m, 2H), 3.68 (s, 3H), 3.76 (m, 1H), 6.34 (s, J\(_{Sn-H} = 108\) Hz, 1H);

LRMS (DCI(+), ammonia) \(m/z\) (relative intensity): 463 (^{120}Sn, M^+1, 6), 461 (^{118}Sn, M^+1, 5), 459 (^{116}Sn, M^+1, 3), 405 (100), 403 (74), 401 (39);

HRMS (Cl(+), methane)
\[ m/z \text{ calcd for } C_{21}H_{43}O_3^{118}Sn (M^+1): 461.2228, \text{ found: } 461.2214; \]


3.83 Methyl (Z)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenooate (147)
Methyl (E)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (143) (1.06 g, 2.23 mmol) was converted to 147 following the procedure outlined in Section 3.82. The crude material was purified by radial chromatography, eluting with 25% diethyl ether / pet. ether to afford 0.99 g (93%) of 147 as a colourless oil. Kugelrohr distillation (200 °C / 0.05 mm Hg) from copper wire afforded analytically pure 147.

IR (neat): 3692, 3609, 2957, 2871, 1705, 1600, 1331, 1206 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.87 (t, J = 7.0 Hz, 9H), 0.90-1.03 (m, 6H), (m, 15H), 1.17 (d, J = 6.1 Hz, 3H), 1.20-1.48 (m, 18H), 2.38 (t, 7.0 Hz, 2H), 3.69 (s, 3H), 3.77 (m, 1H), 6.35 (s, J₈-H = 108 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 477 (¹²⁰Sn, M⁺+1, 4), 475 (¹¹⁸Sn, M⁺+1, 3), 473 (¹¹⁶Sn, M⁺+1, 2), 419 (100), 417 (74), 415 (38);

HRMS (Cl(+), ammonia/methane)
m/z calcd for C₂₂H₄₅O₃¹²⁰Sn (M⁺+1): 477.2391, found: 477.2388;


3.84 Methyl (Z)-7-iodo-3-(tri(n-butyl)stannyl)-2-octenoate (148)

Methyl (Z)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate (146) (0.78 g, 1.7 mmol) was converted to 148 following the procedure outlined in Section 3.53. The crude material was purified by radial chromatography, eluting with 1% diethyl ether / pet. ether to afford 0.86 g (89%) of 148 as a colourless oil. Kugelrohr distillation (180 °C / 0.05 mm Hg) from copper wire afforded analytically pure 148.

IR (neat): 2910, 1710, 1597, 1448, 1376, 1328, 1197, 875 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 0.80-0.96 (m, 15H), 1.20-1.82 (m, 16H), 1.90 (d, J = 6.8 Hz, 3H), 2.40 (m, 2H), 3.70 (s, 3H), 4.14 (m, 1H), 6.35 (s, J₈-H = 106 Hz, 1H);
LRMS (DCI(+), ammonia) m/z (relative intensity): 590 \(^{120}\text{Sn}, \text{M}^+ + \text{NH}_4\text{, 27}\), 588 \(^{118}\text{Sn}, \text{M}^+ + \text{NH}_4\text{, 23}\), 586 \(^{116}\text{Sn}, \text{M}^+ + \text{NH}_4\text{, 13}\) 573 \(^{120}\text{Sn}, \text{M}^{+1, 5}\), 571 \(^{118}\text{Sn}, \text{M}^{+1, 3}\), 569 \(^{116}\text{Sn}, \text{M}^{+1, 1}\), 515 (100), 513 (75), 511 (38), 445 (30), 443 (21), 441 (14), 308 (50), 306 (38), 304 (22), 172 (82);

HRMS (Cl(+), isobutane)

m/z calcd for C\(_{21}\)H\(_{42}\)O\(_2\)l\(^{120}\text{Sn}\) (M\(^{+1}\)): 573.1252, found: 573.1266;


3.85 Methyl (Z)-8-iodo-3-(tri(n-butyl)stannyl)-2-nonenoate (149)

\[
\text{MeO}_2\text{C} = \underset{\text{SnBu}_3}{\text{Sn}-\text{H}}
\]

Methyl (Z)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (147) (0.99 g, 2.1 mmol) was converted to 149 following the procedure outlined in Section 3.53. The crude material was purified by flash chromatography, eluting with 1% diethyl ether / pet. ether to afford 0.91 g (75%) of 149 as a colourless oil. Kugelrohr distillation (180 °C / 0.05 mm Hg) from copper wire afforded analytically pure 149.

