EXOCYCLIC ALKENE SYNTHESIS VIA STEREOSELECTIVE RADICAL CYCLIZATIONS

by

Jeffery R. Raymond

B.Sc., University of British Columbia, 1991

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES
Department of Chemistry

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
July 1997

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.
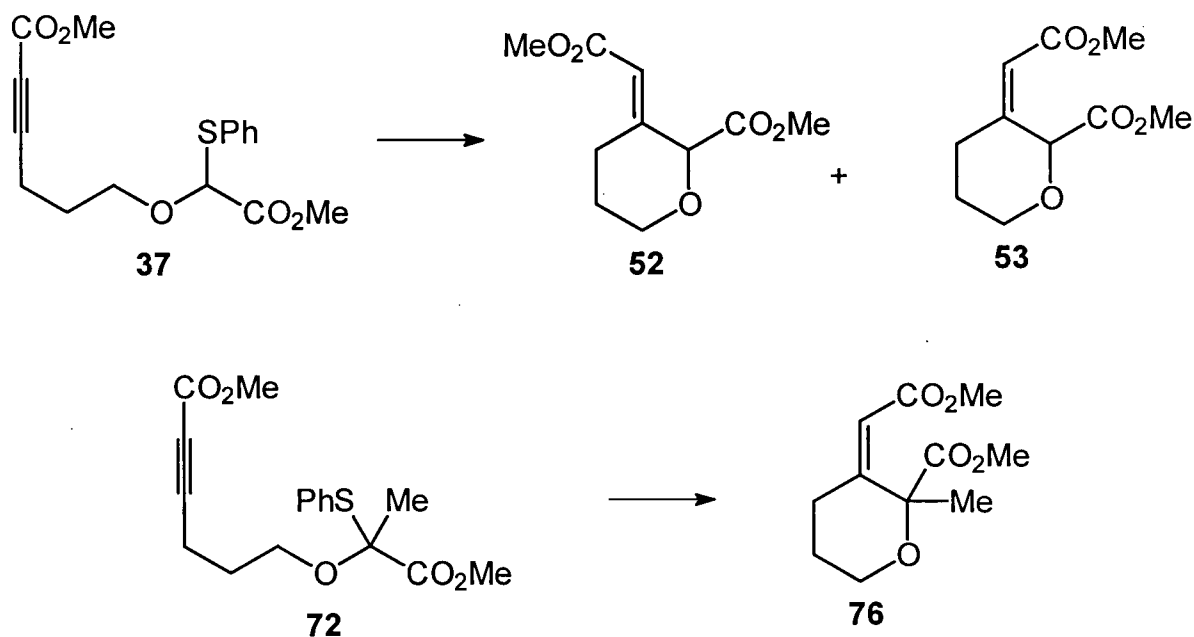
Department of _Chemistry_
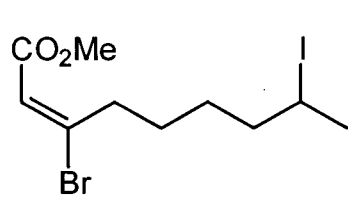
The University of British Columbia
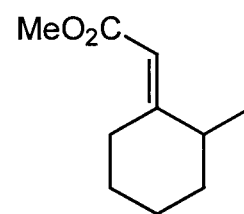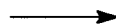Vancouver, Canada

Date _Sept. 29, 1997_

ABSTRACT

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**.
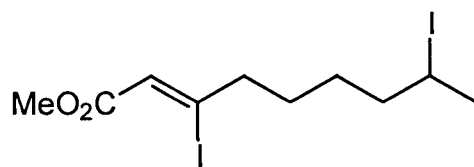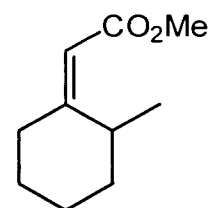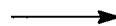
125 → **123**

155 → **124**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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)

xii

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

ACKNOWLEDGEMENTS

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.[7] 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
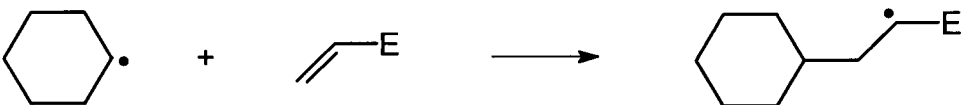
The vast majority of free radical reactions used for carbon-carbon bond formation involve the addition of a radical to a multiple bond, the driving force of the addition being the formation of a strong σ-bond at the expense of a weaker π-bond. The regiochemistry of addition is sensitive to substituent 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 $H_2C=CHPO(OEt)_2$ (from ref 11 and 12).

R:	CH_3	CH_2CH_3	CH_2OCH_3	$CH(CH_3)_2$	$C(CH_3)_3$
k_{rel}:	1	1	2.7	4.8	24
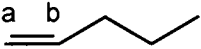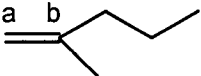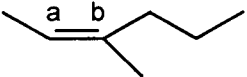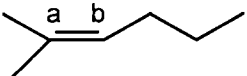
Electron-withdrawing groups on an olefin can effect the relative rates of addition even more significantly. As the data in Table II illustrate, the rate of addition of a radical to an alkene is greatly accelerated by the presence of strongly electron-withdrawing groups on the alkene.

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

E:	C_4H_9	H	Cl	Ph	CO_2CH_3	CN	CHO
k_{rel}:	1	3.75	30	250	1675	6000	8500

An electron-withdrawing group also influences the regioselectivity of radical addition, directing an attacking nucleophilic radical β 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).

Entry	Alkene	% addition to		k_{rel}:
		C_a	C_b	
1		≥95	≤5	1.0
2		≥95	≤5	15.9
3		ca. 50	ca. 50	1.08
4		≥95	≤5	12.9
5		≤5	≥95	12.0

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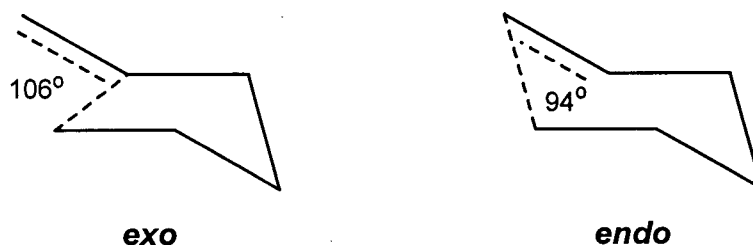
Figure 1. Computer generated models of *exo-* and *endo-*cyclizations of 5-hexenyl radical (from ref 18,19).

The rate of ω-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.

Table IV. Experimental Kinetic Data for Ring Closure of ω-Alkenyl and Related Radicals (from ref 18).

Entry	Radical	k (exo)[a]	k (endo)[a]	k(exo)/k(endo)
1		2.3×10^5	4.1×10^3	56
2		5.2×10^3	8.3×10^2	6.3
3		6.1×10^3	9.0×10^3	0.68
4		5.2×10^6	$< 1 \times 10^5$	>52
5		8.5×10^6	$<1 \times 10^5$	>85
6		2.8×10^4	$<6 \times 10^2$	>47

[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.

65 : 35

25 : 75

83 : 17
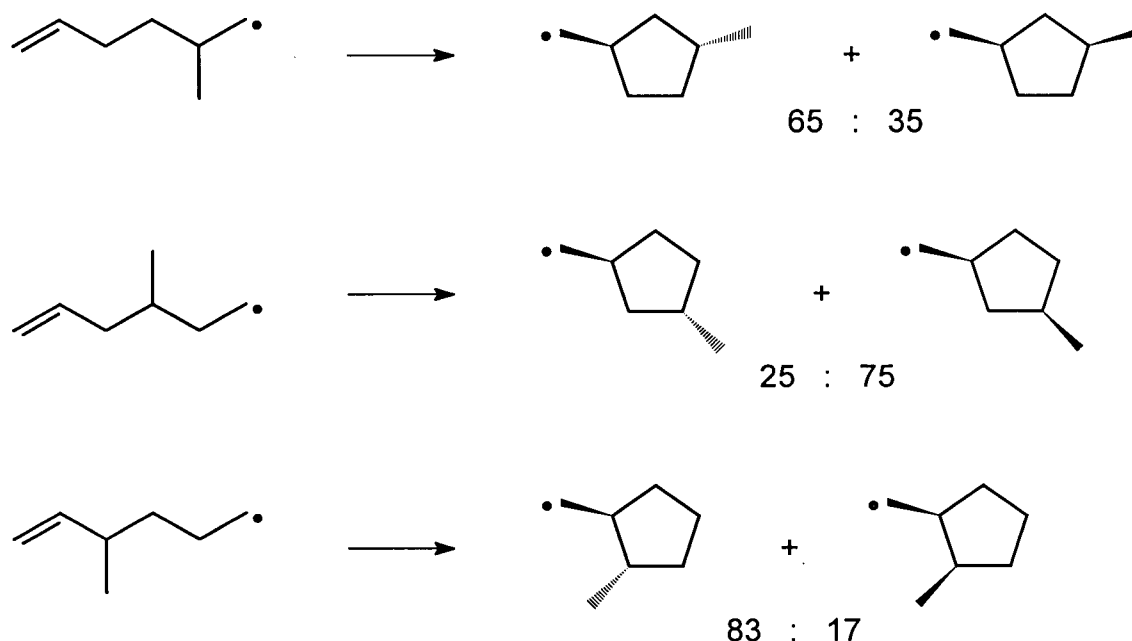
Figure 2. Stereoselective substituted 5-hexenyl radical cyclization (from ref 21).

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]

major   minor

A (0.0 kcal/mol)   B (1.5 kcal/mol)

C (2.5 kcal/mol)   D (0.5 kcal/mol)
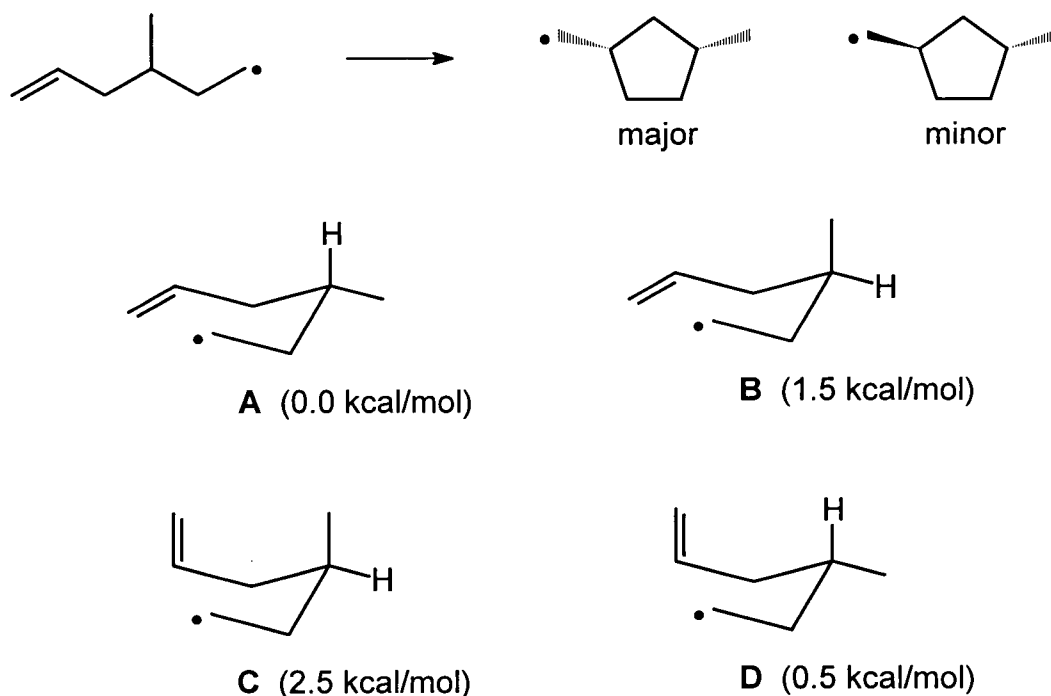
Figure 3. Houk/Spellmeyer model for cyclization of a 3-substituted 5-hexenyl radical (from ref 19).

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).

$$\text{(alkene)}_E \quad + \quad R\text{-}X \quad \xrightarrow{\text{Bu}_3\text{SnH}} \quad R\text{(product)}_E \quad + \quad \text{Bu}_3\text{SnX} \qquad (1)$$
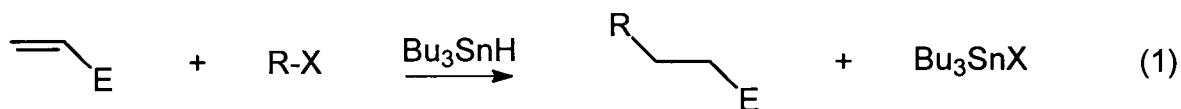
The chain reaction mechanism of the above reaction equation is apparent when the reaction is presented as in Figure 4. A single cycle of the chain begins with tri(n-butyl)tin radical abstraction of the halide, producing tri(n-butyl)tin halide and an alkyl radical. Addition of the alkyl radical to the 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.
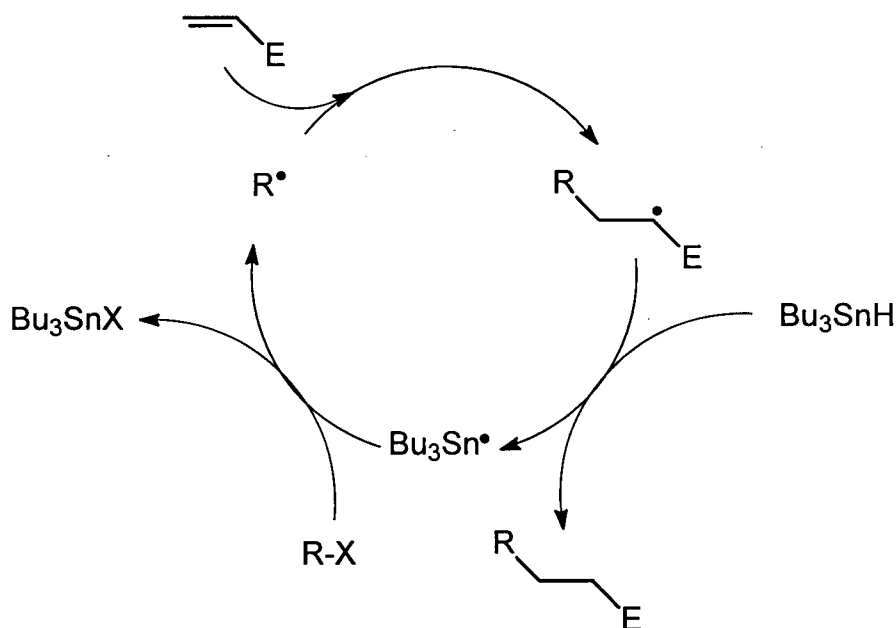
Figure 4. The tin hydride mediated addition of an alkyl halide to an alkene (from ref 5).

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).[23] 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.[24] Beckwith and Pigou have established a reactivity scale for tri(*n*-butyl)tin radical which is useful in synthetic planning.[25] Iodine is often the preferred precursor, as the rate constant for iodine atom abstraction approaches the diffusion-controlled limit.[26]

$$Bu_3Sn\bullet \quad + \quad \overset{}{\underset{E}{\diagup}} \quad \longrightarrow \quad \overset{Bu_3Sn}{\underset{E}{\diagdown\diagup\bullet}} \qquad (2)$$

$$Bu_3Sn\bullet \quad + \quad R\text{-}X \quad \longrightarrow \quad R\bullet \quad + \quad Bu_3SnX \qquad (3)$$
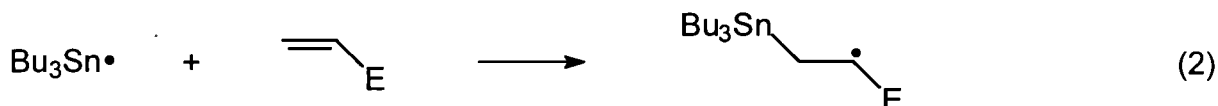
The alkyl radical can compete between hydrogen abstraction from tri(*n*-butyl)tin hydride (eq 4) and alkene addition (eq 5). Hydrogen abstraction can be minimized by maintaining a low concentration of tri(*n*-butyl)tin hydride throughout the duration of the reaction. Low tin hydride concentration can 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 NaBH$_3$CN for the in *situ* generation of tri(*n*-butyl)tin hydride.[27] An electron-withdrawing substituent on the alkene will accelerate addition by nucleophilic alkyl radicals.[13] Also, substituents at the radical center will accelerate addition, while having little effect on the rate of hydrogen abstraction.[28] Thus, proper substitution of the radical center and the alkene can help control the reactivity of the alkyl radical.

$$R\bullet \quad + \quad Bu_3SnH \quad \longrightarrow \quad Bu_3Sn\bullet \quad + \quad R\text{-}H \qquad (4)$$

$$R\bullet \quad + \quad \overset{}{\underset{E}{=}} \quad \longrightarrow \quad \overset{R}{\underset{E}{\diagdown\bullet}} \qquad (5)$$
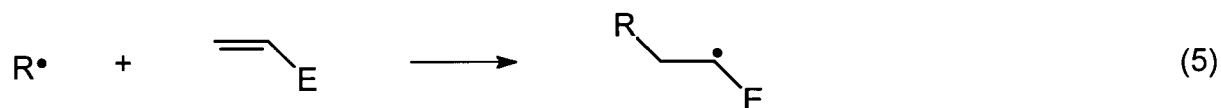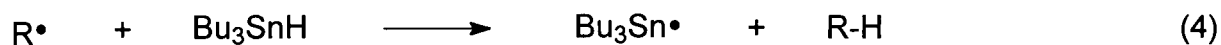
The adduct alkyl radical can compete between alkene addition and hydrogen abstraction from tri(*n*-butyl)tin hydride. An electron-withdrawing substituent on the alkene will render the adduct radical electrophilic, and therefore addition to a second electron-poor alkene (eq 6) will be slow relative to hydrogen abstraction (eq 7).

$$\overset{R}{\underset{E}{\diagdown\bullet}} \quad + \quad \overset{}{\underset{E}{=}} \quad \longrightarrow \quad \overset{R}{\underset{E}{\diagdown}}\overset{\bullet}{\underset{E}{\diagup}} \qquad (6)$$

$$\overset{R}{\underset{E}{\diagdown\bullet}} \quad + \quad Bu_3SnH \quad \longrightarrow \quad Bu_3Sn\bullet \quad + \quad \overset{R}{\underset{E}{\diagdown}} \qquad (7)$$
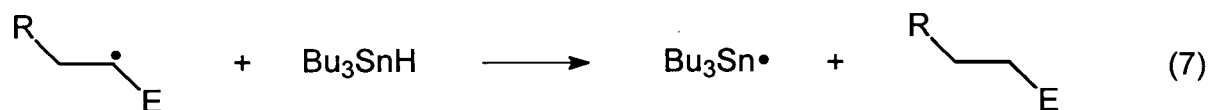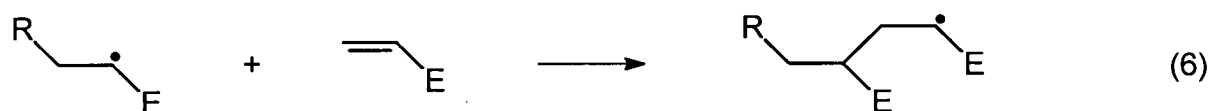
The most commonly used initiators undergo thermally or photochemically promoted homolytic bond cleavage to give two radicals. 2,2'-Azobisisobutyronitrile (AIBN) is the most commonly employed initiator. Exposure of AIBN to heat or light effects its decomposition to two isobutyronitrile radicals (eq 8). AIBN has a half-life of 1 hour at 80 °C and is useful over the temperature range 60-120 °C.[29]

$$NC\overset{}{\diagup}\underset{}{N{=}N}\overset{}{\diagdown}CN \quad \xrightarrow{\Delta \text{ or } h\upsilon} \quad 2\ NC{-}\bullet\overset{}{\diagup} \quad + \quad N_2 \qquad (8)$$
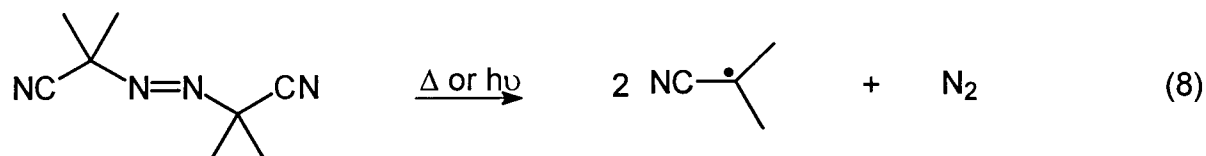
An initiator that has been finding increasing application in organic synthesis is triethylborane. It is usually added to a reaction as a commercially available 1.0 M solution in hexanes. Triethylborane reacts readily with oxygen, generating ethyl radicals which may be responsible for its initiator property.[30] Triethylborane is

particularly attractive because it can effectively generate radicals at low as well as high temperatures.[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.[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.
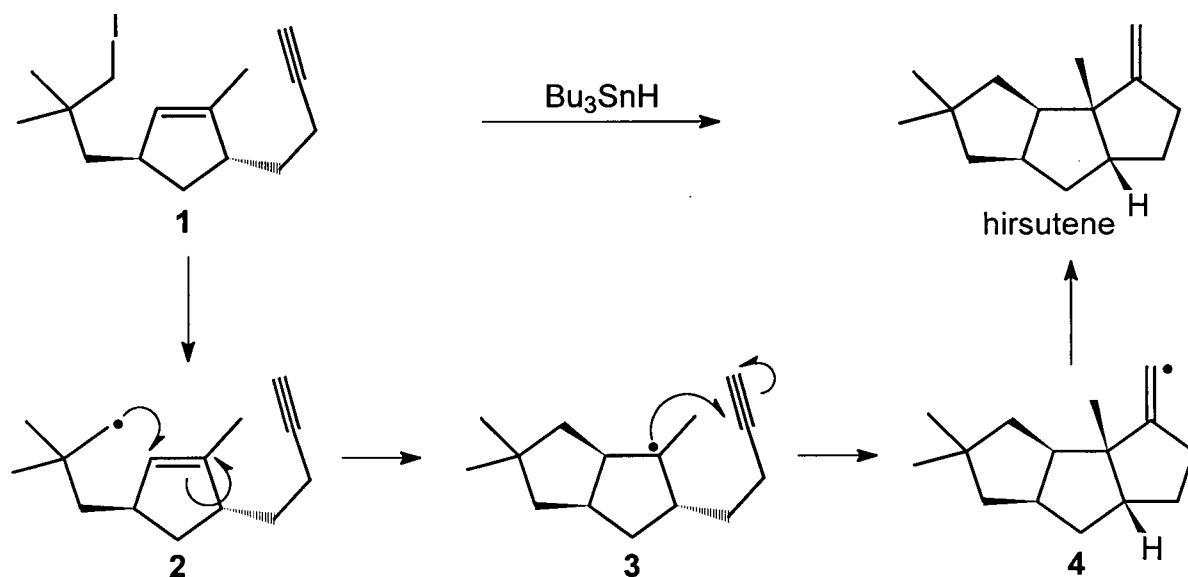
Several features of this reaction are noteworthy. First, the reaction is very efficient, and hirsutene is produced in 80% yield in a single step from the relatively simple *trans*-3,5-disubstituted cyclopentene **1** upon reaction with tri(*n*-butyl)tin hydride. This reaction also demonstrates that radicals are well suited for the formation of sterically hindered carbon-carbon bonds. As can be seen above, the initially-formed radical **2**, which is flanked by a *gem*-dimethyl group on the α-carbon, adds efficiently to the alkene to afford the tertiary radical **3**. In turn, radical **3** adds to the alkyne to give the vinyl radical **4**, forming a quaternary center in the process. Finally, radical **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.[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.
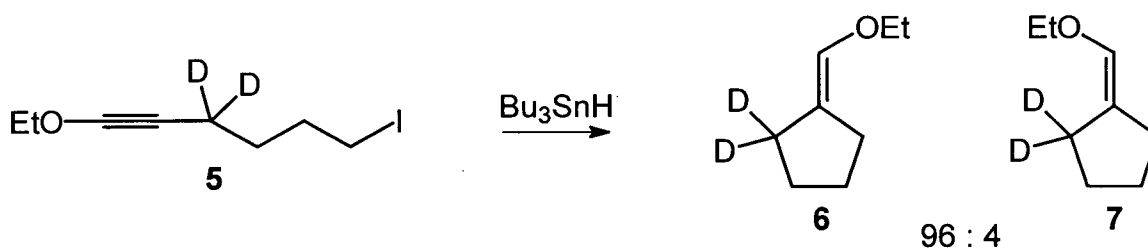
The almost exclusive formation of the E-isomer suggested that the radical center which has attacked the acetylenic bond and the newly generated half-filled sp^2 hybrid orbital are disposed in a *trans* orientation in the initial vinylic radical (Figure 5). Hydrogen transfer to the vinyl radical at a 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.[34]
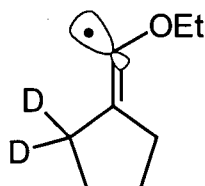
Figure 5. Stereochemistry of initial vinyl radical upon cyclization of the radical derived from **5**.

This result was in good agreement with the Wedegaertner *et* al. observation of stereoselective addition of ethyl mercaptan to ethoxyacetylene (Figure 6).[35]   This intermolecular addition afforded initial *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 *cis-* and *trans*-vinyl radicals. The *cis/trans* product ratio gradually decreased throughout the course of the reaction. This was attributed to isomerization of the products by thiyl radicals.

EtS• + H———≡———OEt
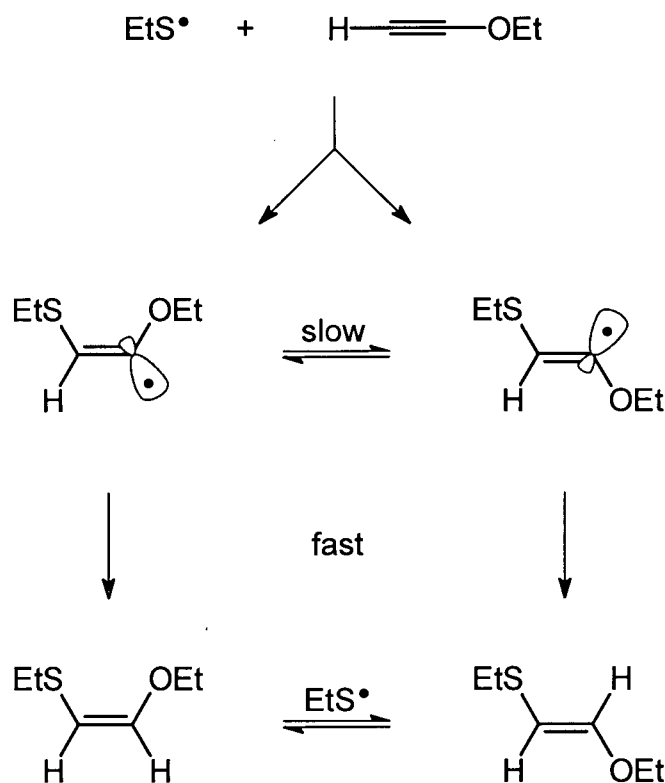
Figure 6. Rationale for the stereoselective addition of ethyl mercaptan to ethoxyacetylene.