IR (neat): 2922, 2853, 1709, 1596, 1448, 1329, 1201 cm\(^{-1}\);

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \(\delta\): 0.86 (t, J = 7.0 Hz, 9H), 0.90-1.02 (m, 6H), 1.22-1.52 (m, 16H), 1.60 (m, 1H), 1.82 (m, 1H), 1.89 (d, J = 6.7 Hz, 3H), 2.38 (t, J = 7.0 Hz, 2H), 3.70 (s, 3H), 4.15 (sextet, J = 6.7 Hz, 1H), 6.35 (s, J\(_{\text{Sn-H}}\) = 108 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 604 \(^{120}\text{Sn}, \text{M}^+ + \text{NH}_4\text{, 5}\), 602 \(^{118}\text{Sn}, \text{M}^+ + \text{NH}_4\text{, 4}\), 600 \(^{116}\text{Sn}, \text{M}^+ + \text{NH}_4\text{, 2}\), 587 \(^{120}\text{Sn}, \text{M}^{+1, 8}\), 585 \(^{118}\text{Sn}, \text{M}^{+1, 6}\), 583 \(^{116}\text{Sn}, \text{M}^{+1, 3}\), 529 (100), 527 (70), 525 (36), 401 (49), 399 (38), 397 (18);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C\(_{18}\)H\(_{34}\)O\(_2\)l\(^{120}\text{Sn}\) (M\(^{-}\text{C}_4\)H\(_9\)): 529.0628, found: 529.0622;
144

Anal. Calcd for C_{22}H_{43}O_{2}I_{2}Sn: C, 45.16; H, 7.41. Found: C, 45.31; H, 7.46.

3.86 Methyl (E)-3,7-diiodo-2-octenoate (150)

\[ \text{CO}_2\text{Me} \]

Iodine (0.08 g, 0.3 mmol) was added to a stirred solution of methyl (E)-3-(tri(n-butyl)stanny1)-7-iodo-2-octenoate (144) (0.19 g, 0.33 mmol) in 1.7 mL of dry methylene chloride. After 1 hour the reaction mixture was diluted to 100 mL with ethyl acetate, washed with saturated Na_2S_2O_3 solution and then dried. The ethyl acetate solution was filtered and concentrated to a yellow oil which was purified by radial chromatography, eluting with 2% diethyl ether / pet. ether, followed by Kugelrohr distillation (170 °C / 0.2 mm Hg) to afford 0.12 g (86%) of 150 as a colourless oil.

IR (neat): 2941, 1719, 1610, 1437, 1343, 1203, 1174, 1140 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.66 (m, 2H), 1.71-1.88 (m, 2H), 1.90 (d, J = 6.7 Hz, 3H), 3.12 (m, 2H), 3.67 (s, 3H), 4.18 (m, 1H), 6.65 (s, 1H);

\(^1^3\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\): 28.85, 29.22, 29.60, 39.86, 41.12, 51.55, 129.20, 131.41, 164.32;

LRMS (DCI(\(+\)), ammonia) \(m/z\) (relative intensity): 426 (M\(^+\)+NH\(_4\), 100), 281 (31), 51 (58);

HRMS (Cl(+), ammonia/methane)

\(m/z\) calcd for C\(_9\)H\(_{15}\)O\(_2\)I\(_2\) (M\(^+\)+1): 408.9162, found: 408.9147;


3.87 Methyl (E)-3,8-diiodo-2-nonenoate (151)

\[ \text{CO}_2\text{Me} \]

\[ \text{I} \]
Methyl (E)-8-iodo-3-(tri(n-butyl)stannyl)-2-nonenoate (145) (0.14 g, 0.24 mmol) was converted to 151 following the procedure outlined in Section 3.86. The crude yellow oil was purified by flash chromatography, eluting with 2% diethyl ether / pet. ether to afford 0.10 g (100%) of 151 as a colourless oil. Kugelrohr distillation (180 °C / 0.1 mm Hg) from copper wire afforded analytically pure 151.

IR (neat): 2933, 2858, 1720, 1610, 1439, 1341, 1198, 1172, 1120 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.34-1.66 (m, 5H), 1.86 (m, 1H), 1.89 (d, J = 6.7 Hz, 3H), 3.09 (t, J = 7.2 Hz, 2H), 3.67 (s, 3H), 4.14 (sextet, J = 6.7 Hz, 1H), 6.64 (s, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 440 (M⁺+NH₄, 100), 295 (31);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₁₀H₁₇O₂I₂ (M⁺+1): 422.9318, found: 422.9301;


3.88 Methyl 7-iodo-2-octynoate (152)

Methyl 7-hydroxy-2-octynoate (103) (0.40 g, 2.4 mmol) was converted to 152 following the procedure outlined in Section 3.53. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 0.63 g (95%) of 152 as a colourless oil. Kugelrohr distillation (130 °C / 0.2 mm Hg) from copper wire afforded analytically pure 152.

IR (neat): 2943, 2237, 1714, 1438, 1261, 1076, 752 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.60-1.90 (m, 4H), 1.91 (d, J = 7.0 Hz, 3H), 2.35 (t, J = 6.7 Hz, 2H), 3.73 (s, 3H), 4.14 (m, 1H);

LRMS (Cl(+), ammonia) m/z (relative intensity): 298 (M⁺+NH₄, 100), 281 (M⁺+1, 20), 153 (25), 121 (30), 93 (65);
3.89 Methyl 8-iodo-2-nonynoate (153)

\[
\text{MeO}_2\text{C}-\equiv-\text{CH}_{10}^\text{IH}_0\text{O}_2\text{I}^\text{I}
\]

Methyl 8-hydroxy-2-nonynoate (133) (0.34 g, 1.9 mmol) was converted to 153 following the procedure outlined in Section 3.53. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 0.52 g (96%) of 153 as a colourless oil. Kugelrohr distillation (140 °C / 0.1 mm Hg) from copper wire afforded analytically pure 153.

IR (neat): 2939, 2863, 2236, 1715, 1438, 1260, 1077, 752 cm\(^{-1}\);

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 1.40-1.67 (m, 5H), 1.80 (m, 1H), 1.90 (d, J = 6.8 Hz, 3H), 2.34 (t, J = 6.6 Hz, 2H), 3.74 (s, 3H), 4.15 (m, 1H);

LRMS (DCI(+), ammonia) \(m/z\) (relative intensity): 312 (M\(^+\)+NH\(_4\), 98), 295 (M\(^+\)+1, 8), 167 (100);

HRMS (Cl(+), isobutane) \(m/z\) calcd for C\(_{10}\)H\(_{15}\)O\(_2\)I (M\(^+\)+1): 295.0195, found: 295.0194;


3.90 Methyl (Z)-3,7-diiodo-2-octenoate (154)

\[
\text{MeO}_2\text{C}^\equiv-\text{CH}_{10}^\text{IH}_0\text{O}_2\text{I}^\text{I}
\]

A solution of methyl 7-iodo-2-octynoate (152) (0.61 g, 2.1 mmol) and sodium iodide (0.51 g, 3.4 mmol) in acetic acid (0.80 mL, 14 mmol) was heated in 115 °C oil bath for 1.5 hours. The reaction mixture was diluted with diethyl ether, washed consecutively with water, saturated NaHCO\(_3\) solution, saturated Na\(_2\)S\(_2\)O\(_3\) solution and brine and then dried. This was filtered and concentrated to a yellow oil which was
purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 0.63 g (72%) of 154 as a colourless oil. Kugelrohr distillation (150 °C / 0.1 mm Hg) afforded analytically pure 154.

IR (neat): 2937, 1726, 1622, 1440, 1298, 1181 cm\(^{-1}\);

\(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 1.50-1.84 (m, 4H), 1.89 (d, \(J = 6.8\) Hz, 3H), 2.69 (br t, \(J = 6.3\) Hz, 2H), 3.72 (s, 3H), 4.13 (m, 1H), 6.33 (t, \(J = 1.1\) Hz, 1H);

LRMS (DCI(+), ammonia) \(m/z\) (relative intensity): 426 (M\(^+\)+NH\(_4\), 100), 409 (M\(^+\)+1, 8), 298 (22);

HRMS (Cl(+), ammonia/methane)

\(m/z\) calcd for C\(_{9}\)H\(_{15}\)O\(_2\)I\(_2\) (M\(^+\)+1): 408.9162, found: 408.9152;

UV (CH\(_3\)CN) \(\lambda (\epsilon): 332 (570), 250 (7000), 200 nm (9100);


3.91 Methyl (Z)-3,8-diiodo-2-nonenoate (155)

Methyl 8-iodo-2-nonynoate (153) (0.29 g, 1.0 mmol) was converted to 155 following the procedure outlined in Section 3.90. The crude yellow oil was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 0.26 g (62%) of 155 as a colourless oil. Kugelrohr distillation (180 °C / 0.1 mm Hg) from copper wire afforded analytically pure 155.