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 *E* and *Z* isomeric products **9** and **10**.[36]
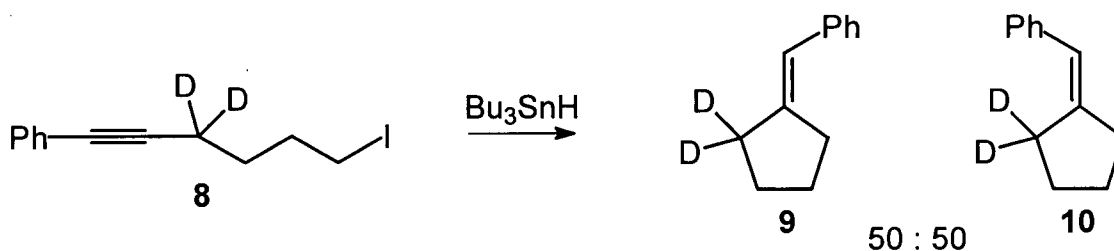
In this case the cyclization is proposed to yield the vinyl radical in a linear form. Thus, hydrogen abstraction would occur with equal probability from both sides of the vinyl radical. This is in agreement with the observation by Bennett and Howard that the electron spin resonance spectrum of the α-styryl 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.

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**.
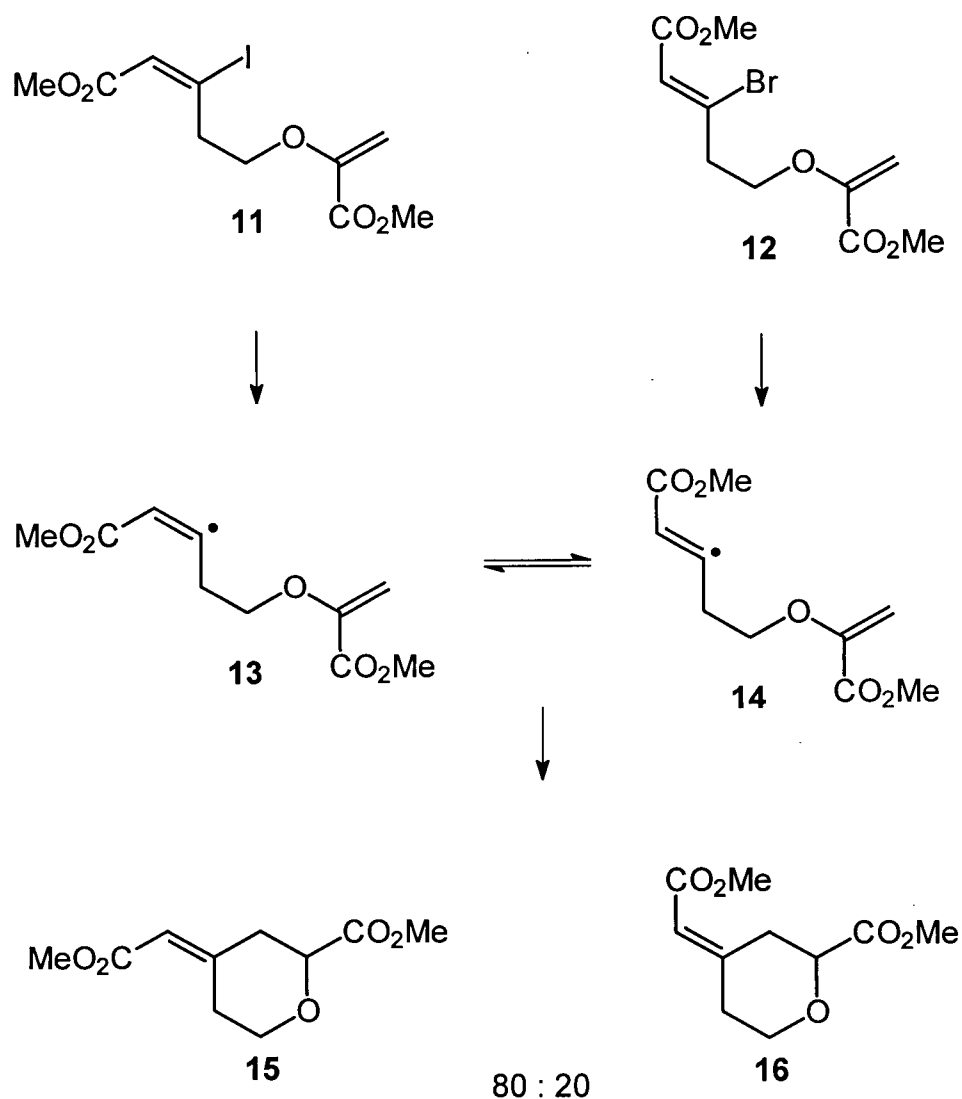
Both Baldwin and Russell have used a radical addition-elimination strategy to effect intermolecular vinylations. The general strategy for this radical reaction is shown in Figure 8. An initially formed alkyl radical adds to an alkene which bears a suitable leaving group Q. An electron-withdrawing substituent 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.
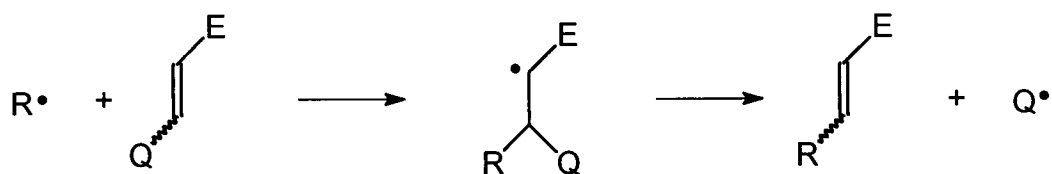
Figure 8. General strategy of addition-elimination reaction.

For example, Baldwin and Kelly studied reactions of alkyl radicals with *E*- and *Z*-vinyl stannanes (Figure 9).[41] 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.
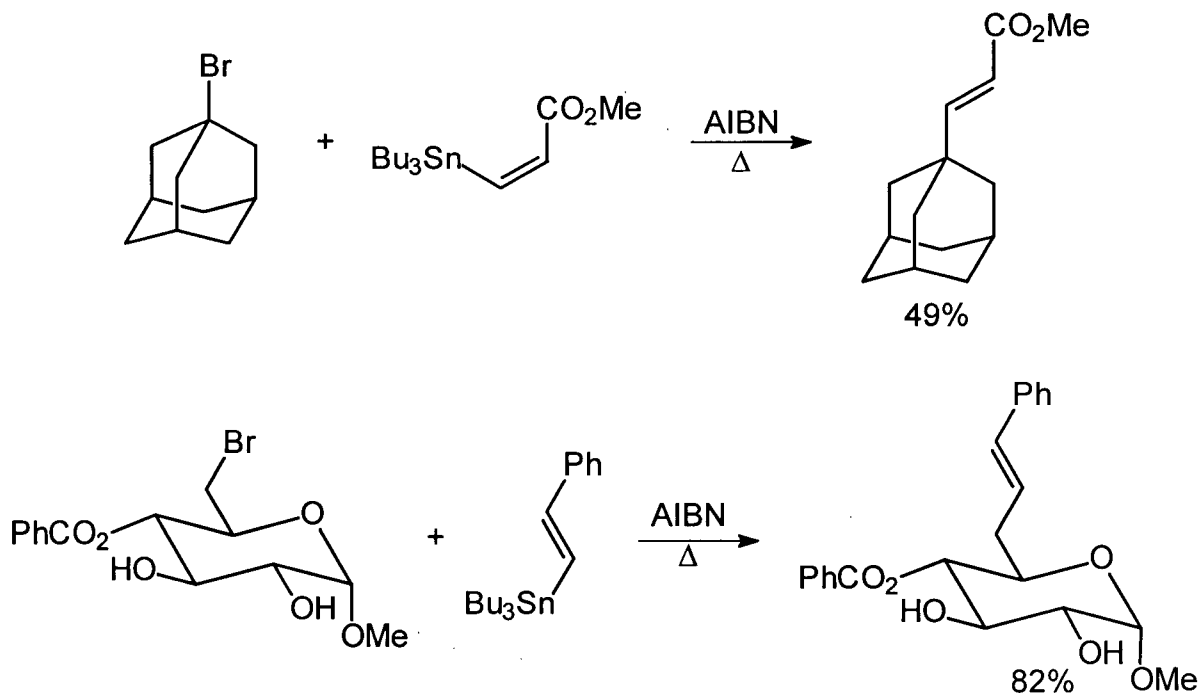
Figure 9. *E*-Selective addition-elimination reactions (from ref 41).

In addition to trialkylstannyl 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.[42] 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.[42b]
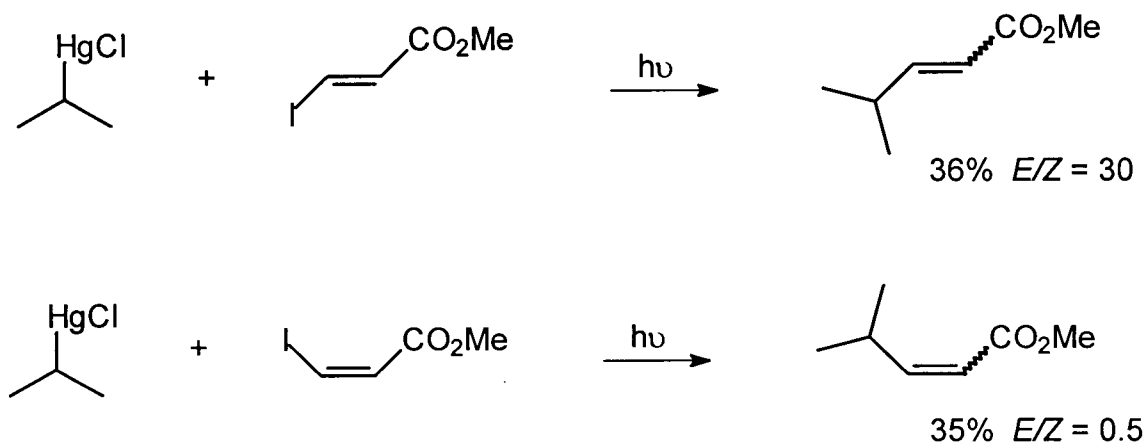
Figure 10. Stereospecific addition-elimination reaction (from ref 42b).

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.[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.

17

Bu₃SnH, PhH
AIBN, Δ

18
(35%) (*E:Z*=1:14)

+

19 (35%)

20

Bu₃SnH, PhH
AIBN, Δ

21
(48%) (*E:Z*=77:1)

+ **19** (48%
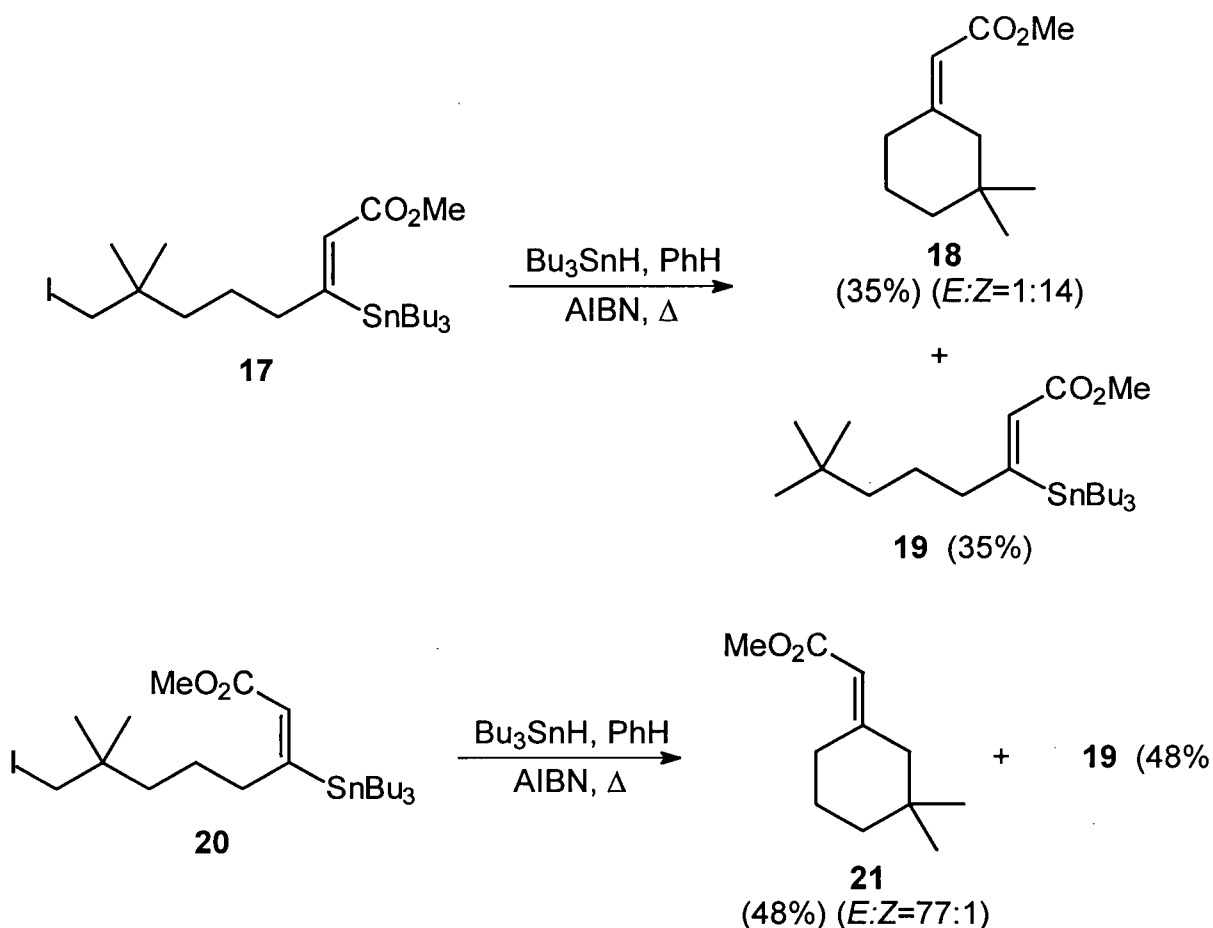
Later it was shown by Lowinger[44] that reaction of the *Z*-vinyl stannane **17** with tris(trimethylsilyl)silane resulted in the exclusive formation of the *Z*-exocyclic alkene **18** in 55% yield along with 40% of the acyclic reduction product **19**. Under the same conditions, reaction of the *E*-vinyl 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.[45]

The possible mechanism of the addition-elimination reaction sequence put forth by Lowinger[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.
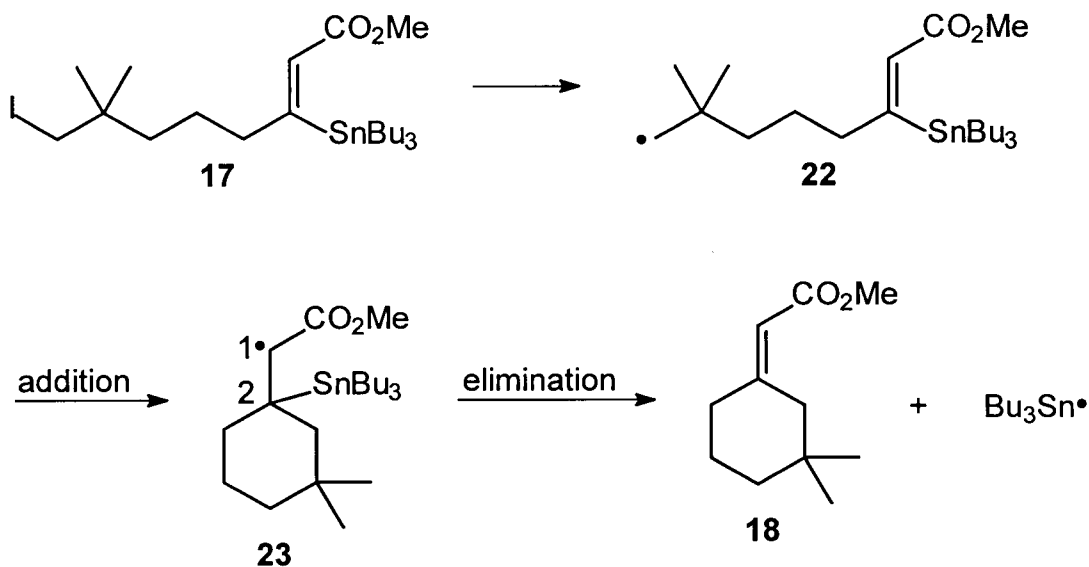
One complication to the task of synthesizing alkenes stereoselectively by radical cyclization, is their susceptibility to isomerization under radical reaction conditions.[46,47] In fact, double bond isomerization by radicals can be useful in synthesis. Thiyls,[47] tris(trimethylsilyl)silyl,[48] and tri(n-butyl)tin[44] 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.

24 → E:Z = 96:4
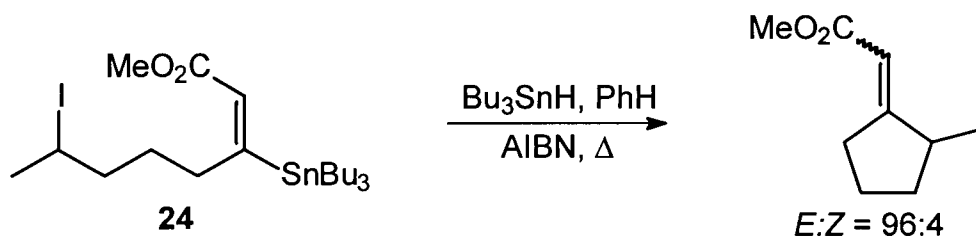
Reaction of the Z-vinyl stannane **25** resulted in an 84:16 ratio of E- and Z-exocyclic alkenes. Thus, the reactions were not stereospecific since in each case the E-isomer was more prevalent.

25 → E:Z = 84:16
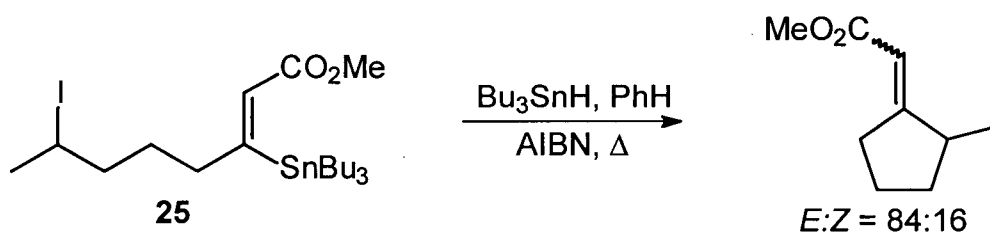
The Z-exocyclic alkene was shown to be unstable to the cyclization conditions by exposing pure Z-exocyclic alkene to the tri(n-butyl)tin radical conditions. After 1 hour the ratio of E- and Z-exocyclic alkenes was 98:2.

E:Z = 98:2
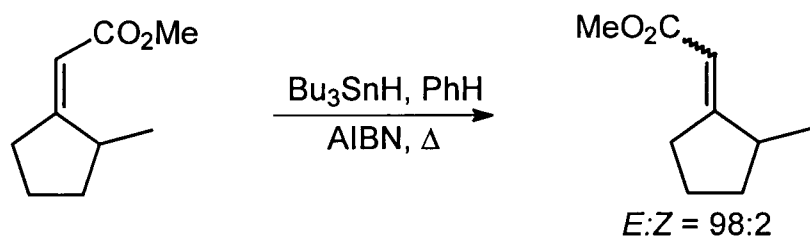
Investigation into the reactivity of the next higher homologues revealed similar results. The E-vinyl stannane **26** was reacted with tri(n-butyl)tin hydride to selectively produce the E-exocyclic alkene in 82% yield.

26 → 82%
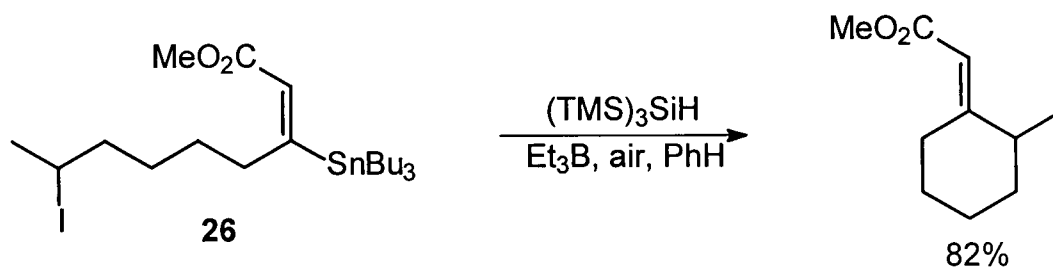
As was the case with the lower homologue, the Z-vinyl stannane **27** reacted to give a mixture of E- and Z-exocyclic alkenes which was richer in the E-product.
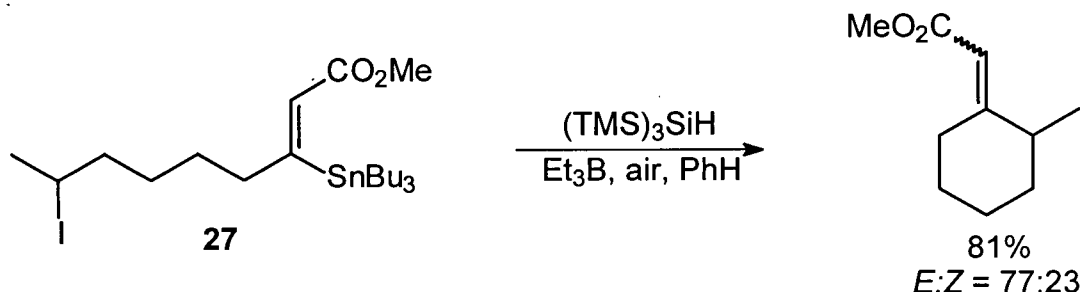
No difference in selectivity for the formation of 6-membered rings was realized for reactions mediated by tris(trimethylsilyl)silane versus tri(n-butyl)tin hydride. However, tris(trimethylsilyl)silane mediated reactions had the advantage of producing less of the acyclic reduction products.

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.
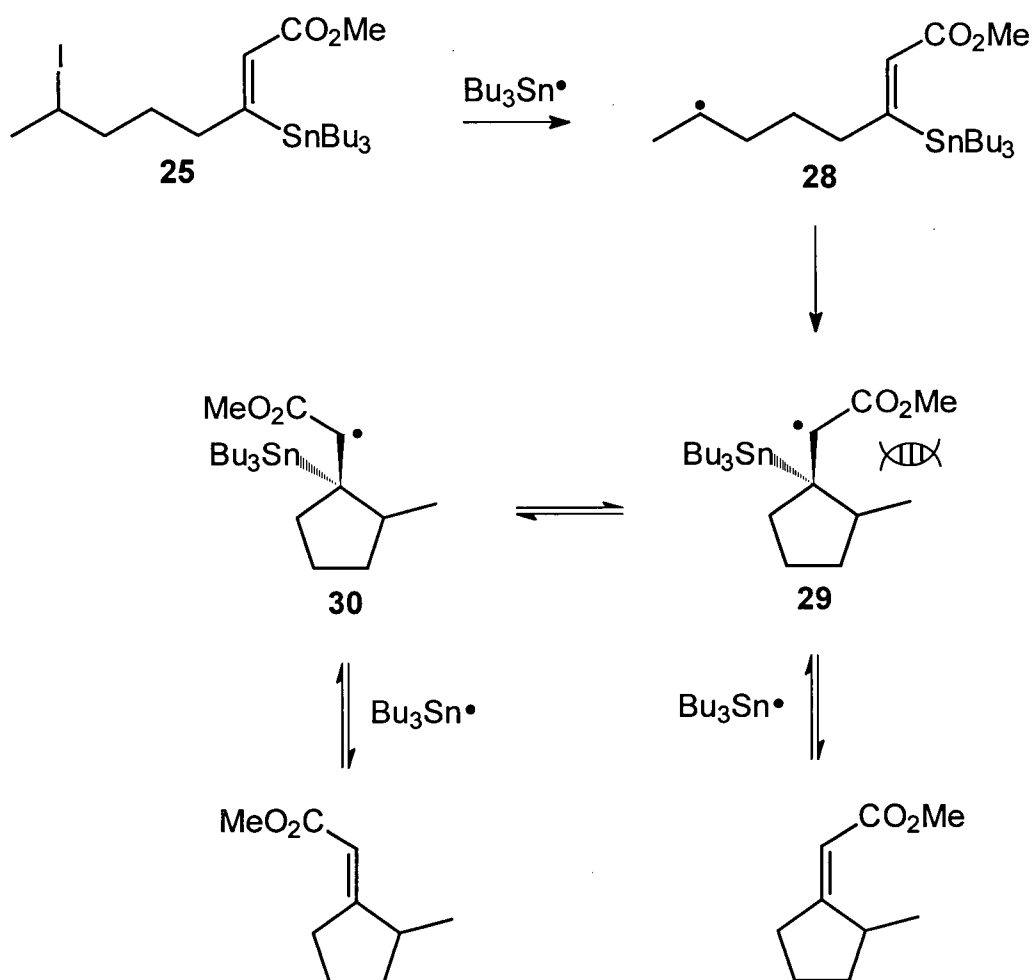
Lowinger and Weiler solved the difficulty in making Z-exocyclic alkenes by using the ring substituent to their advantage.[50] Reaction of the acetylene **31** with tri(*n*-butyl)tin hydride at 80 °C afforded a 98:2 ratio of E-and Z-alkenes. While reaction of **31** with tris(trimethylsilyl)silane at -78 °C afforded an 11:89 ratio of E-and Z-alkenes.
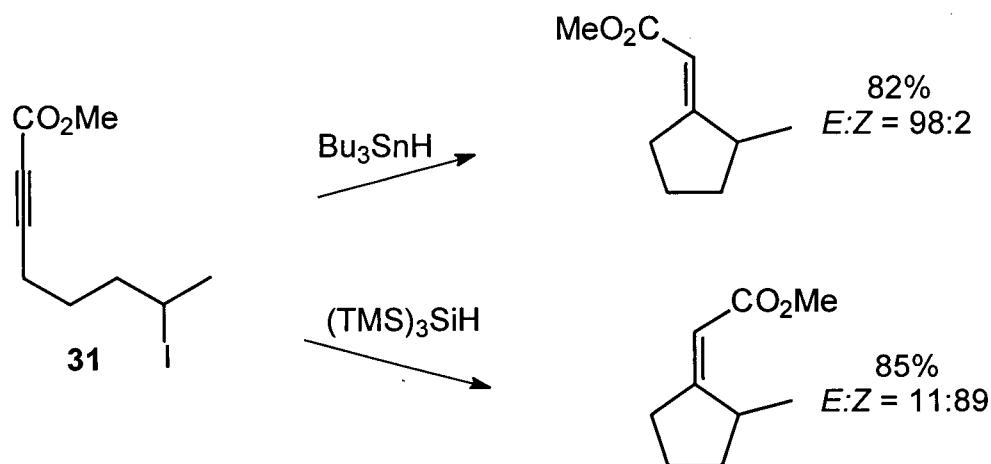
Similar results were obtained for synthesizing the 6-membered ring alkenes. Reaction of **32** with tri(*n*-butyl)tin hydride at 80 °C afforded a 98:2 ratio of *E*- and *Z*-alkenes, while reaction with tris(trimethylsilyl)silane at -78-25 °C afforded 9:91 ratio of *E*- and *Z*-alkenes. Thus, by specific choice of reaction conditions, it was possible to prepare either *E*- or *Z*-exocyclic alkenes stereoselectively from the same precursors.
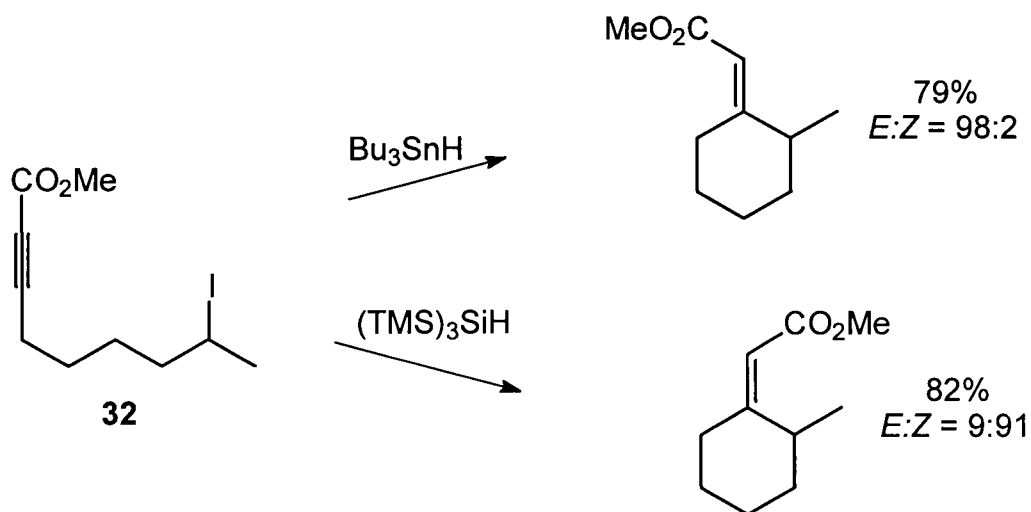
The following rationale was offered for the selectivity in these reactions.[44] Abstraction of the iodine atom from **31** affords the secondary alkyl radical **33**. Cyclization gives a vinyl radical, which can exist in two isomeric forms, **34** and **35**. The final step required in the reaction is 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.
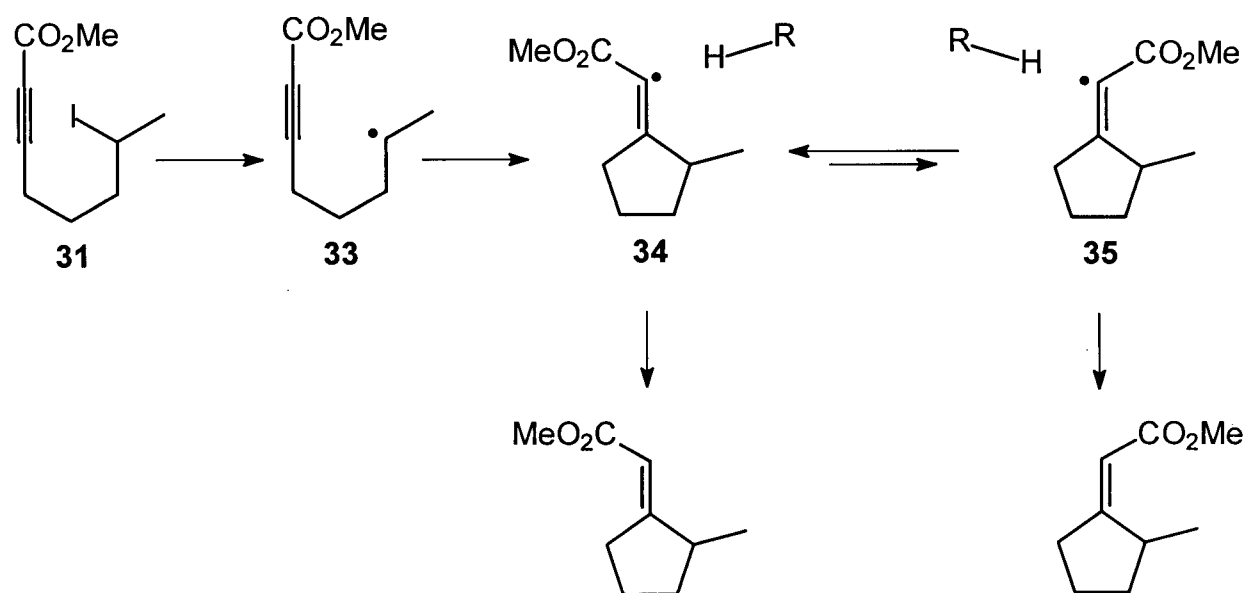
CHAPTER 2

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.

$$\text{(9)}^{51}$$

88%
($E:Z$ = 50:50)
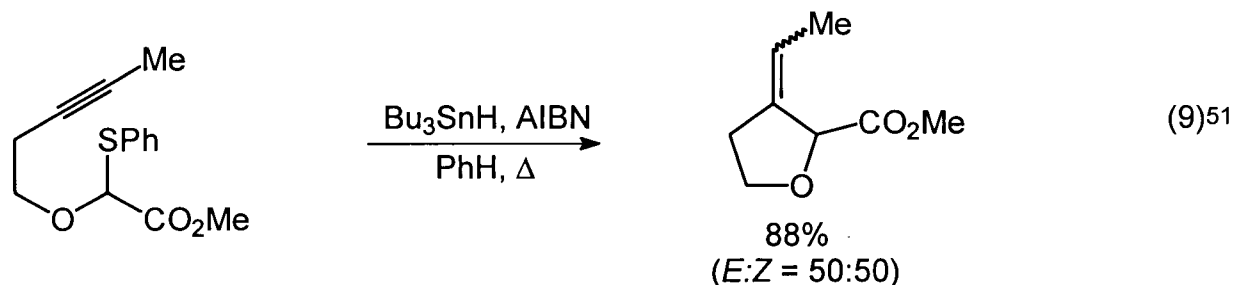
We were interested to know if our methods of controlling the stereochemistry of exocyclic alkenes by choice of reducing agent and reaction conditions could be applied for the stereoselective production of exocyclic alkenes in tetrahydrofuran and tetrahydropyran derivatives.　We chose compounds **36** and **37** as cyclization substrates

36　　　　　　　　　　　　　　　**37**
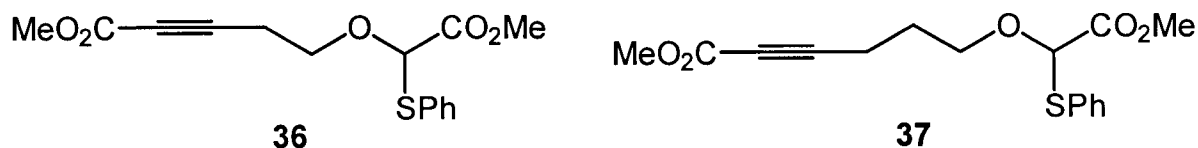
for this study. Alkynes substituted with a carbomethoxy group were chosen following the substrates on which the stereoselective methodology had been developed. Also, the ester group provides an additional handle for further synthetic transformations. Such a handle could conceivably be important for the 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)**.
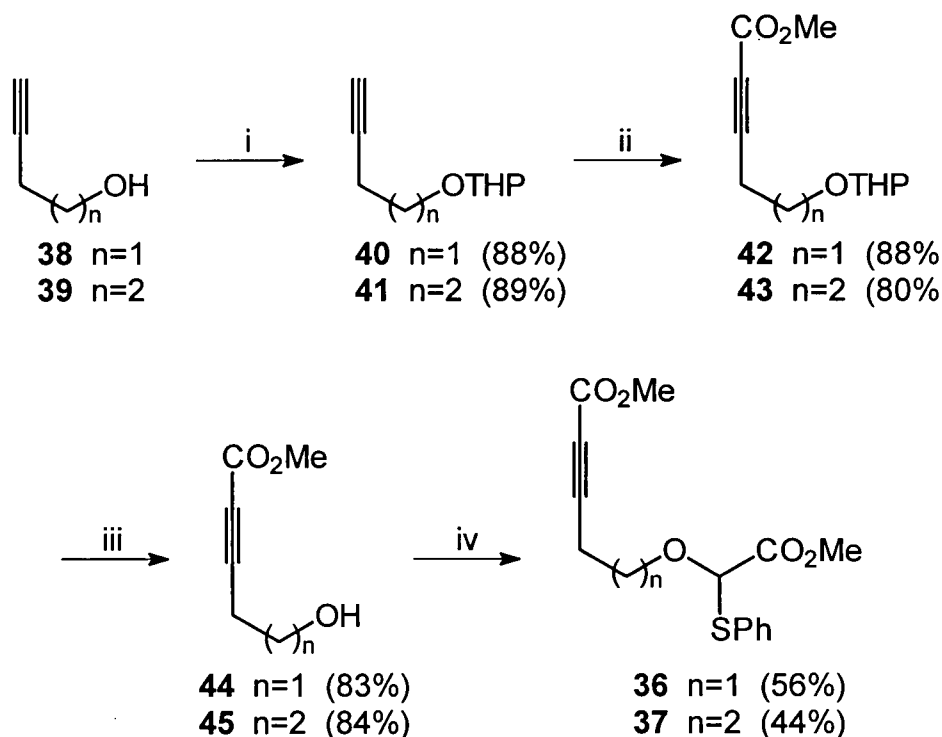
Scheme I. i. DHP, p-TsOH·H_2O, CH_2Cl_2; ii. MeLi, ClCO$_2$Me, THF, -78 °C; iii. p-TsOH·H_2O, MeOH; iv. **48**, Zn(OAc)$_2$·2H$_2$O, PhH, Δ.

The alkyne was deprotonated by methyllithium and addition of methyl chloroformate afforded methyl 5-(2-tetrahydropyranyloxy)-2-pentynoate **(42)** and methyl

6-(2-tetrahydropyranyloxy)-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.
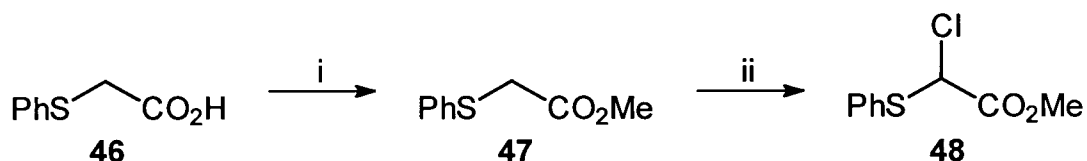
Scheme II. i. MeOH, p-TsOH·H_2O, 93%; ii. N-chlorosuccinimide, CCl_4 76%.

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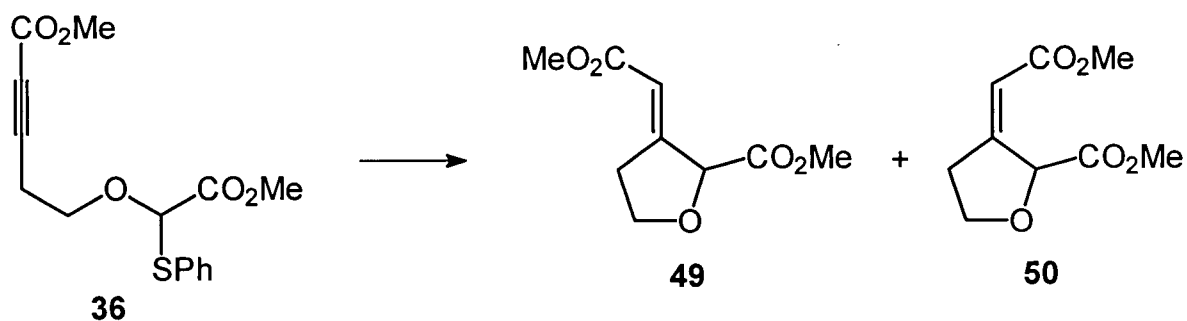
The results of the cyclizations of compound **36** to compounds **49** and **50** are summarized in Table V. Initial reactions were focused on the use of tri(*n*-butyl)tin hydride as the radical reducing agent. Selectivity for the *E*-isomer was expected for tri(*n*-butyl)tin hydride mediated reactions.

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

Entry	Reducing Agent	Initiator	Solvent	Temp (°C)	Yield (%)[a]	*E:Z* Ratio[b] (**49:50**)
1	Bu_3SnH	AIBN	PhH	80	72	62:38
2	Bu_3SnH	Et_3B/air	PhH	80	95	75:25
3	Bu_3SnH	Et_3B/air	PhH	25	82	66:34
4	$(TMS)_3SiH$	AIBN	PhH	80	82	22:78
5	$(TMS)_3SiH$	Et_3B/air	PhH	80	90	19:81
6	$(TMS)_3SiH$	Et_3B/air	PhH	25	82	15:85

[a] Determined by GC analysis using tetradecane as internal standard.
[b] 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^{-1} of the starting material was replaced by C=C band ca. 1670 cm^{-1} 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 $C_9H_{12}O_5$. The absence of

vinyl protons in the ^{1}H NMR spectrum of **51** was consistent with the assigned endocyclic alkene structure.
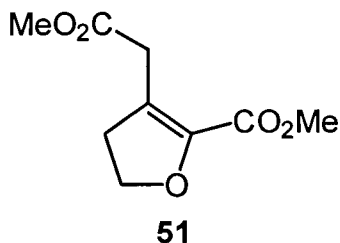
MeO$_2$C

CO$_2$Me

O

51

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 δ 3.02-3.20 assigned to the allylic methylene hydrogens and a one-proton doublet at δ 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 δ 2.78 and δ 2.86 and a one-proton triplet at δ 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 δ 4.95 upon irradiation of the vinyl proton at δ 6.10 . Similarly, irradiation of the vinyl proton at δ 6.02 of compound **50** exhibited a weak NOE to the methylene protons at δ 2.78 and 2.86.

MeO$_2$C   H ◄—— δ 6.10   δ 6.02 ——► H   CO$_2$Me

δ 3.02-3.20 ——► H   H ◄—— δ 4.95   δ 2.78 ——► H   H ◄—— δ 5.4

H   CO$_2$Me   δ 2.86 ——► H   CO$_2$Me

O   O

49   **50**
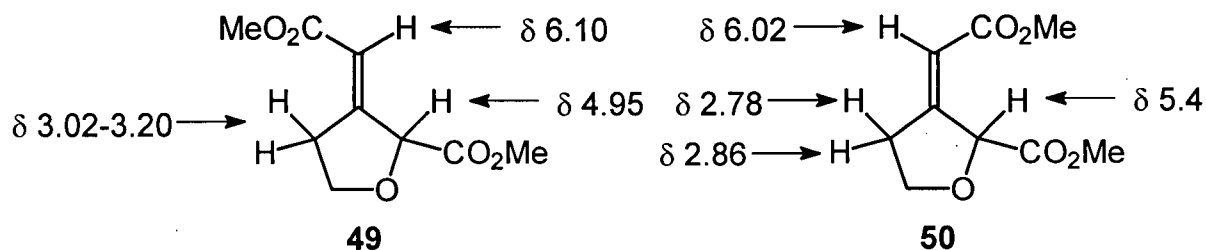
The reaction in Entry 4, in which tris(trimethylsilyl)silane was used in place of tri(*n*-butyl)tin hydride, was performed using the same procedure as for the reaction in Entry 1. After 6 hours, GC analysis indicated 11% of the starting material remained and an 82% yield of **49** and **50** in 22:78 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.[44] 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.
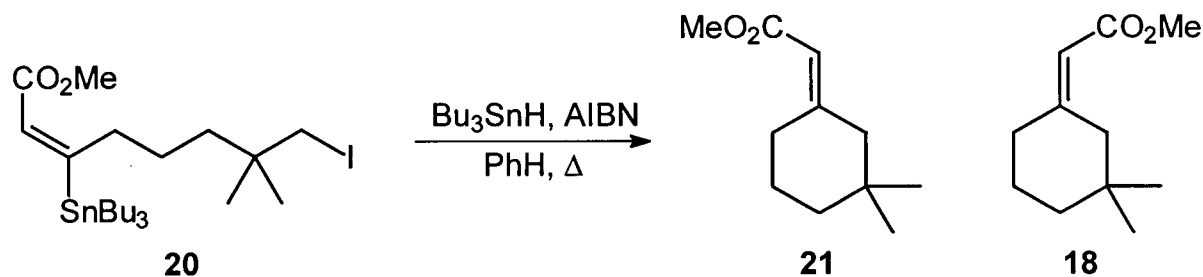
Comparison of the tris(trimethylsilyl)silane mediated reactions in Entries 5 and 6 shows that the preferred Z-isomer selectivity increased slightly from an E:Z ratio of 19:81 for reaction at 80 °C to a 15:85 for reaction at 25 °C. That the selectivity was improved at the lower reaction temperature, even 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.
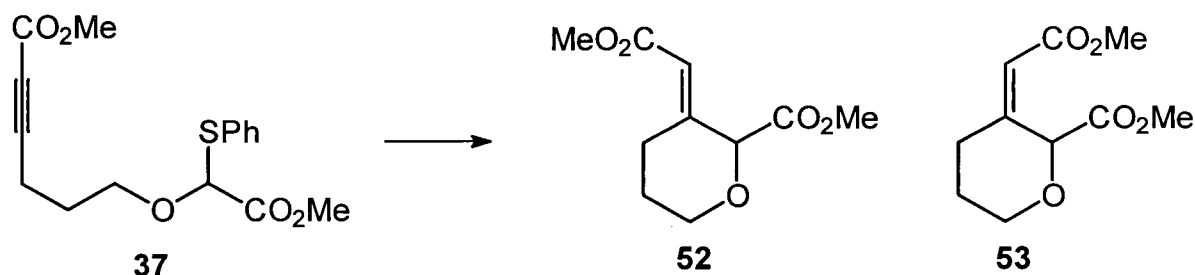
Table VI. Tri(*n*-butyl)tin Hydride and Tris(trimethylsilyl)silane Mediated Cyclizations of Compound **37**.

Entry	Reducing Agent	Initiator	Solvent	Temp (°C)	Yield (%)[a]	E:Z Ratio[b] (52:53)
1[c]	Bu$_3$SnH	AIBN	PhH	80	39	50:50
2	Bu$_3$SnH	Et$_3$B/air	PhH	80	8	50:50
3	(TMS)$_3$SiH	AIBN	PhH	80	54	43:57
4	(TMS)$_3$SiH	Et$_3$B/air	PhH	80	47	48:52

[a] Product yields were determined by GC analysis using tetradecane as internal standard.

[b] Isomer ratios were determined by gas chromatography.

[c] 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. Perfoming 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 ^{1}H and nuclear Overhauser enhancement (NOE) NMR spectral data. The ^{1}H NMR spectrum of compound **52** exhibited a one-proton doublet of triplets at δ 3.39 and a

one-proton multiplet at δ 2.61 assigned to the allylic methylene hydrogens and a one-proton singlet at δ 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 δ 2.40 and a one-proton singlet at δ 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 δ 5.74 upon irradiation of the methine proton at δ 4.58. Similarly, irradiation of the methylene protons at δ 2.40 of compound **53** produced an NOE of the vinyl proton at δ 5.82.
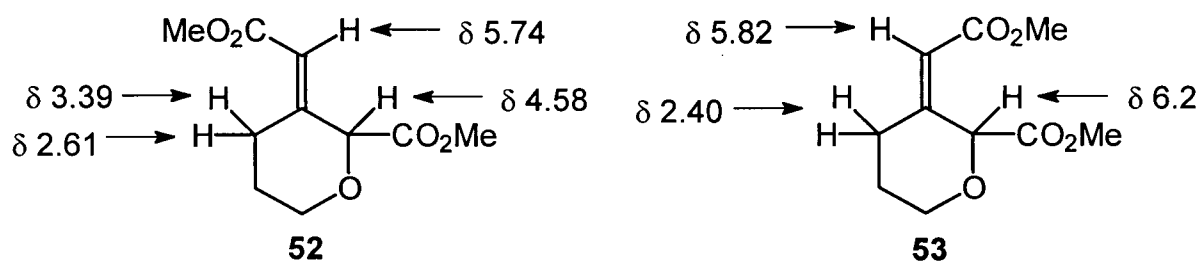
The reaction in Entry 3 was performed using the same procedure described for Entry 4 in Table V. After 6 hours, GC analysis indicated that only a trace of the starting material remained and a 54% yield of **52** and **53** in a 43:57 ratio.

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 $C_{10}H_{14}O_5$. The IR showed a C≡C band at 2237 cm^{-1}. The ^{1}H NMR included a two-proton singlet at δ 4.03 for the methylene between O and CO_2Me.

MeO$_2$C————————O——CO$_2$Me

54
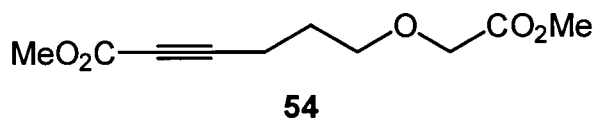
The opportunity to use the reducing agent and reaction conditions to control the stereoselectivity of *E*- or *Z*-exocyclic alkene formation from substrates **36** and **37** showed only limited success. For compound **36**, modest selectivity for the *E*-isomer **49** resulted from tri(*n*-butyl)tin 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.

MeO$_2$C . H—ML$_3$ —Me

L$_3$M—H . —CO$_2$Me —Me

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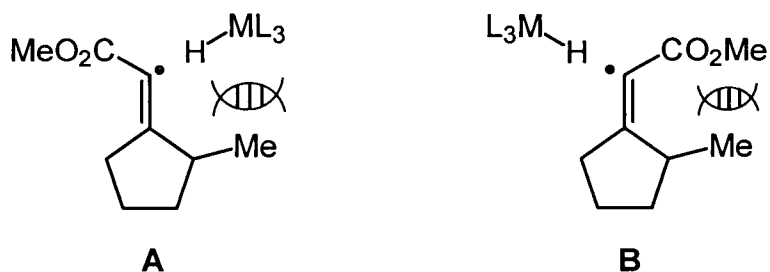
Figure 11. An abbreviated version of Lowinger's rationale for reaction selectivity.

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,[53] and by methyl, 1.74 kcal/mol.[54] 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. $A_{1,3}$ 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.
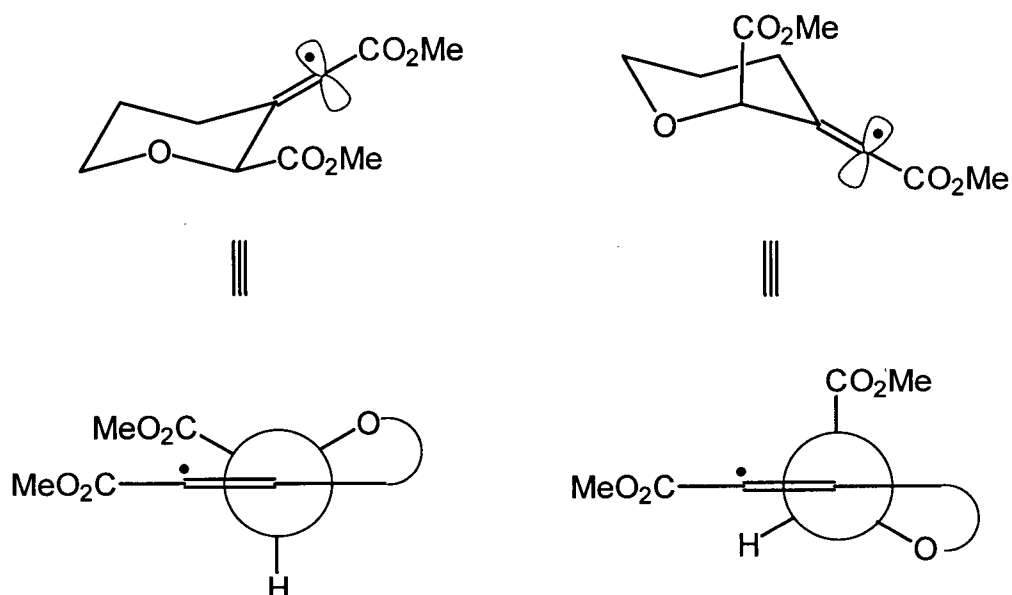
Figure 12. Analysis of potential ring conformation effects on the reaction selectivity.

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.[55] 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**.
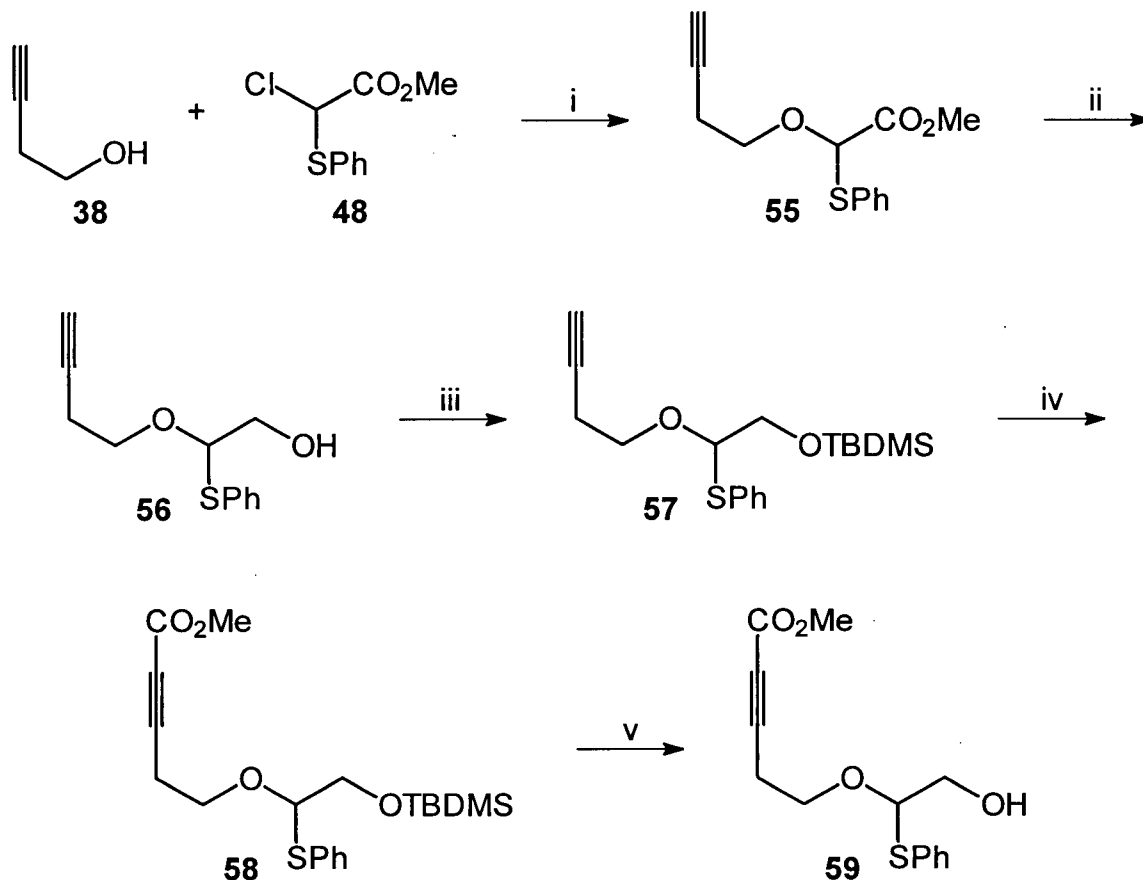
Scheme III. i. Zn(OAc)$_2$·2H$_2$O, PhH, Δ, 60%; ii. LiAlH$_4$,THF, 0 °C, 90%; iii. TBDMSCl, imidazole, DMF, 95%; iv. MeLi, ClCO$_2$Me, THF, -20 °C, 79%; v. 2,4,6-trimethylpyridinium fluoride, CH$_2$Cl$_2$, 97%.