IR (neat): 2933, 2858, 1726, 1623, 1441, 1377, 1307, 1182, 1040, 850, 729 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 1.35-1.70 (m, 5H), 1.83 (m, 1H), 1.89 (d, \(J = 6.9\) Hz, 3H), 2.68 (dt, \(J = 1.0 \& 7.3\) Hz, 2H), 3.72 (s, 3H), 4.13 (sextet, \(J = 6.9\) Hz, 1H), 6.32 (d, \(J = 1.0\) Hz, 1H);
$^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$: 28.34, 28.92, 29.71, 42.43, 47.61, 51.58, 102.84, 121.43, 124.72, 164.81;

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 440 (M$^+$+NH$_4^+$, 100), 423 (M$^+$+1, 8);

HRMS (Cl(+), ammonia/methane)

$m/z$ calcd for C$_{10}$H$_{17}$O$_2$I$_2$ (M$^+$+1): 422.9318, found: 422.9300;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$I$_2$: C, 28.46; H, 3.82. Found: C, 28.50; H, 3.87.

3.92 (E)-3-Bromo-7-iodo-2-octen-1-ol (156)

![Chemical structure](image)

Diisobutylaluminum hydride (2.0 mL of 1.0 M solution in hexanes, 2.0 mmol), was added dropwise to a dry ice / acetone cooled solution of methyl (E)-3-bromo-7-iodo-2-octenoate (108) (0.33 g, 0.91 mmol) in 5.0 mL of dry methylene chloride. During the addition of the DIBAL, the initially colourless solution became yellow and then returned to colourless upon complete addition. After stirring 30 minutes at -78 °C, TLC analysis indicated that the reaction was completed. The reaction mixture was diluted with 20 mL of ethyl acetate and 5 mL of 1 M HCl and allowed to warm to room temperature. The reaction mixture was diluted to 100 mL with ethyl acetate and washed successively with 1 M HCl, saturated NaHCO$_3$ and brine, and then dried. The ethyl acetate solution was filtered and concentrated to a cloudy oil which was purified by radial chromatography, eluting with 40% diethyl ether / pet. ether followed by Kugelrohr distillation (180 °C / 0.1 mm Hg) to afford 0.29 g (97%) of 156 as a slightly blue oil.

IR (neat): 3332, 2948, 2921, 2864, 1644, 1444, 1143, 1015 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.46 (m, 1H), 1.55-1.70 (m, 2H), 1.78 (m, 2H), 1.90 (d, J = 6.7 Hz, 3H), 2.49 (m, 2H), 4.10 (m, 2H), 4.15 (sextet, J = 6.7 Hz, 1H), 6.11 (t, J = 7.2 Hz, 1H);
LRMS (DCI(+), ammonia) \( m/z \) (relative intensity): 352 (\(^{81}\text{Br}, \text{M}^++\text{NH}_4, 100\)), 350 (\(^{79}\text{Br}, \text{M}^++\text{NH}_4, 97\)), 334 (\(^{81}\text{Br}, \text{M}^++1, 7\)), 332 (\(^{79}\text{Br}, \text{M}^++1, 7\));

HRMS (Cl(+), ammonia/methane)
\( m/z \) calcd for \( \text{C}_8\text{H}_{18}\text{NO}^{81}\text{Br} \) (\( \text{M}^++\text{NH}_4 \)): 351.9596, found: 351.9583;
\( m/z \) calcd for \( \text{C}_8\text{H}_{18}\text{NO}^{79}\text{Br} \) (\( \text{M}^++\text{NH}_4 \)): 349.9617, found: 349.9614;

Anal. Calcd for \( \text{C}_8\text{H}_{14}\text{O}^{81}\text{Br} \): C 28.85, H 4.24. Found: C 29.09, H 4.11.

3.93 (E)-1-Acetoxy-3-bromo-7-iodo-2-octene (157)

Pyridine (150 \( \mu l, 1.8 \) mmol) was added to a room temperature solution of (E)-3-bromo-7-iodo-2-octen-1-ol (156) (0.30 g, 0.90 mmol) and acetic anhydride (110 \( \mu l, 1.2 \) mmol) in 5.0 mL of dry methylene chloride. After 40 hours, TLC analysis indicated the reaction was completed. The reaction mixture was diluted to 100 mL with ethyl acetate, washed successively with 1 M HCl, saturated NaHCO\(_3\) and brine, and then dried. This was filtered and concentrated to a colourless oil which was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (170 °C / 0.1 mm Hg) to afford 0.33 g (97%) of 157 as a colourless oil.

IR (neat): 2941, 2864, 1741, 1646, 1444, 1379, 1362, 1234, 1146, 1027 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 1.53-1.69 (m, 2H), 1.78 (m, 2H), 1.90 (d, \( J = 6.7 \) Hz, 3H), 2.04 (s, 3H), 2.51 (m, 2H), 4.14 (sextet, \( J = 6.7 \) Hz, 1H), 4.49 (d, \( J = 7.6 \) Hz, 2H), 6.05 (t, \( J = 7.6 \) Hz, 1H);

LRMS (DCI(+), ammonia) \( m/z \) (relative intensity): 394 (\(^{81}\text{Br}, \text{M}^++\text{NH}_4, 100\)), 392 (\(^{79}\text{Br}, \text{M}^++\text{NH}_4, 87\));
3.94 (Z)-3-Bromo-7-iodo-2-octen-1-ol (158)

Methyl (Z)-3-bromo-7-iodo-2-octenoate (109) (2.67 g, 10.5 mmol) was converted to 158 following the procedure outlined in Section 3.92. The crude cloudy oil was purified by radial chromatography, eluting with 40% diethyl ether / pet. ether followed by Kugelrohr distillation (160 °C / 0.1 mm Hg) to afford 0.34 g (87%) of 158 as a slightly yellow oil.

IR (neat): 3338, 2941, 2914, 2863, 1657, 1447, 1142, 1088, 1012 cm⁻¹;

1H NMR (400 MHz, CDCl₃) δ: 1.61 (m, 2H), 1.70-1.85 (m, 2H), 1.89 (d, J = 7.0 Hz, 3H), 2.44 (m, 2H), 4.14 (sextet, J = 7.0 Hz, 1H), 4.23 (d, J = 5.9 Hz, 2H), 5.92 (t, J = 5.9 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 352 (⁸¹Br, M⁺+NH₄, 100), 350 (⁷⁹Br, M⁺+NH₄, 92), 334 (⁸¹Br, M⁺+1, 2), 332 (⁷⁹Br, M⁺+1, 2);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₈H₁₈NO⁸¹Br (M⁺+NH₄): 351.9596, found: 351.9591;
m/z calcd for C₈H₁₈NO⁷⁹Br (M⁺+NH₄): 349.9617, found: 349.9624;


3.95 (Z)-1-Acetoxy-3-bromo-7-iodo-2-octene (159)
(Z)-3-Bromo-7-iodo-2-octen-1-ol (158) (0.43 g, 1.3 mmol) was converted to 159 following the procedure outlined in Section 3.93. The crude colourless oil was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (180 °C / 0.1 mm Hg) to afford 0.44 g (92%) of 159 as a colourless oil.

IR (neat): 2936, 2864, 1742, 1660, 1442, 1374, 1237, 1031 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.55-1.69 (m, 2H), 1.77 (m, 2H), 1.89 (d, J = 6.7 Hz, 3H), 2.04 (s, 3H), 2.45 (m, 2H), 4.14 (sextet, J = 6.7 Hz, 1H), 4.65 (d, J = 6.1 Hz, 2H), 5.86 (t, J = 6.1 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 394 (³¹Br, M⁺+NH₄, 100), 392 (⁷⁹Br, M⁺+NH₄, 89);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₁₀H₂₀NO₂⁸¹Br (M⁺+NH₄): 393.9702, found: 393.9713;
m/z calcd for C₁₀H₂₀NO₂⁷⁹Br (M⁺+NH₄): 391.9722, found: 391.9728;

Anal. Calcd for C₁₀H₁₆O₂Br: C 32.03, H 4.30. Found: C 32.04, H 4.35.

3.96 (E)-7-Iodo-3-(tri(n-butyl)stannyl)-2-octen-1-ol (160)

Methyl (E)-7-iodo-3-(tri(n-butyl)stannyl)-2-octenoate (144) (0.78 g, 1.4 mmol) was converted to 160 following the procedure outlined in Section 3.92. The crude cloudy oil was purified by radial chromatography, eluting with 25% diethyl ether / pet. ether to afford 0.69 g (93%) of 160 as a colourless oil. Kugelrohr distillation (180 °C / 0.05 mm Hg) afforded analytically pure 160.

IR (neat): 3319, 2956, 2923, 2853, 1456, 1376, 1019 cm⁻¹;
$^1$H NMR (200 MHz, CDCl$_3$) $\delta$: 0.72-1.04 (m, 15H), 1.20-1.81 (m, 16H), 1.89 (d, $J = 6.8$ Hz, 3H), 2.08-2.42 (m, 2H), 4.14 (m, 1H), 4.21 (d, $J = 6.1$ Hz, 2H), 5.73 (t, $J = 6.1$ Hz, $J_{Sn-H} = 67$ Hz, 1H);

LRMS (El) $m/z$ (relative intensity) 487 ($^{120}$Sn M$^+$-C$_4$H$_9$, 4), 485 ($^{118}$Sn M$^+$-C$_4$H$_9$, 2), 483 ($^{116}$Sn M$^+$-C$_4$H$_9$, 1), 361 (100), 359 (95), 357 (61), 305 (30), 303 (23), 301 (14), 67 (47);

HRMS (El) $m/z$ calcd for C$_{16}$H$_{32}$O$^{120}$Sn (M$^+$-C$_4$H$_9$): 487.0520, found: 487.0524;

Anal. Calcd for C$_{20}$H$_{41}$O$^1$Sn: C 44.23, H 7.61. Found: C 43.93, H 7.63.