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.
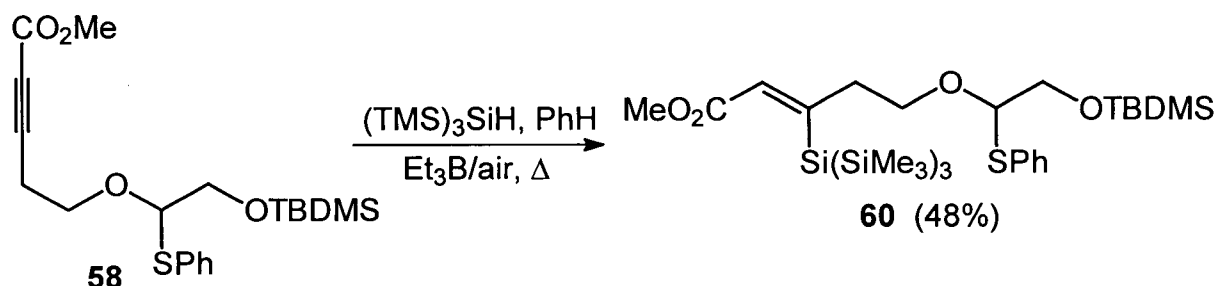
The addition product **60** was presumed to have been produced through the following radical chain reaction. Tris(trimethylsilyl)silyl radical could add to the activated acetylene in substrate **58** to afford the vinyl radical intermediate **61**. Abstraction of hydrogen from tris(trimethylsilyl)silane would produce compound **60** and tris(trimethylsilyl)silyl radical which would continue the chain reaction process.
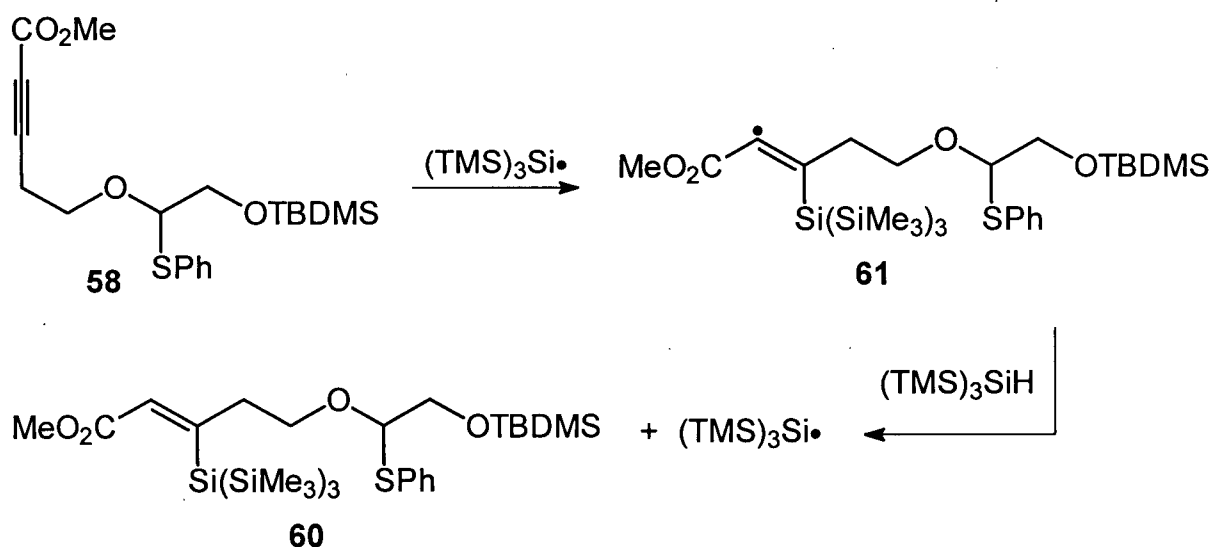
Treatment of the alcohol **58** under the same conditions resulted in complete consumption of starting material and addition product **62** was isolated in 64% yield. The Z stereochemistry of **60** and **62** was assigned by the chemical shift of the vinyl protons. A trace of the E-isomer of **62** 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**.

62 (64%)
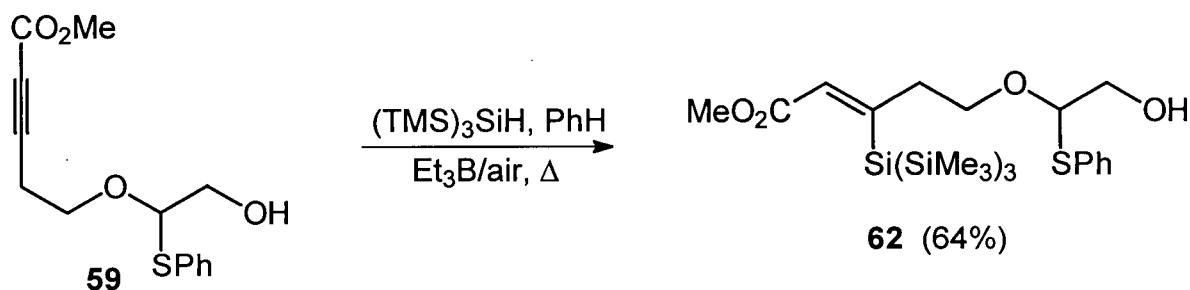
Reaction of **59** with tri(*n*-butyl)tin hydride afforded a 34% yield of the *Z*-addition product **63**. All of the starting substrate was consumed in the reaction. The *Z* stereochemistry of the alkene was assigned by the vinyl hydrogen to tin coupling constant of 105 Hz.

63 (34%)
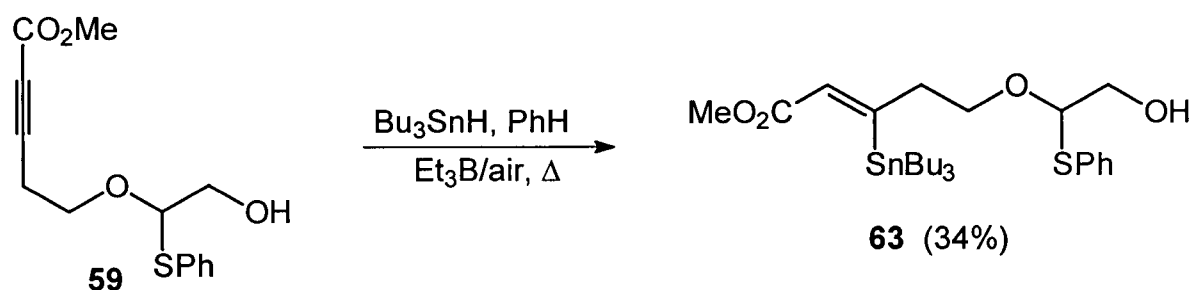
In each of the reactions, no products resulting from abstraction of the phenylthio group were isolated. These results show that tri(*n*-butyl)tin and tris(trimethylsilyl)silyl radicals add to the triple bond of these propargyl esters at a faster rate than they abstract the phenylthio group. Although 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]

64   **65** (72%)
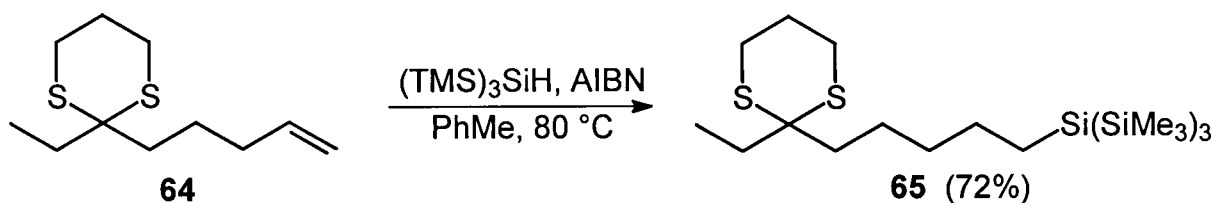
In contrast, Yadav and Fallis did not report any competitive addition in the tri(*n*-butyl)tin hydride cyclization of **66**.[57]

66   Bu₃SnH, AIBN   **67** (66%)
                          ―――――――――――→
                          PhH, Δ
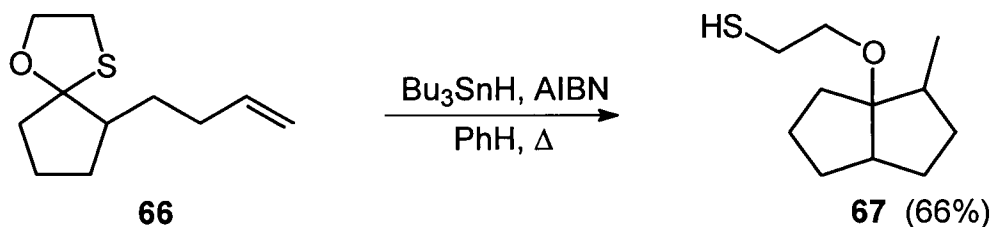
Burke and Jung found that the stereoselectivity in the synthesis of 2,3-substituted tetrahydrofurans was improved when the 2-position was substituted by both an ester group and a methyl group.[58] This selectivity has been rationalized by the lower energy of the chair-like transition state **68**, with the methyl group in a pseudo-equatorial position. The nonbonded interactions with the pseudo-axial hydrogens and a *t*-butylester 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.
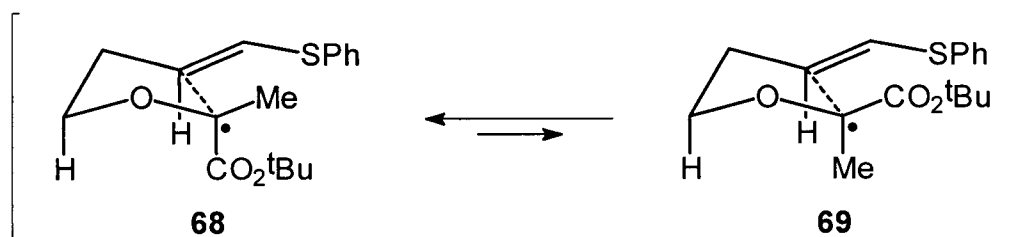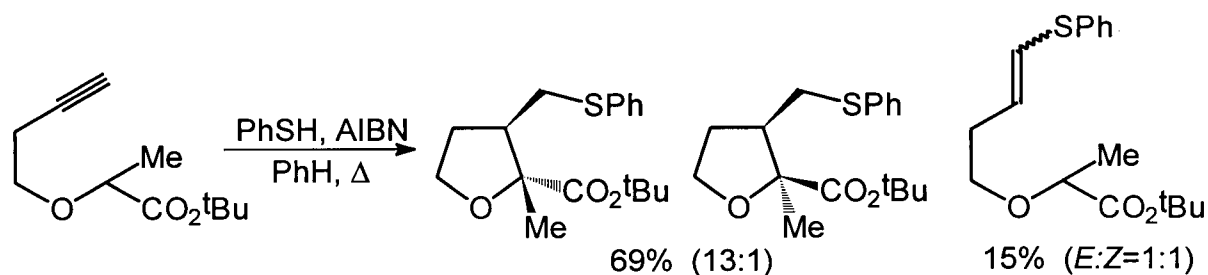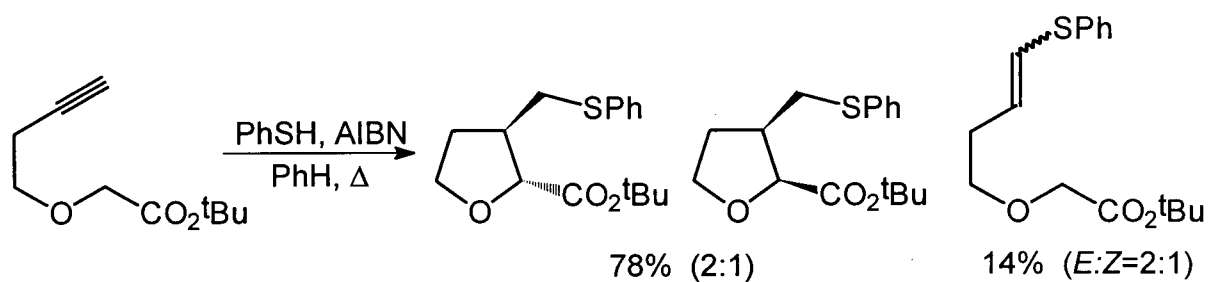
2.1.6 Synthesis of Dimethyl 7-Methyl-6-oxa-7-(phenylthio)-2-octynedioate (71) and Dimethyl 8-Methyl-7-oxa-8-(phenylthio)-2-nonynedioate (72)

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**.
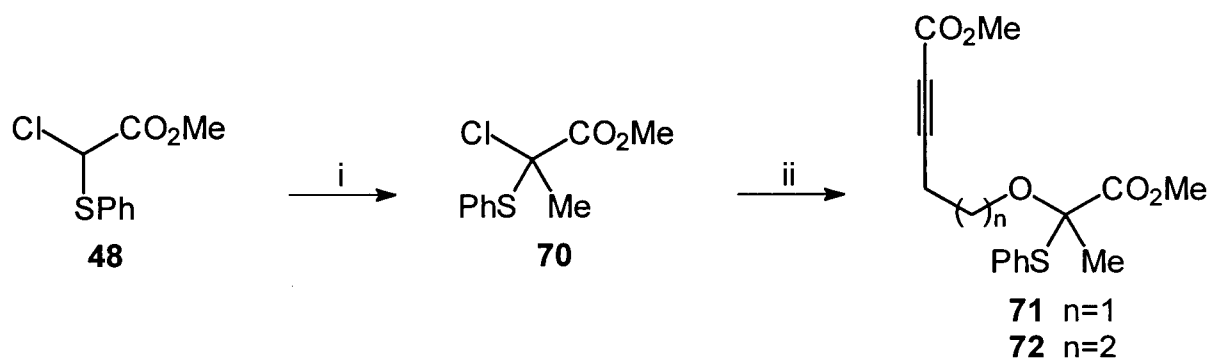
Scheme IV. i. LDA, MeI, THF, -78 °C; ii. **44**, Zn(OAc)$_2$·2H$_2$O, PhH, Δ, 20% of **71**; **45**, Zn(OAc)$_2$·2H$_2$O, PhH, Δ, 19% of **72**.

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.
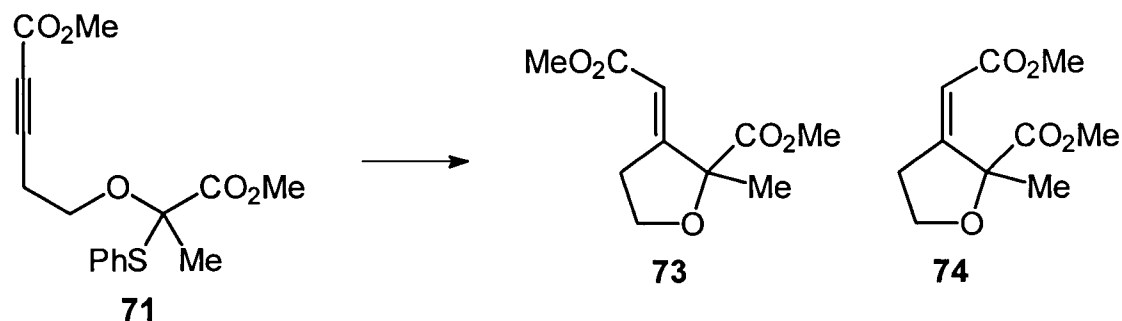
The stereochemistry of the exocyclic alkenes was assigned by analysis of their ^{1}H and NOE NMR spectral data. The ^{1}H NMR spectrum of compound **73** exhibited one-proton multiplets at δ 3.06 and at δ 3.16 assigned to the allylic methylene hydrogens. The analogous signal in the ^{1}H NMR spectrum of compound **74** was a two-proton multiplet at δ 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 δ 5.97 upon irradiation of the methyl protons at δ 1.55. In addition, irradiation of the vinyl proton at δ 5.97 produced an NOE of the methyl protons at δ 1.55. Similarly, irradiation of the methylene protons at δ 2.73-2.93 of compound **74** produced an NOE of the vinyl proton at δ 5.92. Here also, irradiation of the vinyl proton at δ 5.92 produced an NOE of the methylene protons at δ 2.73-2.93.
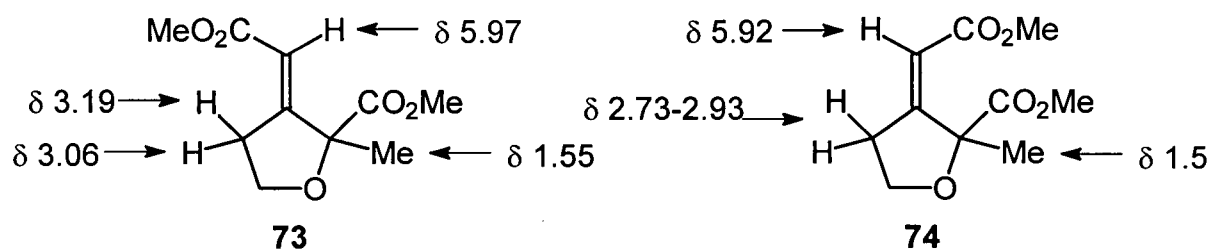
After 3 hours in refluxing benzene with tri(*n*-butyl)tin hydride and AIBN, heterocycle **74** was converted to a 96:4 mixture of **73** and **74**. Heterocycle **73** was unchanged after treatment for 2 hours under these isomerizing conditions. This suggested that **73** was the thermodynamically more 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.

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.

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.

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 ^{1}H 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.

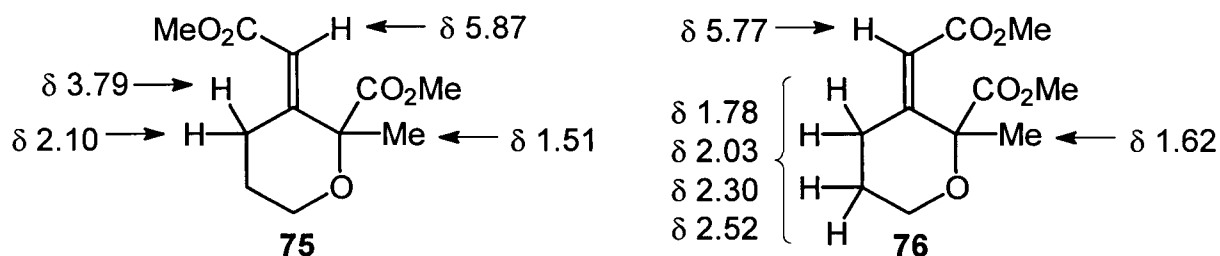The selectivity of the tris(trimethylsilyl)silane mediated radical reaction of substrate **72** to the tetrahydropyran **76** was similar to that reported by Lowinger and Weiler for the formation of the Z-carbocycle shown on page 23 of the Introduction. It seems likely that in both cases the lowest energy 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.[50] 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 Et$_3$B/air as initiator. We have observed that reactions initiated by Et$_3$B/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.[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.
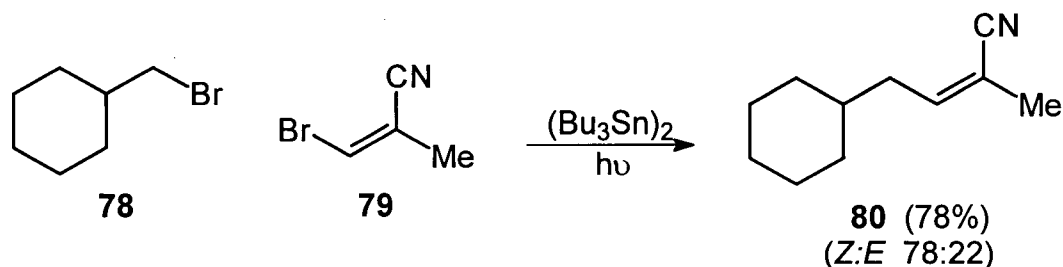
Earlier studies in our group have shown that an addition-elimination sequence may also be involved in the stereoselective production of exocyclic alkenes.[44] The yield of desired exocyclic alkene was occasionally diminished by the formation of acyclic reduction products. This complication occurred in the reactions promoted by either tri(*n*-butyl)tin hydride or tris(trimethylsilyl)silane (eq. 10).

(10)
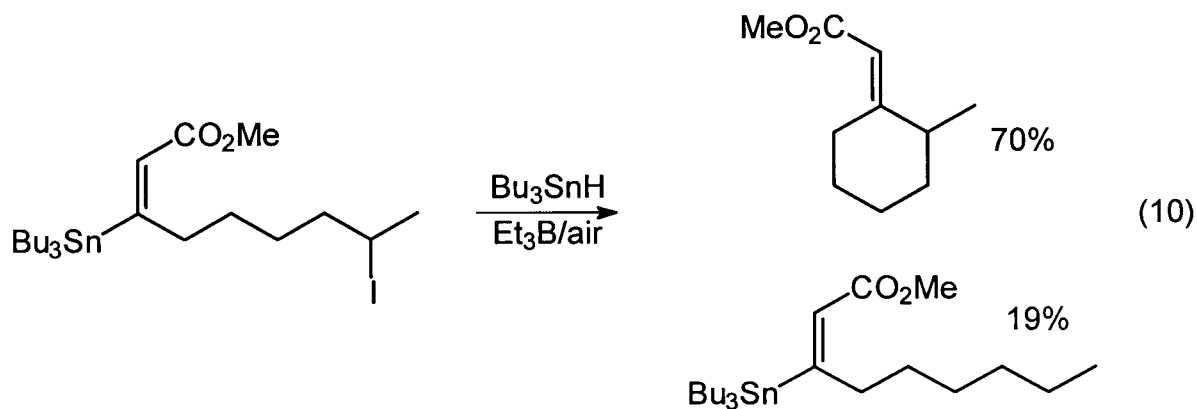
The fact that in the photochemical method the radical chain carrier is derived from hexa(n-butyl)ditin rather than from tri(n-butyl)tin hydride suggested that the yield of cyclic products could be improved by eliminating a pathway to acyclic reduction products. Curran and Chang[60] had shown that reaction 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.[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.
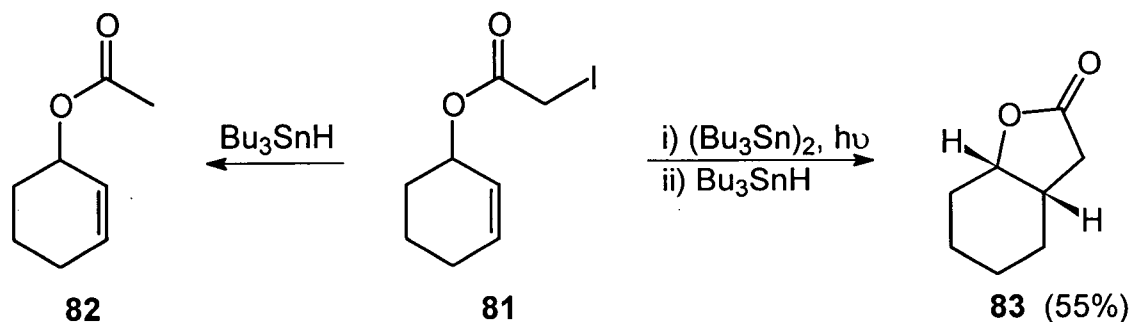
2.2.1 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3,7-Dibromo-2-heptenoate (90) and (91).

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).
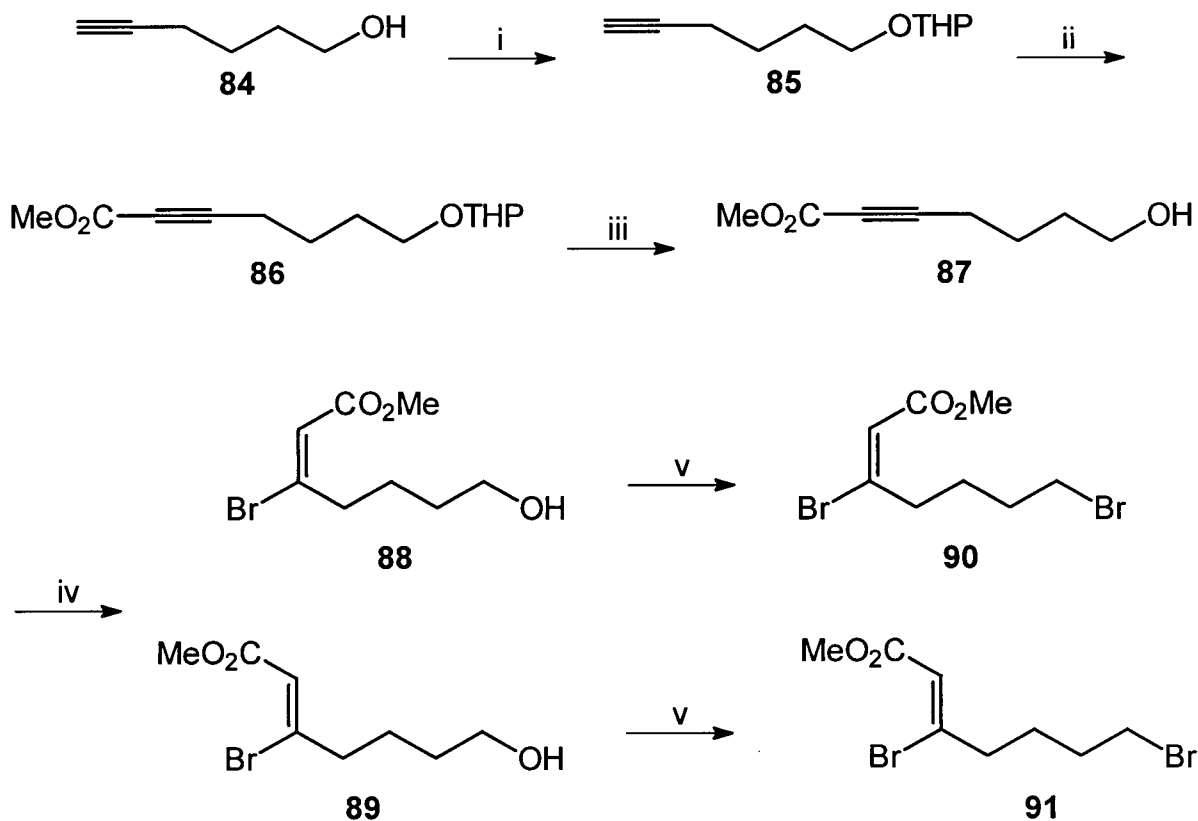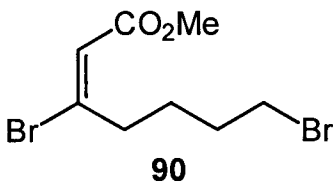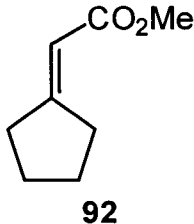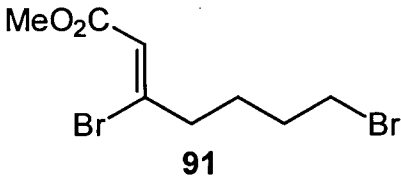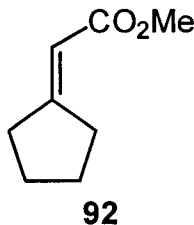
Scheme V. i. DHP, p-TsOH·H$_2$O, CH$_2$Cl$_2$, 86%; ii. MeLi, ClCO$_2$Me, THF, -20 °C, 92%; iii. p-TsOH·H$_2$O, MeOH, 98%; iv. HBr, Et$_2$O, 0 °C, 88 (21%), 89 (34%); v. CBr$_4$, P(Ph)$_3$, CH$_2$Cl$_2$, 90 (83%), 91 (54%).