3.97 (E)-1-Acetoxy-3,7-diiodo-2-octene (162)

(E)-7-Iodo-3-(tri(n-butyl)stannyl)-2-octen-1-ol (160) (0.69 g, 1.3 mmol) was converted to (E)-1-acetoxy-7-iodo-3-(tri(n-butyl)stannyl)-2-octene (161) following the procedure outlined in Section 3.93. Purification by radial chromatography, eluting with 5% diethyl ether / pet. ether afforded 0.68 g (92%) of 161 as colourless oil. Compound 161 (0.37 g, 0.63 mmol) was converted to 162 following the procedure outlined in Section 3.85. The crude yellow oil was purified by radial chromatography, eluting with 8% diethyl ether / pet ether followed by Kugelrohr distillation (180 °C / 0.1 mm Hg) to afford 0.26 g (96%) of 162 as a colourless oil.

IR (neat): 2937, 2862, 1740, 1631, 1443, 1377, 1234, 1027 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 1.60 (m, 2H), 1.68-1.83 (m, 2H), 1.91 (d, $J = 7.0$ Hz, 3H), 2.04 (s, 3H), 2.47 (m, 2H), 4.14 (sextet, $J = 7.0$ Hz, 1H), 4.47 (d, $J = 7.3$ Hz, 2H), 6.36 (t, $J = 7.3$ Hz, 1H);

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 440 (M$^+$+NH$_4^+$, 100);
3.98 (Z)-7-Iodo-3-(tri(n-butyl)stannyl)-2-octen-1-ol (163)

Methyl (Z)-7-iodo-3-(tri(n-butyl)stannyl)-2-octenoate (148) (0.86 g, 1.5 mmol) was converted to 163 following the procedure outlined in Section 3.92. The crude cloudy oil was purified by radial chromatography, eluting with 15% diethyl ether / pet. ether to afford 0.74 g (90%) of 163 as a colourless oil.

IR (neat): 3347, 2922, 2853, 1455, 1377, 1004 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.82-1.02 (m, 15H), 1.12 (t, J = 6.0 Hz, 1H), 1.25-1.60 (m, 14H), 1.78 (m, 1H), 1.89 (d, J = 7.0 Hz, 3H), 2.20 (m, 2H), 4.03 (t, J = 6.1 Hz, 2H), 4.15 (sextet, J = 7.0 Hz, 1H), 6.21 (t, J = 6.1 Hz, JSn-H = 124 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 487 (¹²⁰Sn, M⁺-C₄H₉, 44), 485 (¹¹⁸Sn, M⁺-C₄H₉, 39), 483 (¹¹⁶Sn, M⁺-C₄H₉, 23), 378 (100), 376 (68), 374 (39), 359 (77), 308 (100), 306 (78), 304 (43), 109 (82);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₁₆H₃₂O¹²₀Sn (M⁺-C₄H₉): 487.0520, found: 487.0512.

3.99 (Z)-1-Acetoxy-3,7-diiodo-2-octene (165)

(Z)-7-Iodo-3-(tri(n-butyl)stannyl)-2-octen-1-ol (163) (0.74 g, 1.4 mmol) was converted to (Z)-1-acetoxy-7-iodo-3-(tri(n-butyl)stannyl)-2-octene (164) following the procedure outlined in Section 3.93. Purification by radial chromatography, eluting with
5% diethyl ether / pet. ether afforded 0.64 g (86%) of 164 as a colourless oil. Compound 164 (0.30 g, 0.51 mmol) was converted to 165 following the procedure outlined in Section 3.62. The crude yellow oil was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (170 °C / 0.05 mm Hg) to afford 0.19 g (86%) of 165 as a colourless oil.

IR (neat): 2932, 2862, 1741, 1646, 1441, 1374, 1236, 1031 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.59 (m, 2H), 1.68-1.83 (m, 2H), 1.90 (d, J = 6.7 Hz, 3H), 2.05 (s, 3H), 2.51 (m, 2H), 4.14 (sextet, J = 6.7 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H), 5.80 (t, J = 6.0 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 440 (M⁺+NH₄⁺, 100);

HRMS (Cl(+), ammonia/methane)

m/z calcd for C₁₀H₂₀N₂O₂I₂ (M⁺+NH₄⁺): 439.9584, found: 439.9588;


3.100 (E)-2-(2-Methylcyclopentylidene)ethanol (166)

Method A. Via cyclization of compound 156.

(E)-3-Bromo-7-iodo-2-octen-1-ol (156) (79.6 mg, 0.220 mmol) was converted to 166 following the procedure outlined in Section 3.40. The concentrated crude material was purified by radial chromatography, eluting with 35% diethyl ether / pet. ether to afford 24.0 mg (69%) of a 92:8 ratio of 166 and 167.

Method B. Via reduction of compound 93.

Lithium aluminum hydride (45.7 mg, 1.14 mmol) was added to an ice cooled solution of methyl (E)-(2-methylcyclopentylidene)acetate (93) (88.0 mg, 0.571 mmol) in 2.9 mL of dry diethyl ether. After 30 minutes the reaction was diluted with diethyl ether and then quenched by the slow addition of 1 mL of saturated Na₂SO₄ solution. The
white precipitate was filtered, the organic layer was separated and was washed with NaHCO₃ and brine, and then dried. The solution was filtered and concentrated to a colourless oil. The crude material was purified radial chromatography, eluting with 35% diethyl ether / pet. ether to afford 58.7 mg (82%) of 166 as a colourless oil. Kugelrohr distillation (110 °C / 20 mm Hg) afforded analytically pure 166.

IR (neat): 3339, 2950, 2867, 1675, 1454, 1003 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.04 (d, J = 6.7 Hz, 3H), 1.15 (m, 1H), 1.28 (br s, 1H), 1.53 (m, 1H), 1.74 (m, 1H), 1.87 (m, 1H), 2.20-2.40 (m, 3H), 4.12 (d, J = 6.7 Hz, 2H), 5.36 (m, 1H);

LRMS (Cl(+), isobutane) m/z (relative intensity): 127 (M⁺+1, 0.7), 126 (M⁺, 4), 125 (5), 109 (100), 82 (26), 67 (28);

HRMS (Cl(+), isobutane) m/z calcd for C₈H₁₅O (M⁺+1): 127.11229, found: 127.11253;


3.101 (Z)-2-(2-Methylcyclopentylidene)ethanol (167)

Method A. Via cyclization of compound 163.

(Z)-7-Iodo-3-(tri(n-butyl)stannyl)-2-octen-1-ol (163) (77.2 mg, 0.142 mmol) was converted to 167 according to the procedure outlined in Section 3.40, with the exception that only 14 μL (0.028 mmol) of hexa(n-butyl)ditin was used. The crude material was purified by radial chromatography, eluting with 35% diethyl ether / pet. ether to afford 8.7 mg (49%) of 167 and 166 in 67:33 ratio as a colourless oil.

Method B. Via reduction of compound 94.

Methyl (Z)-(2-methylcyclopentylidene)acetate (94) (179.3 mg, 1.16 mmol) was converted to 167 according to the procedure outlined in Section 3.100, Method B. The crude material was purified by radial chromatography, eluting with 35% diethyl ether /
pet. ether to afford 122.7 mg (84%) of 167 as a colourless oil. Kugelrohr distillation (110 °C / 20 mm Hg) afforded analytically pure 167.

IR (neat): 3331, 2949, 2869, 1676, 1449, 1019 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 0.99 (d, J = 7.0 Hz, 3H), 1.27 (br s, 1H), 1.38 (m, 1H), 1.55 (m, 1H), 1.68 (m, 1H), 1.81 (m, 1H), 2.21 (m, 1H), 2.35 (m, 1H), 2.73 (m, 1H), 4.14 (m, 2H), 5.43 (t, J = 7.3 Hz, 1H);

LRMS (Cl(+), isobutane) m/z (relative intensity): 127 (M⁺+1, 0.5), 126 (M⁺, 2), 125 (3), 109 (100);

HRMS (Cl(+), isobutane) m/z calcd for C₈H₁₅O (M⁺+1): 127.1122, found: 127.1120;


3.102 (E)-1-(2-Acetoxyethylidene)-2-methylcyclopentane (168)

Method A. Via cyclization of compound 162.

(E)-1-Acetoxy-3,7-diiodo-2-octene (162) (58.3 mg, 0.138 mmol) was converted to 168 according to the procedure outlined in Section 3.40. The crude material was purified by radial chromatography, eluting with 5% diethyl ether / pet. ether to afford 19.8 mg (85%) of 168 and 169 in a 92:8 ratio.

Method B. Via acetylation of compound 166.