The alkyne was deprotonated and acylated with methyl chloroformate to afford methyl 7-(2-tetrahydropyranyloxy)-2-heptynoate (86). The hydroxy group was deprotected by hydrolysis of the acetal using acidic methanol to afford methyl 7-hydroxy-2-heptynoate (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.[40] That the reaction had occurred was easily seen by the loss of the C≡C in the IR and by the appearance of

new vinyl signals in the ^{1}H NMR at δ 6.31 for **88** and at δ 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 δ 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 δ 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.[61] 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 $C_8H_{12}O_2$ which is consistent with structure **92**. The ^{1}H NMR spectrum of **92** shows a pair of two-proton broad triplets at δ 2.41 and δ 2.75, assigned to the allylic protons. The lower field signal at δ 2.75 is due to deshielding by the *cis* ester group. The remaining four ring hydrogens make up the multiplet centered at δ 1.68.

Table VII. Photochemical Cyclization of Compounds **90** and **91**.

Entry	Cyclization Substrate	Product	Isolated Yield (%)
1	**90**	**92**	54
2	**91**	**92**	61

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.[50] These compounds had been fully characterized and had been shown to be separable on GC and TLC.

93   **94**
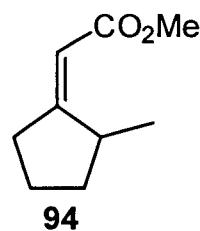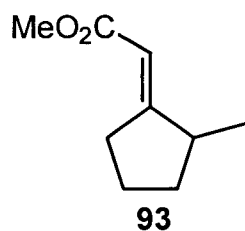
2.2.2 Synthesis and Photochemical Cyclization of Methyl (*E*)- and (*Z*)-3,7-Dibromo-2-octenoate (106) and (107)

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.[62] Addition of compound **97** to a solution of lithium acetylide in dimethyl sulfoxide afforded 1-heptyn-6-one ethylene acetal (**98**).
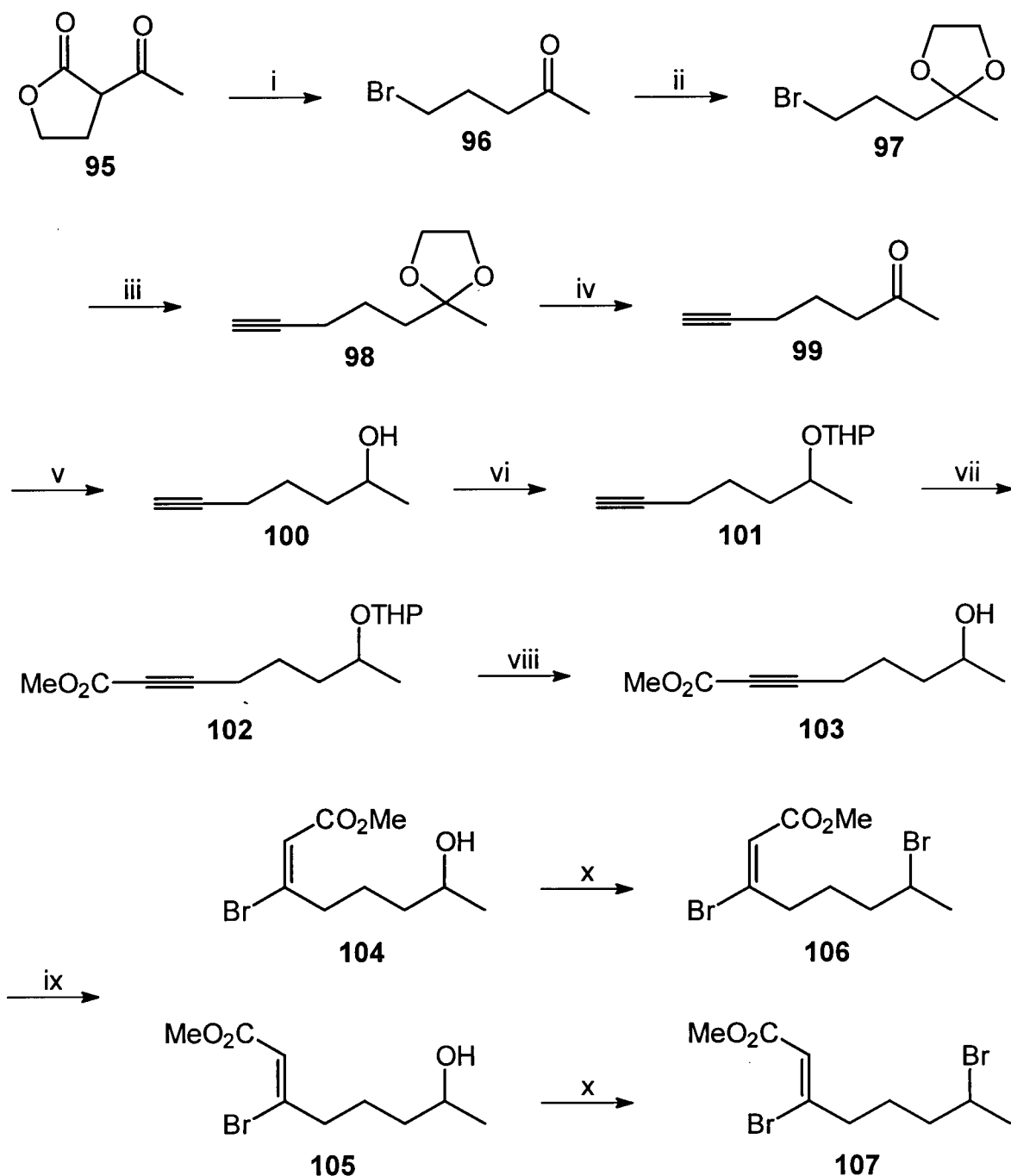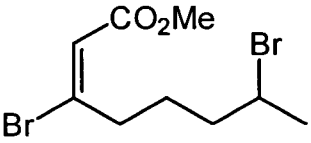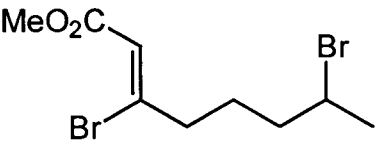
Scheme VI. i. HBr, H_2O, Δ, 50%; ii. $(HOCH_2)_2$, p-TsOH·H_2O, PhMe, Δ, 82%; iii. LiCCH·EDA, DMSO, 78%; iv. PPTs, acetone, Δ, 77%; v. LiAlH$_4$, THF, 0 °C, 90%; vi. DHP, p-TsOH·H_2O, CH_2Cl_2, 92%; vii. MeLi, ClCO$_2$Me, THF, -20 °C, 94%; viii. p-TsOH·H_2O, MeOH, 89%; ix. HBr, Et$_2$0, 0 °C, **104** (34%), **105** (52%); x. CBr$_4$, P(Ph)$_3$, CH_2Cl_2, **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 tetrahydropyranyl 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 δ 1.09 and at δ 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-tetrahydropyranyloxy)-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.[40] 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 δ 3.07 due to deshielding by the *cis* ester group. The allylic protons in **105** at δ 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**.

Entry	Cyclization Substrate	*E:Z* Ratio (**93:94**)[a]	Isolated Yield (%)
1	**106**	89:11	NA
2	**107**	34:66	NA

[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

107 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.[63] 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)
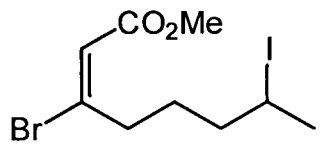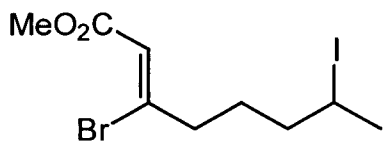
The iodides **108** and **109** were prepared by adding iodine to solutions of each of the alcoholic substrates **104** and **105** with triphenylphosphine and imidazole, as shown below.[64]
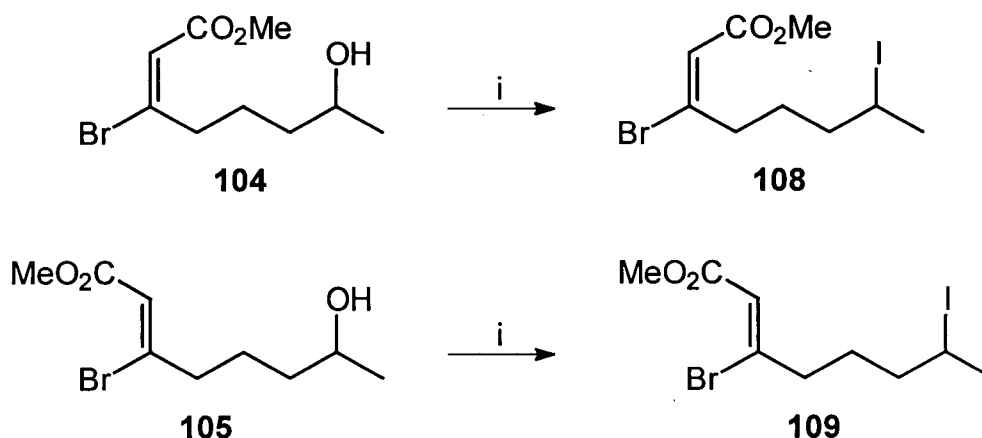
Scheme VII. i. I$_2$, P(Ph)$_3$, imidazole, Et$_2$O, MeCN, **108** (82%), **109** (84%).

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**.

Entry	Cyclization Substrate	$E:Z$ Ratio (**93:94**)[a]	Isolated Yield (%)
1	**108**	96:4	76
2	**109**	7:93	76

[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)
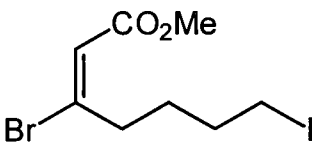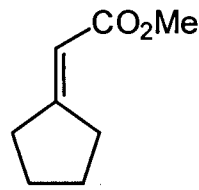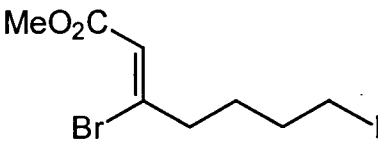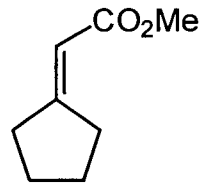
For completeness, the primary iodide analogues of **90** and **91** were prepared as outlined in Scheme VIII. Each of the iodides **110** and **111** was prepared from the alcohols **88** and **89** as shown below.[64]

Scheme VIII. i. I_2, P(Ph)$_3$, imidazole, Et$_2$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**.

Entry	Cyclization Substrate	Product	Isolated Yield (%)
1	**110**	**92**	75
2	**111**	**92**	68

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)
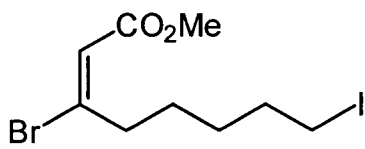
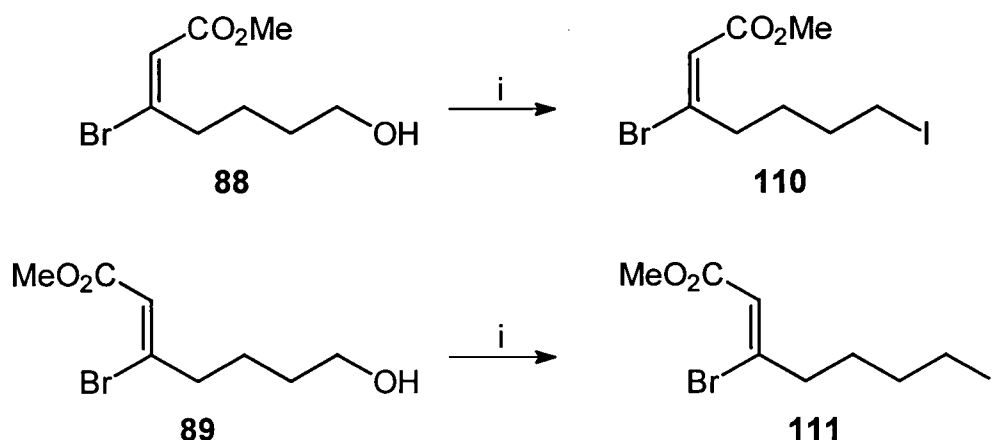Methyl (*E*)- and (*Z*)-3-bromo-8-iodo-2-octenoate (**120**) and (**121**) were prepared as outlined in Scheme IX. The synthesis started with commercially available 1,5-pentandiol (**112**) which was converted into 5-bromo-1-pentanol (**113**).[65] The hydroxyl group was protected and the bromide of **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.[64]
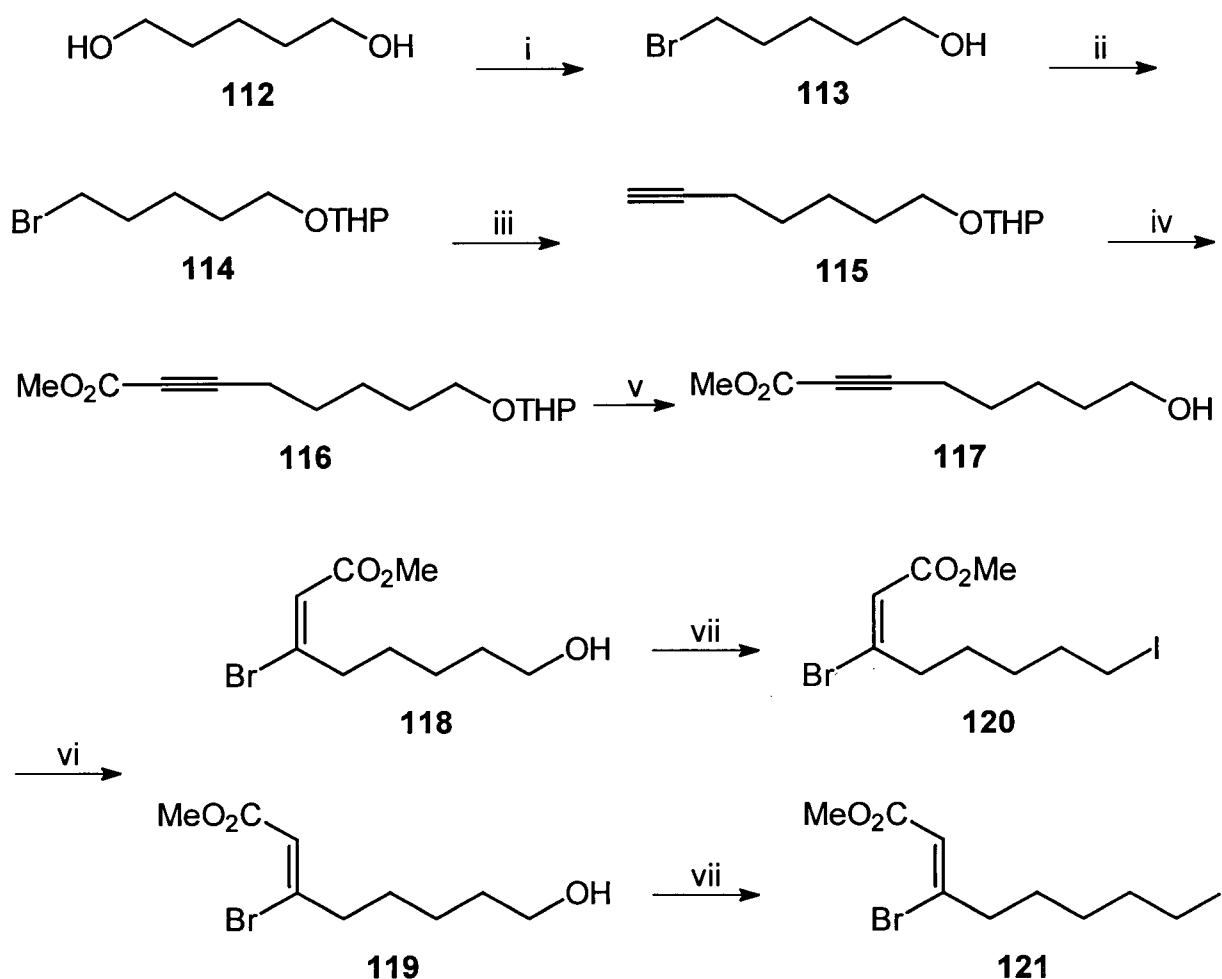
Scheme IX. i. HBr, PhH, Δ, 73%; ii. DHP, *p*-TsOH·H$_2$O, CH$_2$Cl$_2$, 86%; iii. LiCCH·EDA, DMSO, 66%; iv. MeLi, ClCO$_2$Me, THF, -20 °C, 92%; v. *p*-TsOH·H$_2$O, MeOH, 94%; vi. HBr, Et$_2$0, 0 °C, **118** (39%), **119** (47%); vii. I$_2$, P(Ph)$_3$, imidazole, Et$_2$O, MeCN, **120** (75%), **121** (85%).

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 δ 2.17 and δ 2.80, assigned the allylic methylene hydrogens. The lower field signal at δ 2.80 is due to deshielding by the *cis* ester group. The remaining six ring hydrogens are in the methylene envelope at δ 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**.

Entry	Cyclization Substrate	Product	Isolated Yield (%)
1	**120**	**122**	70
2	**121**	**122**	60

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]

123

124
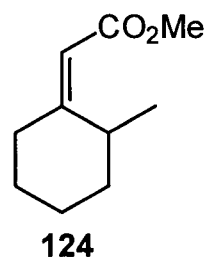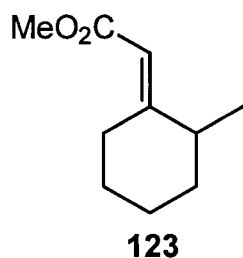
2.2.6 Synthesis and Photochemical Cyclization of Methyl (E)- and (Z)-3-Bromo-8-iodo-2-nonenoate (134) and (135)
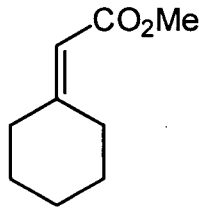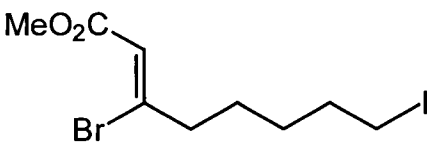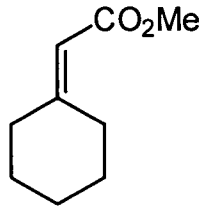
Methyl (E)- and (Z)-3-bromo-8-iodo-2-nonenoate (**134**) and (**135**) were synthesized as outlined in Scheme X. The synthesis started with the conversion of 5-hexynol (**125**) to 6-bromo-1-hexene (**126**). Oxymercuration of the double bond followed by reductive cleavage of the oxymercurial afforded 6-bromo-2-hexanol (**127**).[66]
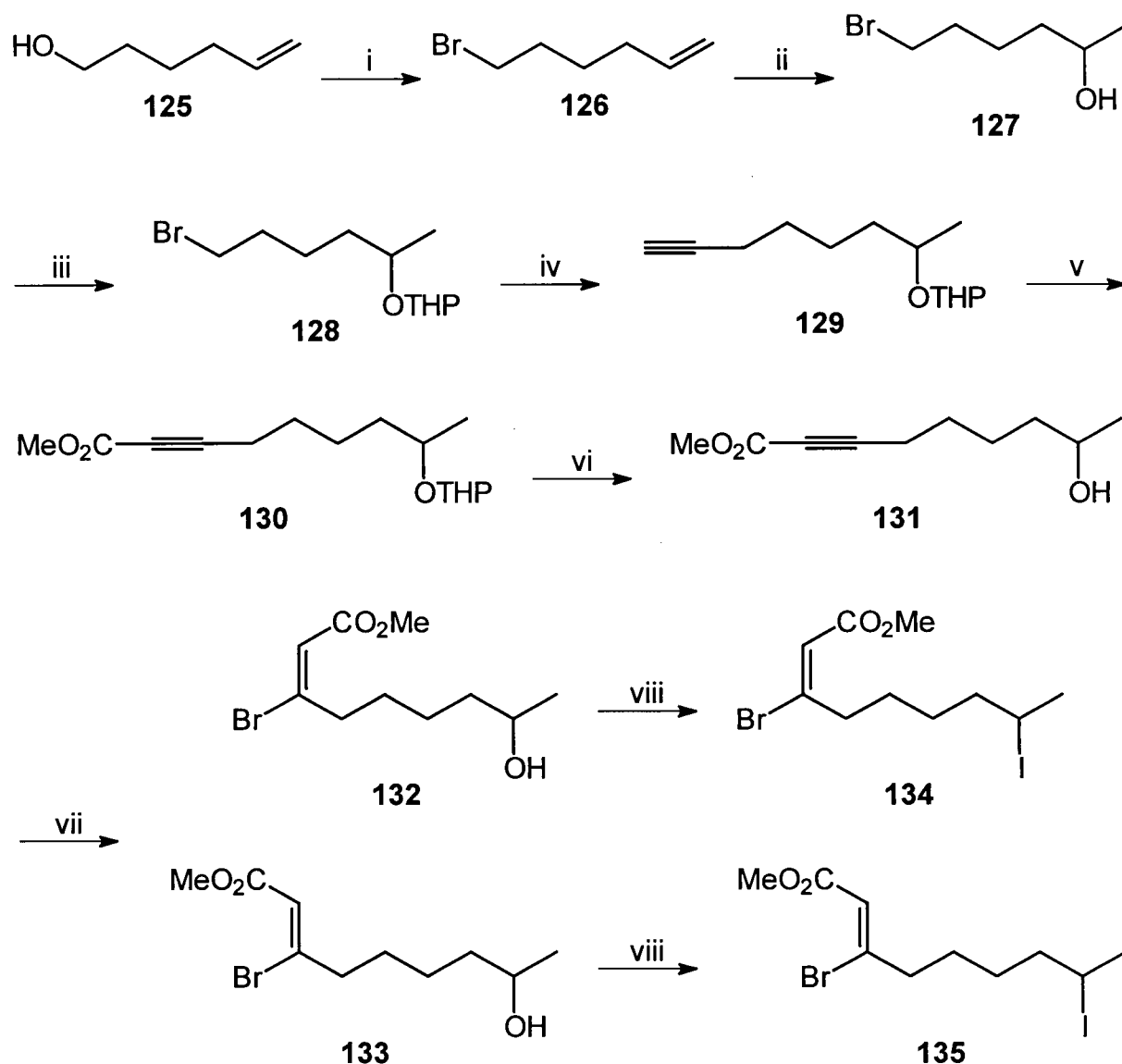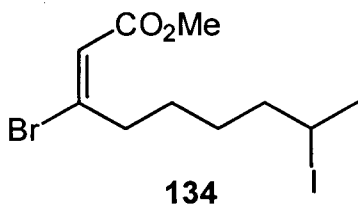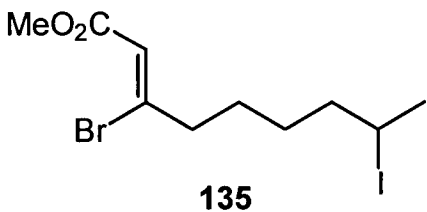
Scheme X.   i. Br_2, $P(Ph)_3$, CH_2Cl_2, 0 °C; ii. $Hg(OAc)_2$, NaOH, $NaBH_4$, THF, H_2O; iii. DHP, p-TsOH·H_2O, CH_2Cl_2, (46% for 3 steps); iv. LiCCH·EDA, DMSO, 74%; v. MeLi, $ClCO_2Me$, THF, -20 °C, 95%; vi. p-TsOH·H_2O, MeOH, 98%; vii. HBr, Et_2O, 0 °C, **132** (32%), **133** (53%); viii. I_2, $P(Ph)_3$, imidazole, Et_2O, 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-nonenoate (**132**)

and (133), which were separated by chromatography.[40] 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.[64]

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.
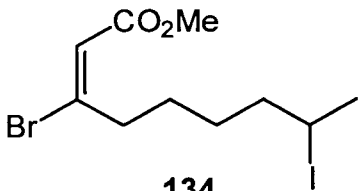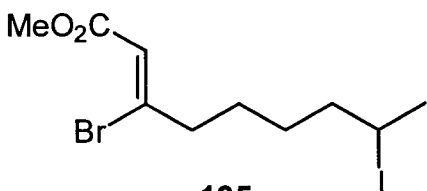
Entry	Cyclization Substrate	E:Z Ratio (123:124)[a]	Isolated Yield (%)
1	134	99:1	90
2	135	75:25	84

[a] 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.

Substrate	123:124 at Irradiation Time[a]					
	1 min	5 min[b]	30 min	1 hour	2 hour	4 hour
134	100:0	100:0	100:0	98:2	97:3	96:4
135	76:24	76:24	75:25	75:25	75:25	75:25

[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.[67] 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.
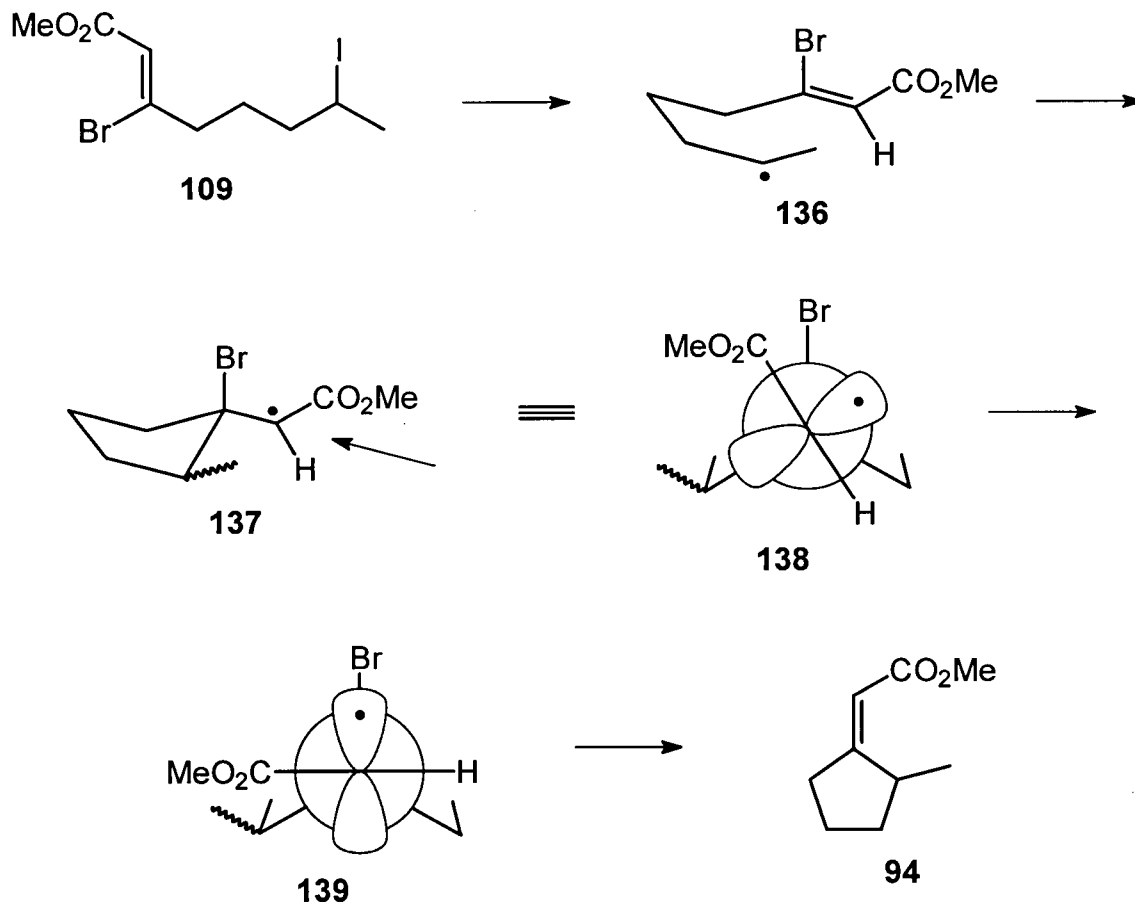
Figure 13. Rationale for retention of stereochemistry in addition-elimination mechanism to rationalize the retention of stereochemistry in the radical cyclization of **109**.

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-Iodo-3-tri(*n*-butyl)stannyl-2-octenoate (144) and (148) and Methyl (E)- and (Z)-8-Iodo-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.,[68] 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.[69] The tetrahydropyranyl ethers were hydrolyzed to afford the alcohols **142** and **143**. The hydroxyl group was converted to the iodide of **144** and **145**.[64]
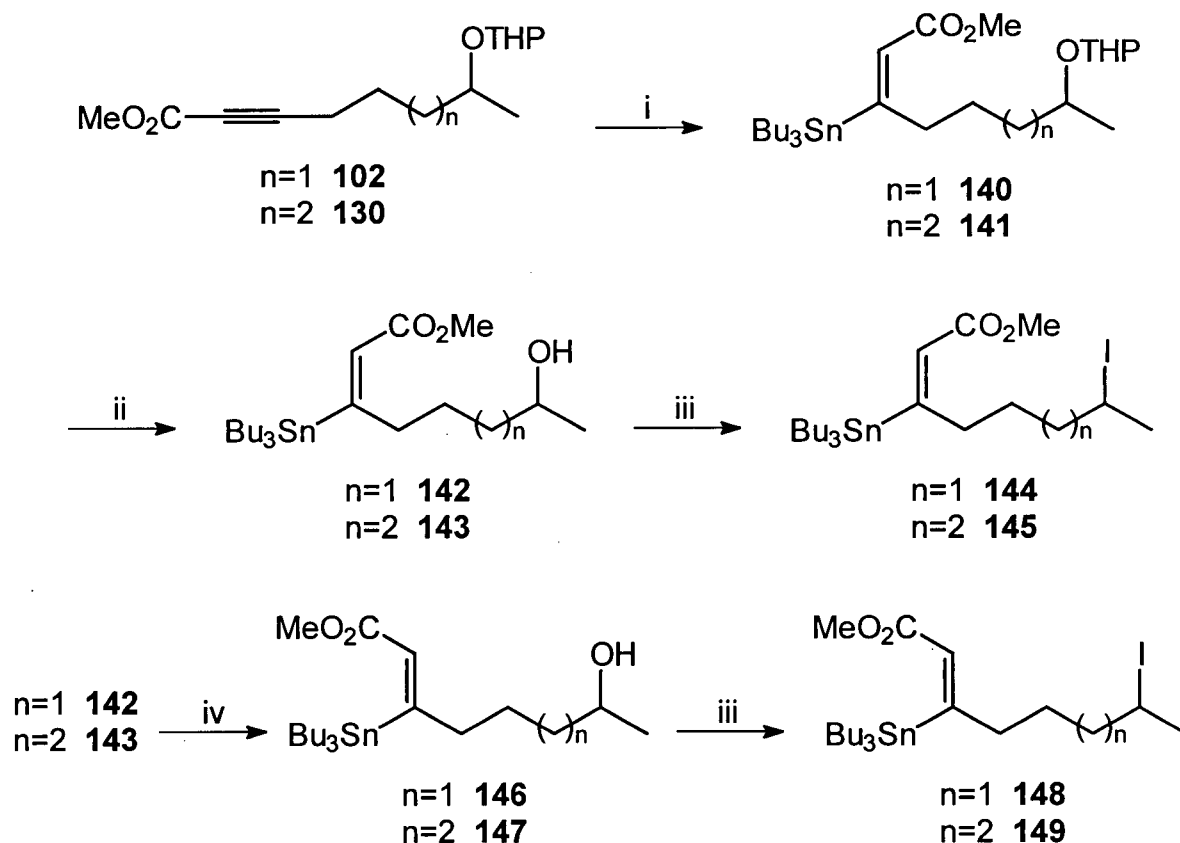
Scheme XI. i. $(Bu_3Sn)_2$, BuLi, $CuBr\cdot SMe_2$, THF, -78 °C, **140** (90%), **141** (93%); ii. *p*-TsOH·2H$_2$O, MeOH, **142** (94%), **143** (94%); iii. I$_2$, P(Ph)$_3$, imidazole, Et$_2$O, MeCN, 0 °C, **144** (86%), **145** (89%), **148** (91%), **149** (75%); iv. Bu$_3$SnH, AIBN, PhH, Δ, **146** (92%), **147** (93%).
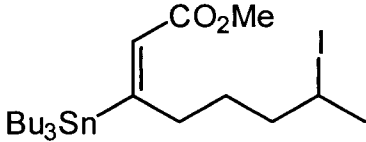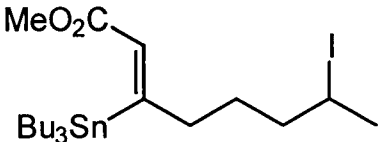
Synthesis of the *Z*-vinyl stannanes was accomplished by treating each of the alcohols **142** and **143** with tri(*n*-butyl)tin hydride and AIBN.[44] This resulted in

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.[69] The hydroxyl group was converted to the iodide of **148** and **149**.[64]

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**.

Entry	Cyclization Substrate	*E:Z* Ratio (**93:94**)[a]	Isolated Yield (%)
1	**144**	89:11	85
2	**148**	54:46	91

[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**.

Entry	Chain Transfer Reagent	Initiator	Temp (°C)	Solvent	E:Z Ratio[a] (93:94)	Yield (%)
1	(Bu$_3$Sn)$_2$	hυ	25	PhH	89:11	85[b]
2[c]	(TMS)$_3$SiH	Et$_3$B/air	25	PhH	88:12	91[a]
3[c]	(TMS)$_3$SiH	Et$_3$B/air	-78	THF	88:12	90[a]

[a] Determined by GC analysis.
[b] Isolated yield.
[c] 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**.

Entry	Chain Transfer Reagent	Initiator	Temp (°C)	Solvent	E:Z Ratio[a] (93:94)	Yield (%)
1	(Bu$_3$Sn)$_2$	hυ	25	PhH	54:46	91[b]
2[c]	(TMS)$_3$SiH	Et$_3$B/air	25	PhH	42:58	86[a]
3[c]	(TMS)$_3$SiH	Et$_3$B/air	-78	THF	46:54	83[a]
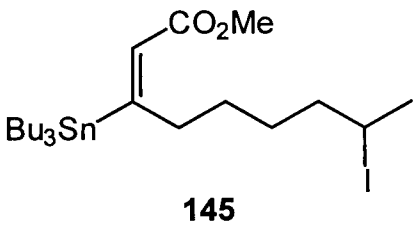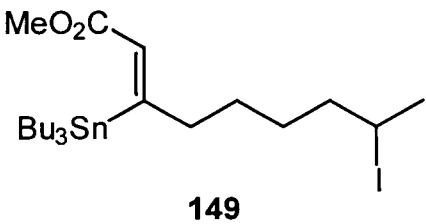
[a] Determined by GC analysis.
[b] Isolated yield.
[c] From reference 44.

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**.

Entry	Cyclization Substrate	*E:Z* Ratio (**123:124**)	Isolated Yield (%)
1	**145**	97:3	62
2	**149**	72:28	66

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)ditin.

Table XVIII. Comparison of Cyclizations of Compounds **145**.

Entry	Chain Transfer Reagent	Initiator	Temp (°C)	Solvent	E:Z Ratio[a] (123:124)	Yield (%)
1	(Bu₃Sn)₂	hʋ	25	PhH	97:3	62[b]
2[c]	(TMS)₃SiH	Et₃B/air	25	PhH	100:0	82[a]
3[c]	Bu₃SnH	Et₃B/air	25	PhH	100:0	70[a]

[a] Determined by GC analysis.
[b] Isolated yield.
[c] 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**.

Entry	Chain Transfer Reagent	Initiator	Temp (°C)	Solvent	E:Z Ratio[a] (123:124)	Yield (%)
1	(Bu₃Sn)₂	hʋ	25	PhH	72:28	66[b]
2[c]	(TMS)₃SiH	Et₃B/air	25	PhH	77:23	81[a]
3[c]	Bu₃SnH	Et₃B/air	25	PhH	75:25	73[a]

[a] Determined by GC analysis.
[b] Isolated yield.
[c] 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.
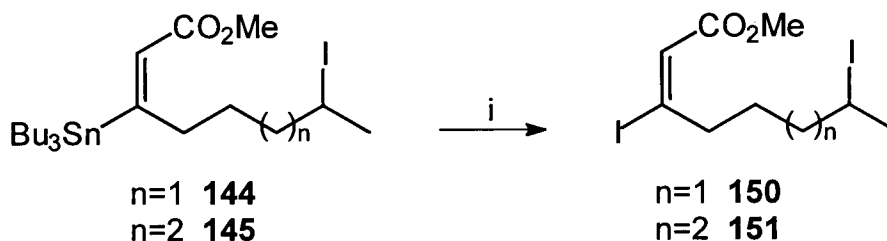
Scheme XII. i. I$_2$, CH$_2$Cl$_2$, **150** (93%), **151** (88%).
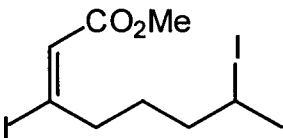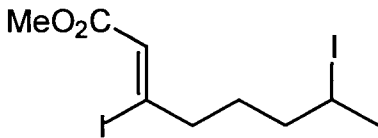
The synthesis of the Z-vinyl iodides is outlined in Scheme XIII. Synthesis of the acetylenic esters **103** and **131** was outlined in Schemes VI and X. The hydroxyl group was converted to the iodide by adding iodine to solutions of each of the substrates **103** and **131** with triphenylphosphine and imidazole.[64] 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**.[70]
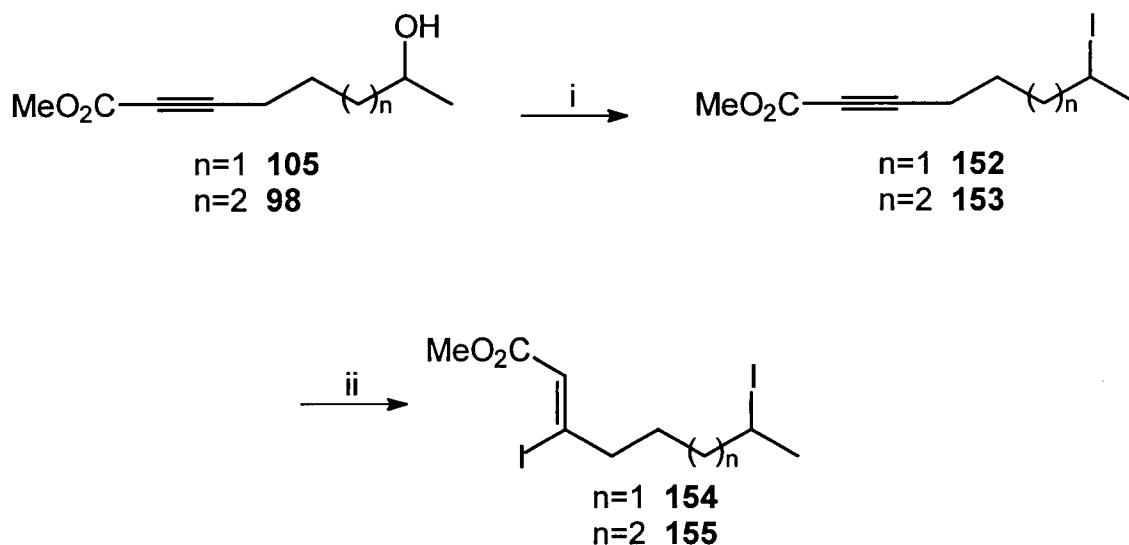
Scheme XIII. i. I$_2$, P(Ph)$_3$, imidazole, Et$_2$O, MeCN, 0 °C, **152** (95%), **153** (96%); ii. NaI, AcOH, Δ, **154** (72%), **155** (63%).

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).
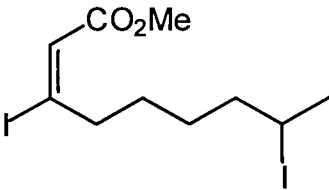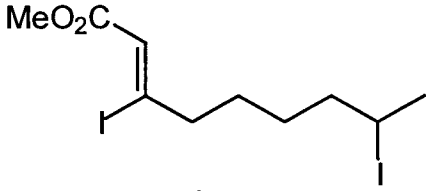
Table XX. Photochemical Cyclization of Compounds **150** and **154**.

Entry	Cyclization Substrate	$E{:}Z$ Ratio (**93:94**)[a]	Isolated Yield (%)
1	**150**	92:8	82
2	**154**	15:85	80

[a] Isomer ratios determined by GC analysis.

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**.

Entry	Cyclization Substrate	E:Z Ratio (**123**:**124**)[a]	Isolated Yield (%)
1	**151**	66:34	82
2	**155**	8:92	85

[a] 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
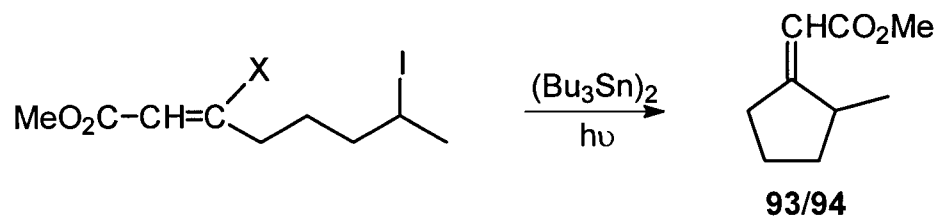
Entry	Substrate	Vinyl Substituent (X)	Substrate Stereochemistry	Product Ratio 93:94
1	**108**	Br	E	96:4
2	**150**	I	E	92:8
3	**144**	Bu$_3$Sn	E	89:11
4	**109**	Br	Z	7:93
5	**154**	I	Z	15:85
6	**148**	Bu$_3$Sn	Z	54:46

Table XXIII. Photochemical Cyclization of Cyclohexyl Precursors

| Entry	Substrate	Vinyl Substituent (X)	Substrate Stereochemistry	Product Ratio 123:124
1	**125**	Br	*E*	99:1
2	**145**	Bu$_3$Sn	*E*	97:3
3	**151**	I	*E*	66:34
4	**155**	I	*Z*	8:92
5	**149**	Bu$_3$Sn	*Z*	72:28
6	**126**	Br	*Z*	75:25

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 acetoxymethylene 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.
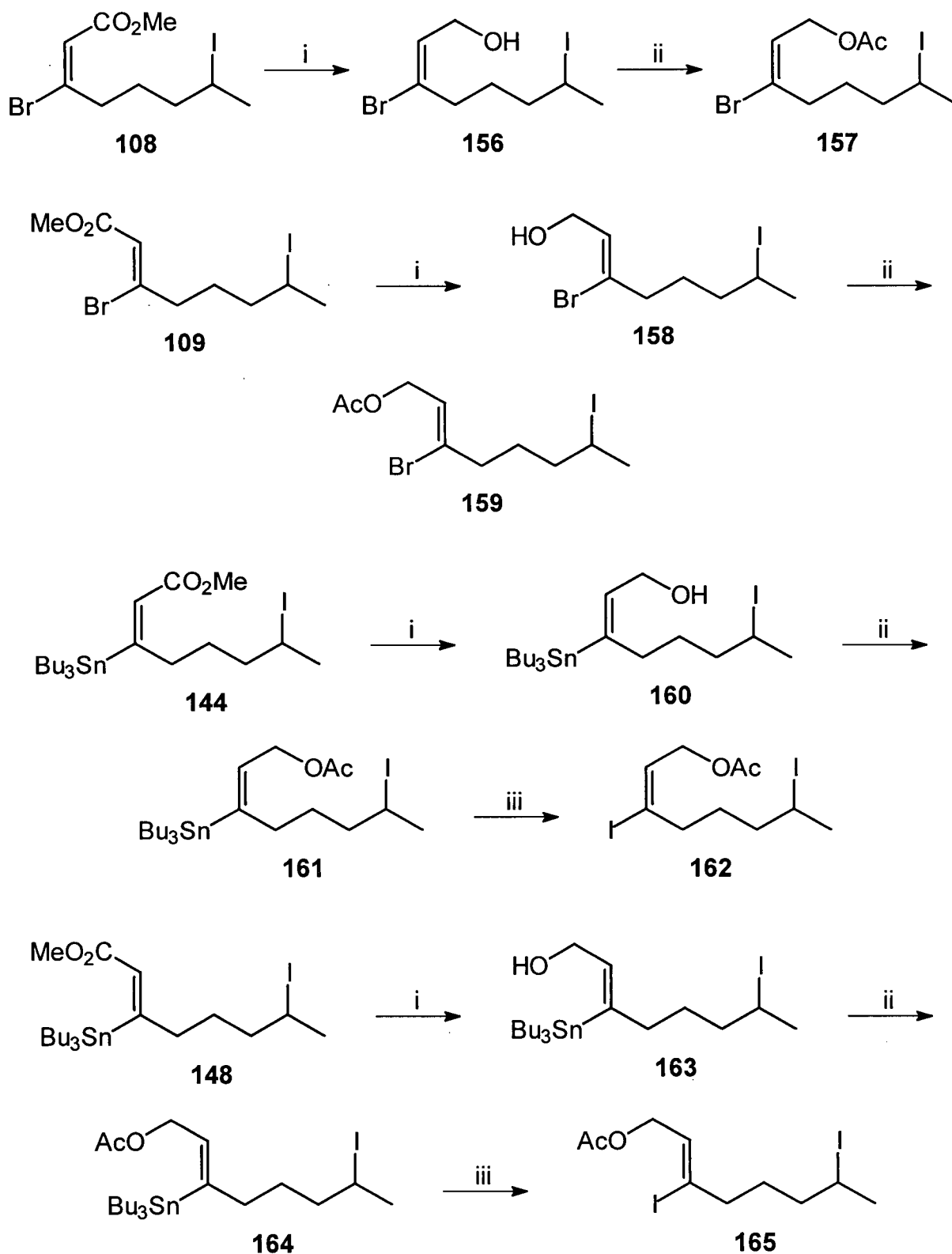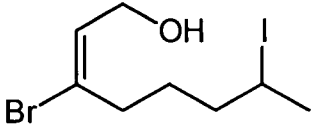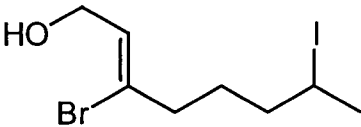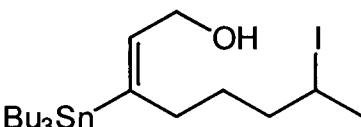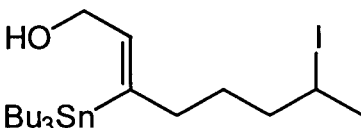
Scheme XIV. i. DIBAL, CH_2Cl_2, -78 °C, 84-97%; ii. Ac_2O, py, CH_2Cl_2, 86-97% iii. I_2, CH_2Cl_2, 86-96%.
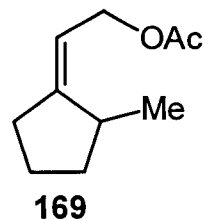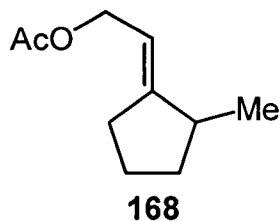
166   **167**
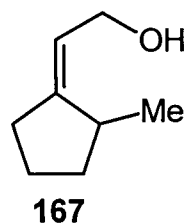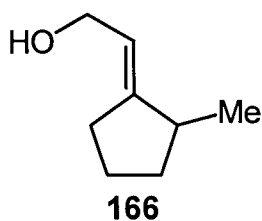
The results of the photochemical cyclizations of the allylic alcohols to the exocyclic alkenes **166** and **167** are presented in Table XXIV. Included in the Table are the results of the cyclization of the analogous ester substrates for comparison. The cyclic products were purified by chromatography but could not be separated. Isomer ratios were determined by integration of the methyl proton doublets in the ^{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 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.

Entry	Cyclization Substrate	$E{:}Z$ (**166**:**167**)[a] Isolated Yield	Analogous Ester $E{:}Z$ (**93**:**94**)[a] Isolated Yield
1	**156** (Br, OH)	92:8 69%	96:4 76%
2	**158** (HO, Br)	50:50 40%	7:93 76%
3	**160** (Bu₃Sn, OH)	94:6 94%	89:11 85%
4	**163** (HO, Bu₃Sn)	33:67 64%	54:46 91%
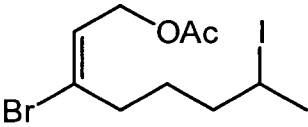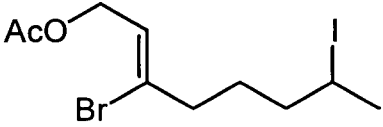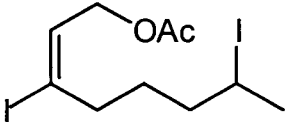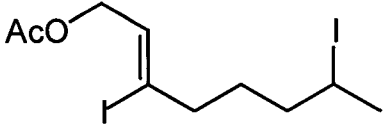
[a] Isomer ratios determined by NMR analysis.

168 (AcO ... Me)   **169** (OAc ... Me)

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.

Entry	Cyclization Substrate	E:Z (**168**:**169**)[a] Isolated Yield	Analogous Ester E:Z (**93**:**94**)[a] Isolated Yield
1	**157**	91:9 77%	96:4 76%
2	**159**	20:80 67%	7:93 76%
3	**162**	92:8 85%	92:8 82%
4	**165**	13:87 69%	15:85 80%

[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 $CaCl_2$/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.[71] Unless otherwise noted, reagents were purchased from the Aldrich Chemical Co. Alkyllithium reagents were standardized by titration against diphenylacetic acid in THF at 0 °C.[72] Tri(n-butyl)tin hydride was either purchased from the Aldrich Chemical Co. or was prepared following the procedure of Kuivila and Beumel.[73] 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.[74]

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[75] 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 R_f 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, PF_{254} with gypsum binder, supplied by EM Science. In most cases, a solvent system was chosen such that the desired product had an R_f 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 (^{1}H 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_{Sn-H}) are given as an average of the coupling constants for the [117]Sn and the [119]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 (CI) 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]Sn, [118]Sn and [116]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)

$$\text{MeO}_2\text{C}-\!\!\!\equiv\!\!\!-\!\!\!\sim\!\!\!\text{O}\!\!-\!\!\overset{|}{\underset{\text{SPh}}{\text{CH}}}\!\!-\!\text{CO}_2\text{Me}$$
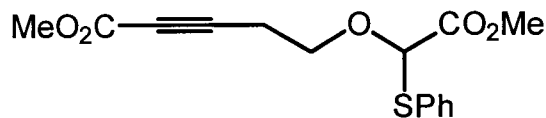
A solution of methyl 5-hydroxy-2-pentynoate (44) (0.51 g, 4.0 mmol), methyl chloro(phenylthio)acetate (48) (0.43 g, 2.0 mmol) and zinc acetate dihydrate (0.53 g, 2.4 mmol) in 10 mL of dry, deoxygenated benzene was refluxed for 6 hours through a Dean Stark apparatus containing anhydrous $CaSO_4$. The 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 ($CDCl_3$): 2942, 2240, 1748, 1714, 1436, 1266, 1075 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) 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);

^{13}C NMR (50 MHz, $CDCl_3$) 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 (EI) m/z (relative intensity): 249 (M^+-CO_2CH_3, 39), 109 (28), 53 (100); (DCI(+), ammonia) m/z (relative intensity): 326 (M^++NH_4, 24), 88 (100);

HRMS (EI) m/z calcd for $C_{15}H_{16}O_5S$: 308.0718, found: 308.0712;

Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.43; H, 5.23. Found: C, 58.42; H, 5.38.

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

$$\text{MeO}_2\text{C}-\!\!\!\equiv\!\!\!-\!\!\!\sim\!\!\!\text{O}\!\!-\!\!\overset{\text{SPh}}{\underset{}{\text{CH}}}\!\!-\!\text{CO}_2\text{Me}$$
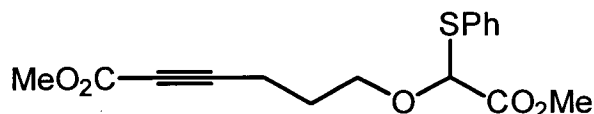
Methyl 6-hydroxy-2-hexynoate (45) (0.57 g, 4.0 mmol) was converted to 37 following the procedure outlined in Section 3.2. The crude yellow oil was purified by

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};

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) 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 (EI) *m/z* (relative intensity): 322 (M$^+$, 26), 263 (82), 84 (100);

(DCI(+), ammonia) *m/z* (relative intensity): 340 (M$^+$+NH$_4$, 100), 323 (M$^+$+1, 33), 88(100);

HRMS (EI) *m/z* calcd for C$_{16}$H$_{18}$O$_5$S: 322.0875, found: 322.0871;

Anal. Calcd for C$_{16}$H$_{18}$O$_5$S: C, 59.61; H, 5.63. Found: C, 59.86; H, 5.69.