A solution of (E)-(2-methylcyclopentylidene)ethanol (166) (52.9 mg, 0.420 mmol), pyridine (68 μL, 0.84 mmol), and acetic anhydride (51 μL, 0.55 mmol) in 2.1 mL of dry methylene chloride was stirred at room temperature for 2 days. The reaction mixture was diluted with diethyl ether and washed consecutively with 1 M HCl, NaHCO₃ and brine, and then dried. The solution was filtered and then concentrated to a colourless oil. The crude material was purified by radial chromatography, eluting with 6% diethyl
ether / pet. ether to afford 61.4 mg (87%) of 168 as a colourless oil. Kugelrohr distillation (110 °C / 15 mm Hg) afforded analytically pure 168.

IR (neat): 2953, 2870, 1740, 1451, 1371, 1238, 1024 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ: 1.05 (d, J = 6.7 Hz, 3H), 1.17 (m, 1H), 1.55 (m, 1H), 1.74 (m, 1H), 1.84 (m, 1H), 2.03 (s, 3H), 2.22-2.45 (m, 3H), 4.55 (d, J = 7.0 Hz, 2H), 5.31 (m, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 186 (M⁺+NH₄⁺, 11), 109 (100), 108 (57), 78 (35);

HRMS (Cl(+), methane) m/z calcd for C₁₀H₁₇O₂ (M⁺+1): 169.1228, found: 169.1229;


3.103 (Z)-1-(2-Acetoxyethylidene)-2-methylcyclopentane (169)

\[ \text{\includegraphics[width=0.2\textwidth]{structure.png}} \]

**Method A.** Via cyclization of compound 165.

(Z)-1-Acetoxy-3,7-diiodo-2-octene (165) (84.3 mg, 0.200 mmol) was converted to 169 according to the procedure outlined in Section 3.40. The crude material was purified by radial chromatography, eluting with 5% diethyl ether / pet. ether to afford 23.2 mg (69%) of 169 and 168 in 87:13 ratio.

**Method B.** Via acetylation of compound 167.

(Z)-(2-Methylcyclopentylidene)ethanol (167) (60.3 mg, 0.479 mmol) was converted to 169 according to the procedure outlined in Section 3.102, Method B. The crude material was purified by radial chromatography, eluting with 6% diethyl ether / pet. ether to afford 70.2 mg (87%) of 169 as a colourless oil.

IR (CDCl₃): 2959, 2871, 1729, 1242, 1024 cm⁻¹;
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 0.99 (d, $J = 7.3$ Hz, 3H), 1.39 (m, 1H), 1.56 (m, 1H), 1.68 (m, 1H), 1.84 (m, 1H), 2.03 (s, 3H), 2.23 (m, 1H), 2.38 (m, 1H), 2.77 (m, 1H), 4.58 (m, 2H), 5.37 (m, 1H);

LRMS (DCI(+), ammonia) $m/z$ (relative intensity): 169 ($M^+ + 1$, 0.3), 168 ($M^+$, 0.3), 167 (1), 109 (100), 108 (32);

HRMS (CI(+), isobutane) $m/z$ calcd for $C_{10}H_{15}O_2$ ($M^+-1$): 167.1072, found: 167.1072.
REFERENCES

1  (a) Gomberg, M. J. Am. Chem. Soc. 1900, 22, 757; (b) Gomberg, M. Chem. Ber. 1900, 23, 3150.


180

57

% Transmittance

Wave number (cm⁻¹)
CO$_2$Me

[Chemical structure diagram]

59

Wave number (cm$^{-1}$)

% Transmittance

Wave number (cm$^{-1}$)
\[
\text{CO}_2\text{Me} \\
\begin{array}{c}
\text{PhS} \\
\text{Me}
\end{array}
\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Me}
\end{array}
\]

72

\[
\begin{array}{c}
\text{Wave number (cm}^{-1}
\end{array}
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\begin{array}{c}
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2400 \\
1600 \\
800
\end{array}
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2.17 \\
1.94 \\
1.81 \\
1.60
\end{array}
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7 \\
6 \\
5 \\
4 \\
3 \\
2 \\
1 \\
0
\end{array}
\]

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90 \\
80 \\
70 \\
60 \\
50 \\
40 \\
30 \\
20 \\
10 \\
0
\end{array}
\]
CO₂Me
\[\text{CO}_2\text{Me}\]
\[\text{Me}\]

74
$\text{CO}_2\text{Me}$

![Chemical structure image]

**87**

**Wave number (cm$^{-1}$)**

**% Transmittance**

**Wave number (cm$^{-1}$)**
Wave number (cm$^{-1}$)
Wave number (cm$^{-1}$)

121