3.4   4-(2-Tetrahydropyranyloxy)-1-butyne (40)
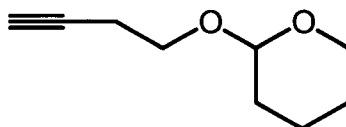
Dihydropyran (7.80 mL, 85.5 mmol) was added dropwise to a solution of 3-butyn-1-ol (**38**) (5.00 g, 71.3 mmol) and *p*-toluenesulfonic acid monohydrate (0.68 g, 3.6 mmol) in 350 mL of dry methylene chloride.   The reaction mixture was stirred overnight and then worked up by washing with saturated NaHCO$_3$ 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 (CDCl$_3$): 3308, 2945, 2876, 2242, 1201, 1128, 1070, 1032 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) 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 C$_9$H$_{13}$O$_2$ (M$^+$-1): 153.0916, found 153.0912;

Anal. Calcd for C$_9$H$_{14}$O$_2$: C, 70.08; H, 9.16. Found: C, 69.89; H, 9.14.

3.5 5-(2-Tetrahydropyranyloxy)-1-pentyne (41)
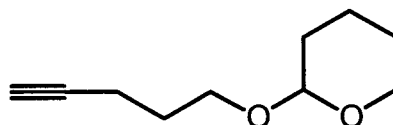
4-Pentyn-1-ol (39) (4.00 g, 47.6 mmol) was converted to 41 following the procedure outlined in Section 3.4. The crude brown oil was purified by flash chromatography, eluting with 7% ethyl acetate / pet. ether to afford 7.14 g (89%) of 41 as a colourless oil.

IR (CDCl$_3$): 3308, 2945, 2873, 2242, 1136, 1068, 1032 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) 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 C$_{10}$H$_{15}$O$_2$ (M$^+$-1): 167.1072, found: 167.1072;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$: C, 71.38; H, 9.59. Found: C, 71.28; H, 9.61.

3.6 Methyl 5-(2-tetrahydropyranyloxy)-2-pentynoate (42)
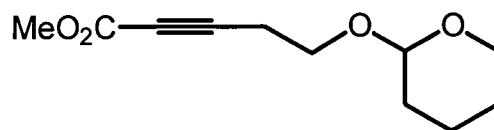
A solution of 4-(2-tetrahydropyranyloxy)-1-butyne (**40**) (4.05 g, 26.3 mmol) in 200 mL of dry THF was cooled to -78 °C and methyllithium (22.5 mL of 1.4 M in hexanes, 31.5 mmol) was added dropwise. The resulting solution was stirred at -78 °C for 10 min., methyl chloroformate (2.43 mL, 31.5 mmol) was 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 $KHCO_3$ 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 ($CDCl_3$): 2949, 2878, 2238, 1711, 1436, 1265, 1129, 1074, 1033 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) 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);

^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.26, 20.28, 25.36, 30.44, 52.58, 62.20, 64.37, 73.51, 86.65, 98.82, 154.04;

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

HRMS (EI) *m/z* calcd for $C_{11}H_{15}O_4$ (M$^+$-1): 211.0970, found: 211.0974;

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.10; H, 7.69.

3.7 Methyl 6-(2-tetrahydropyranyloxy)-2-hexynoate (43)
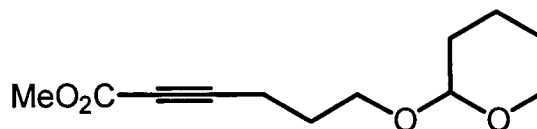
5-(2-Tetrahydropyranyloxy)-1-pentyne (**41**) (6.37 g, 37.9 mmol) was converted to **43** following the procedure outlined in Section 3.7. The crude yellow oil was purified by

flash chromatography, eluting with 12% ethyl acetate / pet. ether to afford 6.75 g (79%) of **43** as a colourless oil.

IR (CDCl$_3$): 2948, 2874, 2237, 1710, 1436, 1265, 1033 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) 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 (EI) *m/z* (relative intensity): 225 (M$^+$-1, 0.3), 167 (6),111 (25), 85 (100), 41 (42);

HRMS (EI) *m/z* calcd for C$_{12}$H$_{17}$O$_4$ (M$^+$-1): 225.1127, found: 225.1135;

Anal. Calcd for C$_{12}$H$_{18}$O$_4$: C, 63.68; H, 8.02. Found: C, 63.59; H, 7.89.

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

$$\text{MeO}_2\text{C} \mathrel{\equiv\!\equiv\!\equiv} \diagup\!\diagdown\!\diagup \text{OH}$$
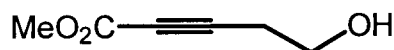
Methyl 5-(2-tetrahydropyranyloxy)-2-pentynoate (**42**) (3.54 g, 16.7 mmol) was dissolved in 250 mL of methanol and *p*-toluenesulfonic acid monohydrate (0.16 g, 0.84 mmol) was added. The reaction mixture was stirred for 2 hours and then concentrated by rotary evaporation. The crude material was dissolved in 500 mL of diethyl ether, washed with saturated KHCO$_3$ 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 (CDCl$_3$): 3615, 2955, 2239, 1712, 1436, 1266, 1077, 1048 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 22.92, 52.70, 59.91, 73.94, 86.86, 154.18;

LRMS (EI) *m/z* (relative intensity): 128 (M$^+$, 3), 110 (22), 98 (60), 79 (100), 66 (38), 44 (36);

HRMS (EI) *m/z* calcd for $C_6H_8O_3$: 128.0473, found: 128.0474;

Anal. Calcd for $C_6H_8O_3$: C, 56.23; H, 6.30. Found: C, 56.00; H, 6.18.

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

$$MeO_2C \text{—}\!\!\equiv\!\!\text{—}\diagdown\!\diagup\diagdown\text{OH}$$
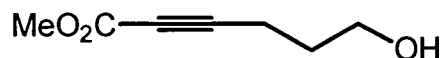
Methyl 6-(2-tetrahydropyranyloxy)-2-hexynoate (**43**) (6.75 g, 29.8 mmol) was converted to **45** following the procedure outlined in Section 3.9. The crude colourless oil was purified by flash chromatography, eluting with 30% diethyl ether / pet. ether to afford 3.56 g (84%) of **45** as a colourless oil.

IR ($CDCl_3$): 3624, 2952, 2236, 1710, 1436, 1265, 1063 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) 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),

^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.09, 30.15, 52.59, 60.77, 72.95, 89.29, 154.27;

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

HRMS (EI) *m/z* calcd for $C_7H_{10}O_3$: 142.0630, found: 142.0631;

Anal. Calcd for $C_7H_{10}O_3$: C, 59.13; H, 7.09. Found: C, 58.92; H, 7.13.

3.10 Methyl (phenylthio)acetate (47)

$$PhS\diagup\diagdown CO_2Me$$
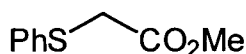
Hydrogen chloride was bubbled for 30 seconds through a room temperature solution of (phenylthio)acetic acid (5.04 g, 30.0 mmol) in 125 mL of dry methanol. The reaction vessel was fitted with a drying tube and stirred overnight at room temperature. The methanol was evaporated under reduced pressure and the residue was diluted to 200 mL with diethyl ether. The ether solution was washed with saturated $KHCO_3$ 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};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 3.62 (s, 2H), 3.72 (s, 3H), 7.32 (m, 3H), 7.48 (m, 2H);

LRMS (EI) *m/z* (relative intensity): 182 (M$^+$, 48), 123 (100).

3.11   Methyl chloro(phenylthio)acetate (48)
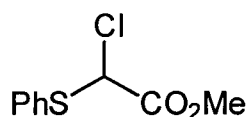
A solution of methyl (phenylthio)acetate (**47**) (5.66 g, 31.0 mmol) and N-chlorosuccinimide (4.56 g, 34.1 mmol) in 150 mL of dry CCl$_4$ was stirred at 0 °C and allowed to warm to room temperature overnight.   The mixture was filtered and concentrated under reduced pressure.   The crude material was 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};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 3.80 (s, 3H), 5.52 (s, 1H), 7.32 (m, 3H), 7.48 (m, 2H);

LRMS (EI) *m/z* (relative intensity): 218 (^{37}Cl, M$^+$, 24), 216 (^{35}Cl, M$^+$, 45), 159 (39), 157 (100), 121 (99), 109 (63);

HRMS (EI) *m/z* calcd for C$_9$H$_9$O$_2$^{37}ClS: 217.9982, found: 217.9974

   m/z calcd for C$_9$H$_9$O$_2$^{35}ClS: 216.0011, found: 216.0011.

3.12   Methyl (*E*)-(2-carbomethoxy-3-oxacyclopentylidene)acetate (49)
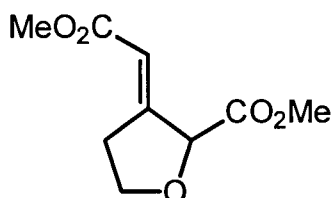
A solution of dimethyl 6-oxa-7-(phenylthio)-2-octynedioate (**36**) (34.3 mg, 0.111 mmol), tri(*n*-butyl)tin hydride (45 μL, 0.22 mmol), and AIBN (1.8 mg, 0.011 mmol) in 1.1 mL of dry benzene was heated in an 82 °C oil bath.   After 1 hour the reaction mixture was cooled to room temperature and then 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$_3$) δ: 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 (EI) *m/z* (relative intensity): 200 (M$^+$, 3), 168 (6), 141 (100), 109 (37), 84 (89), 53 (38);

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

Anal. Calcd for C$_9$H$_{12}$O$_5$: C, 53.98; H, 6.04. Found: C, 54.34; H, 6.16.

3.13   Methyl (Z)-(2-carbomethoxy-3-oxacyclopentylidene)acetate (50)
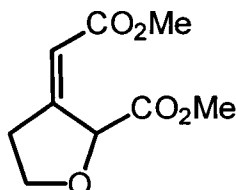
A solution of dimethyl 6-oxa-7-(phenylthio)-2-octynedioate (**36**) (20.4 mg, 0.066 mmol) and tris(trimethylsilyl)silane (41 μL, 0.13 mmol) in 0.3 mL of dry benzene was heated in an 82 °C oil bath. A 0.5 mL portion of air was bubbled through the solution followed by addition of triethylborane (17 μL 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$_3$) δ: 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$_3$) δ: 34.02, 51.53, 52.36, 67.06, 79.97, 114.50, 158.53, 166.10, 169.41;

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

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

Anal. Calcd for C$_9$H$_{12}$O$_5$: C, 53.98; H, 6.04. Found: C, 54.25; H, 6.19.

3.14 Methyl (2-carbomethoxy-3-oxa-1-cyclopentenyl)acetate (51)
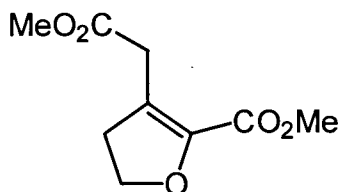
See to Section 3.12.

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

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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 (EI) *m/z* (relative intensity): 200 (M$^+$, 32), 168 (53), 141 (74), 140 (50), 81 (100);

HRMS (EI) *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)
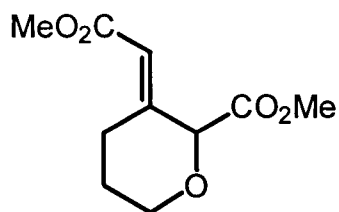
See Section 3.16.

IR (CDCl$_3$): 2946, 1747, 1723, 1659, 1601, 1438, 1246, 1202 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 25.05, 26.45, 51.30, 52.43, 65.36, 79.09, 117.50, 152.67,

170.50, 197.23;

LRMS (EI) *m/z* (relative intensity): 214 (M$^+$, 4), 182 (4), 155 (100), 123 (33), 95 (25),

84 (22), 67 (25);

HRMS (EI) *m/z* calcd for C$_{10}$H$_{14}$O$_5$: 214.0841, found: 214.0835;

Anal. Calcd for C$_{10}$H$_{14}$O$_5$: C, 56.05; H, 6.59. Found: C, 56.36; H, 6.61.

3.16 Methyl (Z)-(2-carbomethoxy-3-oxacyclohexylidene)acetate (53)
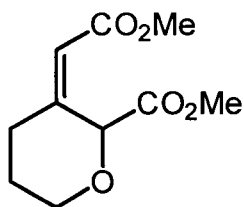
A solution of dimethyl 7-oxa-8-(phenylthio)-2-nonynedioate (37) (30.8 mg, 0.096 mmol) and tris(trimethylsilyl)silane (59 μL, 0.19 mmol) in 0.5 mL of benzene was heated in an 82 °C oil bath. A 0.5 mL portion of air was bubbled through the solution followed by addition of 24 μL triethylborane. A second 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 CaSO$_4$.

IR (CDCl$_3$): 2948, 1740, 1716, 1659, 1602, 1437, 1235, 1206, 1152 cm^{-1};

¹H NMR (400 MHz, CDCl₃) δ: 1.75-1.90 (m, 2H), 2.40 (m, 2H), 3.71 (s, 3H), 3.75 (s, 3H), 3.80-3.90 (m, 2H), 5.82 (s, 1H), 6.29 (s, 1H);

¹³C NMR (50 MHz, CDCl₃) δ: 26.96, 31.15, 51.36, 52.46, 63.90, 72.52, 117.63, 152.72, 170.19, 197.50;

LRMS (EI) *m/z* (relative intensity): 214 (M⁺, 1.0), 182 (11), 155 (100), 123 (30), 95 (30), 84 (35), 67 (29);

HRMS (EI) *m/z* calcd for $C_{10}H_{14}O_5$: 214.0841, found: 214.0838;

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.05; H, 6.59. Found: C, 56.14; H, 6.78.

3.17   Dimethyl 7-oxa-2-nonynedioate (54)

$$MeO_2C \!\!=\!\!\!\!\diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!O\!\!\!\diagup\!\!\!\diagup CO_2Me$$
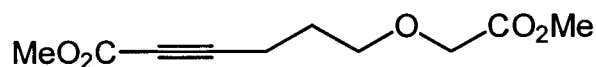
Compound **54** is a side product that was produced in the reaction described in Section 3.16. Purification by radial chromatography, eluting with 30% diethyl ether / pet. ether afforded 1.4 mg (7%) of **54** as a colourless film.

IR (CDCl₃): 2956, 2855, 2237, 1748, 1711, 1437, 1264 cm⁻¹;

¹H NMR (200 MHz, CDCl₃) δ: 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)

$$\equiv\!\!\!\diagup\!\!\!\diagdown\!\!\!O\!\!\!\diagup\!\!\!\diagup CO_2Me$$
$$\underset{SPh}{|}$$
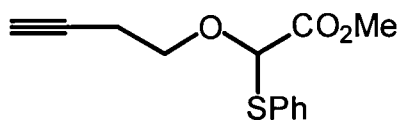
3-Butyn-1-ol (**38**) (2.42 g, 34.5 mmol) was converted to **55** following the procedure outlined in Section 3.2. The procedure was amended such that 3 equiv. of

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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100);

HRMS (CI(+), isobutane) *m/z* calcd for C$_{13}$H$_{14}$O$_3$S: 250.0663, found: 250.0663;

Anal. Calcd for C$_{13}$H$_{14}$O$_3$S: C, 62.38; H, 5.64. Found: C, 62.19; H, 5.67.

3.19   3-Oxa-2-(phenylthio)-6-heptyn-1-ol (56)
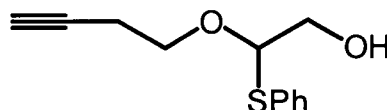
A solution of methyl 3-oxa-2-(phenylthio)-6-heptynoate (**55**) (2.15 g, 8.60 mmol) in 10 mL of dry THF was added to an ice cooled suspension of lithium aluminum hydride (0.69 g, 17 mmol) in 40 mL of dry THF. The ice bath was removed and the reaction was stirred at room temperature for 1 hour. The reaction was then cooled in ice and the reaction was quenched by the slow addition of 20 mL of saturated Na$_2$SO$_4$. The resulting white precipitate was removed by suction filtration and rinsed with ethyl acetate. The organic layer was separated and washed consecutively with NaHCO$_3$, 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 ^{1}H 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};

¹H NMR (400 MHz, CDCl₃) δ: 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⁺+NH₄, 100);

HRMS (CI(+), isobutane) *m/z* calcd for $C_{12}H_{14}O_2S$: 222.0714, found: 222.0714;

Anal. Calcd for $C_{12}H_{14}O_2S$: 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)
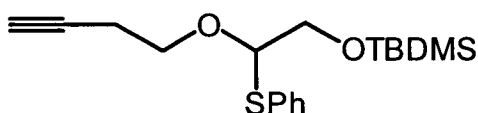
A solution of 3-oxa-2-(phenylthio)-6-heptyn-1-ol (**56**) (1.75 g, 7.88 mmol), *t*-butyldimethylsilyl chloride (1.43 g, 9.46 mmol), and imidazole (1.34 g, 19.2 mmol) in 5 mL of dimethylformamide was stirred at room temperature for 3 hours. The reaction mixture was poured into 100 mL of saturated NH_4Cl 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;

¹H NMR (400 MHz, CDCl₃) δ: 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⁺+NH₄, 100), 284 (39);

HRMS (CI(+), isobutane)

m/z calcd for $C_{18}H_{29}O_2SSi$ (M⁺+1): 337.1657, found: 337.1652;

Anal. Calcd for $C_{18}H_{28}O_2SSi$: C, 64.24; H, 8.39. Found: C, 64.37; H, 8.37.

3.21 Methyl 6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-2-nonynoate (58)
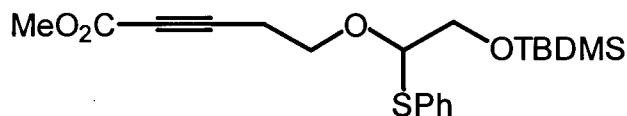
5-Oxa-6-(phenylthio)-7-(t-butyldimethylsilyloxy)-1-heptyne **(57)** (2.65 g, 7.89 mmol) in 40 mL of dry THF was cooled to -78 °C. Methyllithium (11.1 mL of 1.07 M in hexanes, 11.8 mmol) was added to this dropwise and the mixture was stirred at -78 °C for 20 minutes, after which the reaction mixture was 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 $NaHCO_3$ solution and then warmed to room temperature. The reaction mixture was diluted to 200 mL with ethyl acetate and washed with saturated $NaHCO_3$ 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (CI(+), ammonia) m/z (relative intensity): 412 (M$^+$+NH$_4$, 100), 395 (M$^+$+1, 1), 287 (30), 192 (35);

HRMS (CI(+), ammonia/methane)

m/z calcd for $C_{20}H_{34}NO_4SSi$ (M$^+$+NH$_4$): 412.1978, found: 412.1976;

Anal. Calcd for $C_{20}H_{30}O_4SSi$: 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)
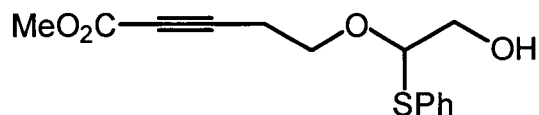
2,4,6-Trimethylpyridinium fluoride (0.12 g, 0.83 mmol) was added to an ice cooled solution of methyl 6-oxa-7-(phenylthio)-8-(t-butyldimethylsilyloxy)-2-nonynoate (58) (0.31 g, 0.79 mmol) in 8 mL of methylene chloride. The reaction vessel was loosely stoppered so as to allow the mixture to slowly concentrate 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$_3$) δ: 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 (EI) m/z (relative intensity): 280 (M$^+$, 2), 249 (20), 171 (73), 139 (100), 109 (45);

HRMS (EI) m/z calcd for $C_{14}H_{16}O_4S$: 280.0769, found: 280.0764;

Anal. Calcd for $C_{14}H_{16}O_4S$: 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)
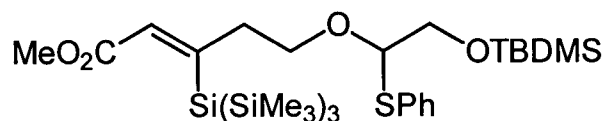
A solution of methyl 6-oxa-7-(phenylthio)-8-(*t*-butyldimethylsilyloxy)-2-nonynoate (**58**) (94.6 mg, 0.240 mmol), tris(trimethylsilyl)silane (148 μL, 0.480 mmol) in 1.2 mL of dry benzene was heated in an 78 °C oil bath. The reaction was initiated by adding 0.5 mL of air followed by triethylborane (60 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100);

HRMS (EI) *m/z* calcd for C$_{29}$H$_{62}$NO$_4$SSi$_5$ (M$^+$+NH$_4$): 660.3245, found: 660.3256.

3.24 Methyl (Z)-8-hydroxy-6-oxa-7-(phenylthio)-3-tris(trimethylsilyl)silyl-2-octenoate (62)
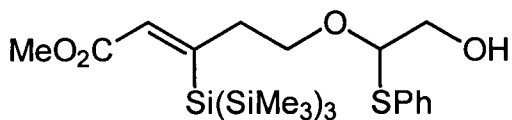
A solution methyl 8-hydroxy-6-oxa-7-(phenylthio)-2-octynoate (**59**) (61.9 mg, 0.221 mmol), tris(trimethylsilyl)silane (136 μL, 0.442 mmol) in 1.1 mL of dry benzene was heated in an 78 °C oil bath. The reaction was initiated by adding 0.5 mL of air followed by triethylborane (55 μL of 1.0 M solution 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 45), 527 (M$^+$+1, 12);

HRMS (EI) *m/z* calcd for C$_{23}$H$_{48}$NO$_4$SSi$_4$ (M$^+$+NH$_4$): 546.2381, found: 546.2367.

3.25 Methyl (*Z*)-8-hydroxy-6-oxa-7-(phenylthio)-3-tri(*n*-butyl)stannyl-2-octenoate (63)
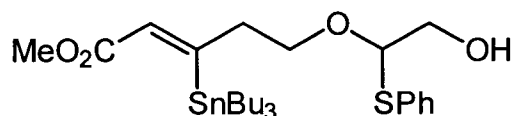
A solution methyl 8-hydroxy-6-oxa-7-(phenylthio)-2-octynoate (**59**) (59.0 mg, 0.211 mmol), tri(*n*-butyl)tin hydride (85 μL, 0.32 mmol) in 1.1 mL of dry benzene was heated in a 78 °C oil bath. The reaction was initiated by adding triethylborane (53 μL of 1.0 M solution in hexanes, 0.053 mmol) followed 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 (CDCl$_3$): 3596, 2957, 2924, 1707, 1599, 1437, 1332, 1201, 1110 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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)
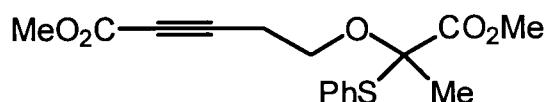
Methyl chloro(thiophenoxy)acetate (**48**) (0.50 g, 2.3 mmol) in 2 mL of dry THF was added over four minutes to a -78 °C solution of lithium diisopropylamide (4.6 mmol) in 12 mL of dry THF. The lithium diisopropylamine was prepared by adding *n*-BuLi (3.5 mL of 1.3 M in hexanes, 4.6 mmol) to a -78 °C 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100), 195 (30);

HRMS (CI(+), isobutane) *m/z* calcd for C$_{16}$H$_{19}$O$_5$S (M$^+$+1): 323.0953, found: 323.0951.

3.27 Dimethyl 7-oxa-8-methyl-8-(phenylthio)-2-nonynedioate (72)
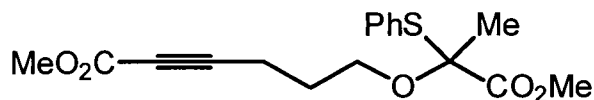
Methyl 6-hydroxy-2-hexynoate (**45**) (0.29 g, 2.3 mmol) was converted to **72** following the procedure outlined in Section 3.26. The crude material was purified by radial chromatography, first by eluting with 10% ethyl acetate / pet. ether and second by eluting with 2% ethyl acetate / benzene to afford 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100);

HRMS (CI(+), isobutane) *m/z* calcd for C$_{17}$H$_{21}$O$_5$S (M$^+$+1): 337.1110, found: 337.1110.

3.28 Methyl (*E*)-(2-carbomethoxy-2-methyl-3-oxacyclopentylidene)acetate (73)
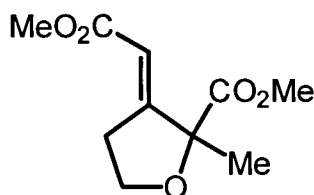
A solution of dimethyl 6-oxa-7-methyl-7-(phenylthio)-2-octynedioate **(71)** (115 mg, 0.357 mmol) and tri(*n*-butyl)tin hydride (144 µL, 0.536 mmol) in 1.8 mL of dry benzene was heated in an 83 °C oil bath. The reaction was initiated by adding triethylborane (89 µL of 1.0 M solution in hexanes, 0.89 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (EI) *m/z* (relative intensity): 214 (M$^+$, 2), 183 (4), 155 (100), 123 (11), 113 (46), 43 (70);

HRMS (EI) *m/z* calcd for C$_{10}$H$_{14}$O$_5$: 214.0841, found: 214.0843;

Anal. Calcd for C$_{10}$H$_{14}$O$_5$: C, 56.07; H, 6.59. Found: C, 56.15; H, 6.64.

3.29 Methyl (*Z*)-(2-carbomethoxy-2-methyl-3-oxacyclopentylidene)acetate (74)
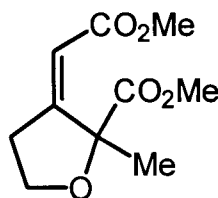
A solution of dimethyl 6-oxa-7-methyl-7-(phenylthio)-2-octynedioate **(71)** (87.6 mg, 0.272 mmol) tris(trimethylsilyl)silane (168 μL, 0.544 mmol) in 1.4 mL of dry benzene was heated in an 83 °C oil bath. The reaction was initiated by adding triethylborane (68 μL of 1.0 M solution in hexanes, 0.68 mmol). 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 C$_{10}$H$_{14}$O$_5$: 214.0841, found: 214.0844;

Anal. Calcd for C$_{10}$H$_{14}$O$_5$: C, 56.07; H, 6.59. Found: C, 56.12; H, 6.53.

3.30   Methyl (*E*)-(2-carbomethoxy-2-methyl-3-oxacyclohexylidene)acetate (75)
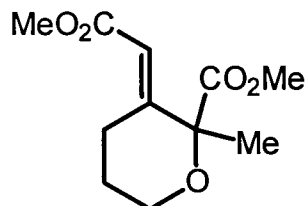
Method A. Via cyclization of compound **72**.

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, 0.066 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 μL 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 μL 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 μL, 0.15 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 μL 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$_3$) δ: 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)
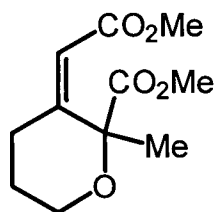
Dimethyl 7-oxa-8-methyl-8-(phenylthio)-2-nonynedioate (72) (102.0 mg, 0.304 mmol) was converted to 76 following the procedure outlined in Section 3.29. The crude material was purified by radial chromatography, eluting with 15% ethyl acetate / pet. ether to afford 30.2 mg (44%) of 76 and 75 in 94:6 ratio, 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$_3$) δ: 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 (EI) m/z (relative intensity): 228 (M$^+$, 1.0), 169 (100), 137 (54), 109 (24), 81 (28), 43 (43);

HRMS (EI) 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)stannyl-2-nonenedioate (77)
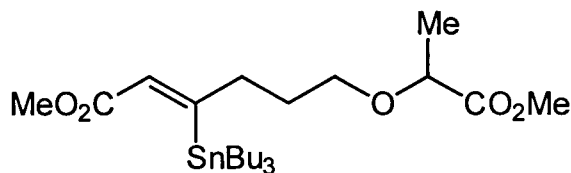
Compound 77 was produced in the reaction described in Section 3.30, Method A. Purification by radial chromatography, eluting with 7% ethyl acetate / pet. ether afforded 25.0 mg (18.0%) of 77 as a colourless oil.

IR (neat): 2954, 1756, 1740, 1708, 1597, 1447, 1329, 1204, 1145 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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$_{Sn-H}$ = 107 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 521 (^{120}Sn, M$^+$+1, 2.3), 519 (^{118}Sn,

M$^+$+1, 1.7), 517 (^{116}Sn, M$^+$+1, 1.1), 463 (100), 461 (77), 459 (41);

HRMS (CI(+), ammonia/methane)

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

3.33   6-(2-Tetrahydropyranyloxy)-1-hexyne (85)
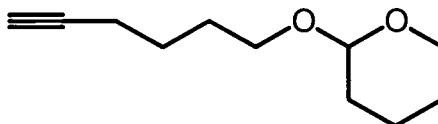
1-Hexyn-6-ol (**84**) (1.00 g, 10.2 mmol) was converted to **85** following the procedure outlined in Section 3.4.   The crude brown oil was purified by flash chromatography, eluting with 15% diethyl ether / pet. ether to afford 1.64 g (89%) of **85** as a colourless oil.

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

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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 (CI(+), 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)
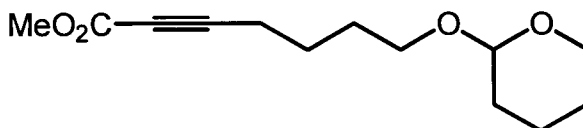
6-(2-Tetrahydropyranyloxy)-1-hexyne (**85**) (1.27 g, 6.98 mmol) was converted to **86** following the procedure outlined in Section 3.21. The crude yellow oil was purified by flash chromatography, eluting with 15% ethyl acetate / pet. ether followed by Kugelrohr distillation (130 °C / 0.05 mm Hg) from K_2CO_3 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};

^{1}H NMR (400 MHz, $CDCl_3$) 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$^+$+NH$_4$, 2), 241 (M$^+$+1, 2), 174 (100), 157 (53);

HRMS (CI(+), isobutane) *m/z* calcd for $C_{13}H_{21}O_4$ (M$^+$+1): 241.1440, found: 241.1440;

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.92; H, 8.19.

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

$$MeO_2C\!\!\equiv\!\!\diagdown\!\!\diagup\!\!\diagdown\!\!OH$$
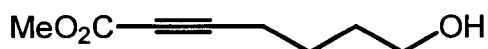
Methyl 7-(2-tetrahydropyranyloxy)-2-heptynoate (**86**) (1.38 g, 5.75 mmol) was converted to **87** following the procedure outlined in Section 3.9. The crude material was purified by flash chromatography, eluting with 50% diethyl ether / pet. ether followed by Kugelrohr distillation (120 °C / 0.1 mm 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};

^{1}H NMR (400 MHz, $CDCl_3$) 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 (EI) *m/z* (relative intensity): 156 (M$^+$, 10), 124 (100), 98 (37), 79 (37), 69 (72);

HRMS (EI) *m/z* calcd for $C_8H_{12}O_3$: 156.0786, found: 156.0781;

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.39; H, 7.93.

3.36 Methyl (*E*)-3-bromo-7-hydroxy-2-heptenoate (88)
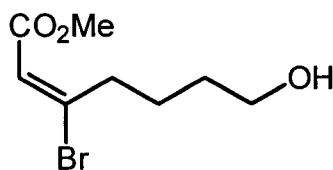
A solution of methyl 7-hydroxy-2-heptynoate (**87**) (0.68 g, 4.4 mmol) in 22 mL of dry diethyl ether was stirred in an ice bath. Hydrogen bromide was bubbled through the stirred solution for 1 minute and the flask was stoppered and sealed with parafilm. The hydrogen bromide addition was repeated twice 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 $NaHCO_3$ 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}.

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 100), 254 (^{79}Br, M$^+$+NH$_4$, 93), 239 (^{81}Br, M$^+$+1, 21), 237 (^{79}Br, M$^+$+1, 9);

HRMS (CI(+), methane) *m/z* calcd for C$_8$H$_{14}$O$_3$^{81}Br (M$^+$+1): 239.0107, found: 239.0111; *m/z* calcd for C$_8$H$_{14}$O$_3$^{79}Br (M$^+$+1): 237.0127, found: 237.0126;

Anal. Calcd for C$_8$H$_{13}$O$_3$Br: C, 40.53; H, 5.53. Found: C, 40.60; H, 5.54.

3.37 Methyl (Z)-3-bromo-7-hydroxy-2-heptenoate (89)
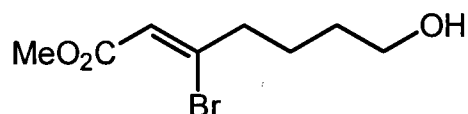
See Section 3.36.

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

^{1}H NMR (400 MHz, CDCl$_3$) δ: 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$_3$) δ: 24.31, 31.28, 43.18, 51.53, 62.32, 119.25, 142.14, 164.63;

LRMS (CI(+), 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 (CI(+), 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;

Anal. Calcd for C$_8$H$_{13}$O$_3$Br: C, 40.53; H, 5.53. Found: C, 40.46; H, 5.40.

3.38 Methyl (E)-3,7-dibromo-2-heptenoate (90)
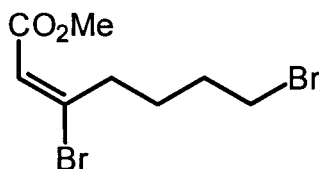
Carbon tetrabromide (0.09 g, 0.3 mmol) was added to an ice cooled solution of methyl (E)-3-bromo-7-hydroxy-2-heptenoate (88) (0.05 g, 0.2 mmol) and triphenylphosphine (0.07 g, 0.3 mmol) in 1.1 mL of dry methylene chloride. The ice bath was removed and the reaction mixture was stirred for 2.5 hours. The 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (2^{81}Br, M$^+$, 2), 300 (^{79}Br^{81}Br, M$^+$, 3), 298 (2^{79}Br, 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 C$_8$H$_{12}$O$_2$^{81}Br$_2$: 301.9163 found: 301.9160;

m/z calcd for C$_8$H$_{12}$O$_2$^{81}Br^{79}Br: 299.9184 found: 299.9191;

m/z calcd for C$_8$H$_{12}$O$_2$^{79}Br$_2$: 297.9204 found: 297.9210;

Anal. Calcd for C$_8$H$_{12}$O$_2$Br$_2$: C, 32.03; H, 4.03. Found: C, 32.31; H, 3.95.

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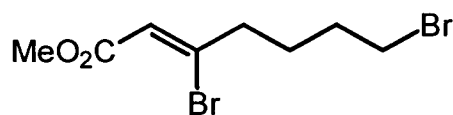
Methyl (Z)-3-bromo-7-hydroxy-2-heptenoate (**89**) was converted to **91** following the procedure outlined in Section 3.31. The crude material was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (120 °C / 0.05 mm Hg) to afford 0.07 g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

IR (neat): 2944, 1727, 1637, 1439, 1293, 1184 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (2^{81}Br, M$^+$, 2), 300 (^{81}Br^{79}Br, M$^+$, 3), 298 (2^{79}Br, 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 (EI) *m/z* calcd for $C_8H_{12}O_2{}^{81}Br_2$: 301.9163, found: 301.9167;

m/z calcd for $C_8H_{12}O_2{}^{81}Br{}^{79}Br$: 299.9184, found: 299.9181;

m/z calcd for $C_8H_{12}O_2{}^{79}Br_2$: 297.9204, found: 297.9201;

Anal. Calcd for $C_8H_{12}O_2Br_2$: C, 32.03; H, 4.03. Found: C, 32.24; H, 4.21.

3.40 Methyl (cyclopentylidene)acetate (92)
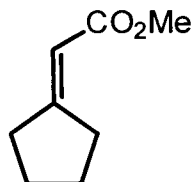
Methyl (*E*)-3-bromo-7-iodo-2-heptenoate (**110**) (88.6 mg, 0.255 mmol), hexa(*n*-butyl)ditin (129 μl, 0.255 mmol) was dissolved in 12.8 mL of benzene in a Pyrex tube. Nitrogen was bubbled through the mixture for 30 min. and then the vessel was capped with a septum and sealed with parafilm. This solution 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};

^{1}H NMR (200 MHz, CDCl$_3$) 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 (EI) *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 (EI) *m/z* calcd for $C_8H_{12}O_2$: 140.0837, found: 140.0835.

3.41 Methyl (E)-(2-methylcyclopentylidene)acetate (93)
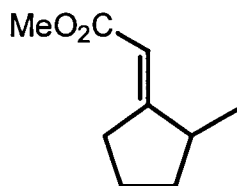
Methyl (E)-3-bromo-7-iodo-2-octenoate **(108)** (59.0 mg, 0.163 mmol) was converted to **93** following the procedure outlined in Section 3.40. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl ether / pet. ether to afford 19.2 mg (76%) of **93** and **94** 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$_3$) δ: 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)-(2-methylcyclopentylidene)acetate (94)
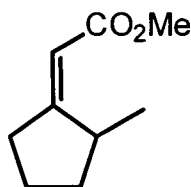
Methyl (Z)-3-bromo-7-iodo-2-octenoate **(109)** (79.6 mg, 0.220 mmol) was converted to **94** following the procedure outlined in Section 3.40. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl ether / pet. ether to afford 25.7 mg (76%) of **94** and **93** 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)
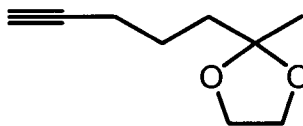
2-Acetylbutyrolactone (20.0 g, 0.160 mmol), hydrobromic acid (40 mL, 0.23 mmol) and 25 mL of water were combined in flask fitted with distillation apparatus. The reaction flask was immersed in an oil bath and the oil bath temperature was increased to 120 °C. Distillation began after about 50 minutes 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, 2116, 1378, 1227, 1134, 1105, 1057 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) 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 (CI(+), methane) *m/z* calcd for C$_9$H$_{15}$O$_2$ (M$^+$+1): 155.1072, found: 155.1068;

Anal. Calcd for C$_9$H$_{14}$O$_2$: C, 70.10; H, 9.15. Found: C, 70.06; H, 9.24.

3.44   1-Heptyn-6-one (99)
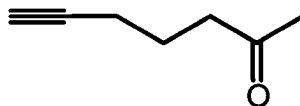
A solution of 1-heptyn-6-one ethylene acetal (**98**) (7.67 g, 49.8 mmol) and pyridinium *p*-toluenesulfonate (3.75 g, 14.9 mmol) in 400 mL of acetone was refluxed overnight. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. The crude material was dissolved in 400 mL of diethyl ether, and was washed consecutively with saturated NaHCO$_3$ 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 (CDCl$_3$): 3285, 2937, 2116, 1714, 1436, 1413, 1365, 1161 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) 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^++NH$_4$, 100), 111 (M^++1, 22);

HRMS (CI(+), methane) *m/z* calcd for $C_7H_{11}O$ (M^++1): 111.0810, found: 111.0810;

Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 75.99; H, 9.33.

3.45 1-Heptyn-6-ol (100)
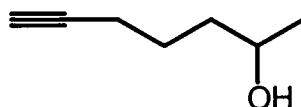
Lithium aluminum hydride (1.74 g, 43.4 mmol) was suspended in 180 mL of dry THF and stirred in an ice bath. To this suspension was added dropwise a solution of 1-heptyn-6-one (**99**) (3.98 g, 36.2 mmol) in 25 mL of dry THF. The cooling bath was removed and stirring was continued for 2.5 hours. The reaction mixture was cooled in an ice bath and quenched by the slow addition of 20 mL of saturated Na$_2$SO$_4$ 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% NaHCO$_3$ 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 (CDCl$_3$): 3367, 3298, 2967, 2932, 2870, 2116, 1457, 1433, 1375, 1128, 1086 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) 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^++NH$_4$, 100), 113 (M^++1, 13);

HRMS (CI(+), methane) *m/z* calcd for $C_7H_{13}O$ (M^++1): 113.0966, found: 113.0968;

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.79; H, 10.70.

3.46 6-(2-Tetrahydropyranyloxy)-1-heptyne (101)
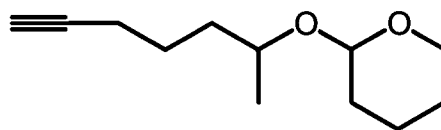
1-Heptyn-6-ol (**100**) (3.50 g, 31.3 mmol) was converted to **101** following the procedure outlined in Section 3.4. The crude brown oil was purified by flash chromatography, eluting with 10% diethyl ether / pet ether followed by Kugelrohr distillation (80-87 °C / 1 mm Hg) from K_2CO_3 to afford 5.62 g (92%) of **101** as a colourless oil.

IR (neat): 3290, 2940, 2871, 1449, 1376, 1339, 1199, 1128, 1077, 1020, 870 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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 $C_{12}H_{19}O_2$ (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)
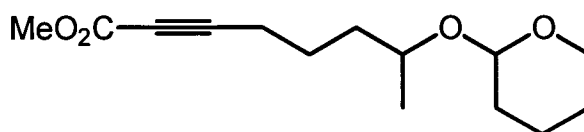
6-(2-Tetrahydropyranyloxy)-1-heptyne (**101**) (5.51 g, 28.1 mmol) was converted to **102** following the procedure outlined in Section 3.21. The crude material was purified by flash chromatography, eluting with 10% ethyl acetate / pet. ether followed by Kugelrohr distillation (95-118 °C / 0.2 mm Hg) from K_2CO_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};

^{1}H NMR (200 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100,), 255 (M$^+$+1, 12);

HRMS (CI(+), methane) *m/z* calcd for C$_{14}$H$_{23}$O$_4$ (M$^+$+1): 255.1596, found: 255.1598;

Anal. Calcd for C$_{14}$H$_{22}$O$_4$: C, 66.12; H, 8.72. Found: C, 66.32; H, 8.77.

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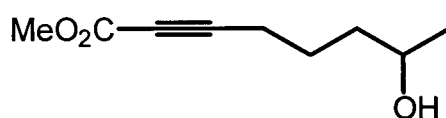
Methyl 7-(2-tetrahydropyranyloxy)-2-octynoate (**102**) (6.75 g, 29.8 mmol) was converted to **103** following the procedure outlined in Section 3.9. The crude material was purified by flash chromatography, eluting with 35% diethyl ether / pet. ether followed by Kugelrohr distillation (112 °C / 0.1 mm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

IR (neat): 3404, 2939, 2237, 1709, 1437, 1268, 1080 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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 C$_9$H$_{14}$O$_3$: 170.0943, found: 170.0937;

Anal. Calcd for C$_9$H$_{14}$O$_3$: C, 63.51; H, 8.29. Found: C, 63.51; H, 8.26.

3.49   Methyl (*E*)-3-bromo-7-hydroxy-2-octenoate (104)
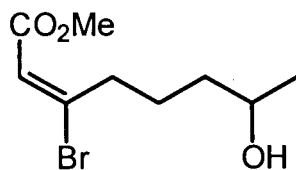
Method A. Via hydrobromination of compound **103**.

   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};

^{1}H NMR (200 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 68), 268 (^{79}Br, M$^+$+NH$_4$, 100), 253 (^{81}Br, M$^+$+1, 7), 251 (^{79}Br, M$^+$+1, 7);

HRMS (CI(+), ammonia/methane)

   m/z calcd for C$_9$H$_{16}$O$_3$^{81}Br (M$^+$+1): 253.0262, found: 253.0253;

   m/z calcd for C$_9$H$_{16}$O$_3$^{79}Br (M$^+$+1): 251.0283, found: 251.0280;

Anal. Calcd for C$_9$H$_{15}$O$_3$Br: C, 43.05; H, 6.02. Found: C, 43.07; H, 5.88.

3.50 Methyl (Z)-3-bromo-7-hydroxy-2-octenoate (105)

MeO$_2$C⎯CH=C(Br)⎯CH$_2$⎯CH$_2$⎯CH$_2$⎯CH(OH)⎯CH$_3$
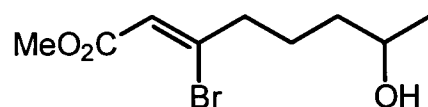
Methyl 7-hydroxy-2-octynoate (103) (0.71 g, 4.2 mmol) was converted to 105 following the procedure outlined in Section 3.36. The crude yellow oil was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (130 °C / 0.1 mm Hg) to afford 0.55 g (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};

^{1}H NMR (200 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 65), 268 (^{79}Br,
M$^+$+NH$_4$, 100);

HRMS (CI(+), ammonia/methane)
m/z calcd for C$_9$H$_{19}$NO$_3$^{81}Br (M$^+$+NH$_4$): 270.0528, found: 270.0523;
m/z calcd for C$_9$H$_{19}$NO$_3$^{79}Br (M$^+$+NH$_4$): 268.0548, found: 268.0558;

Anal. Calcd for C$_9$H$_{15}$O$_3$Br: C, 43.05; H, 6.02. Found: C, 42.61; H, 5.87.

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

CO$_2$Me⎯CH=C(Br)⎯CH$_2$⎯CH$_2$⎯CH$_2$⎯CH(Br)⎯CH$_3$
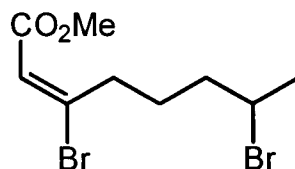
Methyl (E)-3-bromo-7-hydroxy-2-octenoate (104) was converted to 106 following the procedure outlined in Section 3.38. The crude material was purified by radial chromatography, eluting with 5% diethyl ether / pet. ether followed by Kugelrohr distillation (155 °C / 0.2 mm Hg) to afford 0.15 g (63%) 106 as a colourless oil.

IR (neat): 2947, 1722, 1625, 1439, 1346, 1315, 1187, 1123 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (EI) *m/z* (relative intensity): 316 (2^{81}Br, M$^+$, 1), 314 (^{79}Br^{81}Br, M$^+$, 2), 312 (2^{79}Br, M$^+$, 1), 285 (3), 283 (4), 281 (2), 235 (62), 233 (64), 153 (25), 121 (60), 93 (100), 67 (35), 55 (60);

HRMS (EI) *m/z* calcd for C$_9$H$_{14}$O$_2$^{81}Br$_2$: 315.9320, found: 315.9331;

  m/z calcd for C$_9$H$_{14}$O$_2$^{81}Br^{79}Br: 313.9340, found: 313.9341;

  m/z calcd for C$_9$H$_{14}$O$_2$^{79}Br$_2$: 311.9361, found: 311.9358;

Anal. Calcd for C$_9$H$_{14}$O$_2$Br$_2$: C, 34.42; H, 4.49. Found: C, 34.68; H, 4.52.

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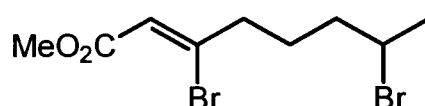
Methyl (Z)-3-bromo-7-hydroxy-2-octenoate (**105**) was converted to **107** following the procedure outlined in Section 3.38. The crude material was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (145 °C / 0.05 mm Hg) to afford 0.14 g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

IR (neat): 2946, 1731, 1636, 1439, 1296, 1183 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (EI) *m/z* (relative intensity): 316 (2^{81}Br, M$^+$, 0.8), 314 (^{79}Br^{81}Br, M$^+$, 2), 312 (2^{79}Br, M$^+$, 0.9), 285 (3), 283 (7), 281 (3), 235 (45), 233 (45), 153 (25), 121 (40), 93 (100), 67 (30), 55 (90);

HRMS (EI) *m/z* calcd for C$_9$H$_{14}$O$_2$^{81}Br$_2$: 315.9320, found: 315.9322;

  m/z calcd for C$_9$H$_{14}$O$_2$^{81}Br^{79}Br: 313.9340, found: 313.9339;

  m/z calcd for C$_9$H$_{14}$O$_2$^{79}Br$_2$: 311.9361, found: 311.9367;

Anal. Calcd for $C_9H_{14}O_2Br_2$: C, 34.42; H, 4.49. Found: C, 34.63; H, 4.53.

3.53   Methyl (E)-3-bromo-7-iodo-2-octenoate (108)
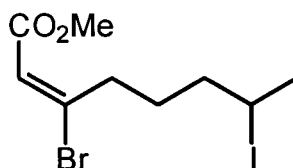
Iodine (0.39 g, 1.6 mmol) was added in one portion to an ice cooled solution of methyl (E)-3-bromo-7-hydroxy-2-octenoate (104) (0.30 g, 1.2 mmol), triphenylphosphine (0.41 g, 1.6 mmol) and imidazole (0.11 g, 1.6 mmol) in 7.5 mL of diethyl ether and 4.5 mL of acetonitrile. After 4 hours, TLC analysis indicated that the reaction was completed. The reaction mixture was diluted to 100 mL with diethyl ether and was washed successively with saturated $Na_2S_2O_3$ solution, saturated $CuSO_4$ 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};

^{1}H NMR (200 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 28.36, 28.83, 29.12, 36.45, 41.33, 51.59, 123.32, 149.50, 164.65;

LRMS (CI(+), ammonia) m/z (relative intensity): 380 (^{81}Br, M$^+$+NH$_4$, 1), 378 (^{79}Br, M$^+$+NH$_4$, 1), 363 (^{81}Br, M$^+$+1, 3), 361 (^{79}Br, 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);

HRMS (CI(+), ammonia)

m/z calcd for $C_9H_{15}O_2{}^{81}BrI$ (M^++1): 362.9280, found: 362.9295;

m/z calcd for $C_9H_{15}O_2{}^{79}BrI$ (M^++1): 360.9300, found: 360.9305;

UV (CH$_3$CN) λ (ε): 232 (8800);

Anal. Calcd for $C_9H_{14}O_2BrI$: C, 29.94; H, 3.91. Found: C, 29.88; H, 3.98.

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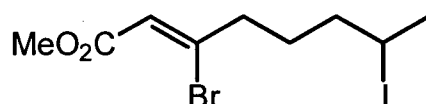
Methyl (Z)-3-bromo-7-hydroxy-2-octenoate (**105**) (0.44 g, 1.75 mmol) was converted to **109** following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 8% diethy ether / pet. ether, followed by Kugelrohr distillation (190 °C / 0.1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

^{1}H NMR (200 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 28.10, 28.72, 28.85, 41.19, 42.42, 51.56, 119.50, 141.54, 164.49;

LRMS (CI(+), ammonia) m/z (relative intensity): 363 (^{81}Br, M^++1, 23), 361 (^{79}Br, 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 (CI(+), ammonia)

m/z calcd for $C_9H_{15}O_2{}^{81}BrI$ (M^++1): 362.9280, found: 362.9292;

m/z calcd for $C_9H_{15}O_2{}^{79}BrI$ (M^++1): 360.9300, found: 360.9304;

Anal. Calcd for $C_9H_{14}O_2BrI$: C, 29.94; H, 3.91. Found: C, 29.83; H, 3.80.

121

3.55 Methyl (*E*)-3-bromo-7-iodo-2-heptenoate (110)
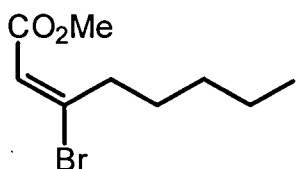
Methyl (*E*)-3-bromo-7-hydroxy-2-heptenoate (**88**) (0.070 g, 0.30 mmol) was converted to **110** following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 5% diethy ether / pet. ether, followed by Kugelrohr distillation (125 °C / 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 11), 364 (^{79}Br, M$^+$+NH$_4$, 11), 349 (^{81}Br, M$^+$+1, 32), 348 (^{81}Br, M$^+$, 14), 347 (^{79}Br, M$^+$+1, 33), 346 (^{79}Br, 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 (CI(+), ammonia)

m/z calcd for C$_8$H$_{13}$O$_2$^{81}BrI (M$^+$+1): 346.9144, found: 346.9127;

m/z calcd for C$_8$H$_{13}$O$_2$^{79}BrI (M$^+$+1): 348.9123, found: 348.9129;

Anal. Calcd for C$_8$H$_{12}$O$_2$BrI: C, 27.69; H, 3.49. Found: C, 27.97; H, 3.61.

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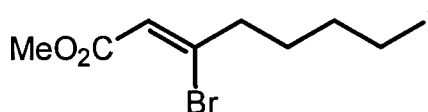
Methyl (Z)-3-bromo-7-hydroxy-2-heptenoate (**89**) (0.11 g, 0.46 mmol) was converted to **111** following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 7% diethy ether / pet. ether followed by Kugelrohr distillation (130 °C / 0.05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

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 5.59, 28.78, 31.94, 42.28, 51.57, 119.53, 141.43, 164.47;

LRMS (CI(+), ammonia) m/z (relative intensity): 366 (^{81}Br, M$^+$+NH$_4$, 26), 364 (^{79}Br, M$^+$+NH$_4$, 27), 349 (^{81}Br, M$^+$+1, 91), 347 (^{79}Br, 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 (CI(+), methane)

m/z calcd for C$_8$H$_{13}$O$_2$^{81}BrI (M$^+$+1): 346.9144, found: 346.9137;

m/z calcd for C$_8$H$_{13}$O$_2$^{79}BrI (M$^+$+1): 348.9123, found: 348.9137;

Anal. Calcd for C$_8$H$_{12}$O$_2$BrI: C, 27.69; H, 3.49. Found: C, 28.00; H, 3.40.

3.57   5-Bromo-1-(tetrahydropyranyloxy)pentane (114)
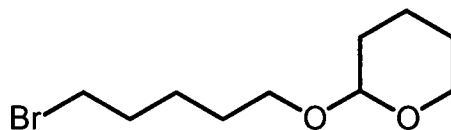
5-Bromopentan-1-ol (**113**) (6.15 g, 35.8 mmol) was converted to **114** following the procedure outlined in Section 3.4. The crude brown oil was purified by distillation (85-103 °C / 0.15 mm Hg) from K$_2$CO$_3$ to afford 7.91 g (86%) of **114** as a colourless oil.

IR (neat): 2907, 1453, 1440, 1354, 1201, 1128, 1074, 1031, 870 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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 (CI(+), 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 (CI(+), 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$_2$Br: C, 47.82; H, 7.62. Found: C, 47.95; H, 7.78.

3.58   7-(2-Tetrahydropyranyloxy)-1-heptyne (115)
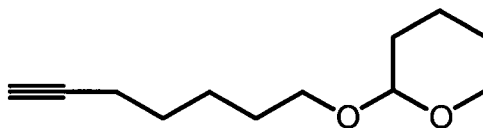
5-Bromo-1-(2-tetrahydropyranyloxy)pentane **(114)** (7.00 g, 27.9 mmol) was converted to **115** following the procedure outlined in Section 3.43. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 3.60 g (66%) of **115** as a colourless oil. 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$_3$) δ: 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$_3$) δ: 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 (CI(+), ammonia) *m/z* (relative intensity): 214 (M$^+$+NH$_4$, 47), 197 (M$^+$+1, 4), 118 (30), 102 (80), 85 (25);

HRMS (CI(+), 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)
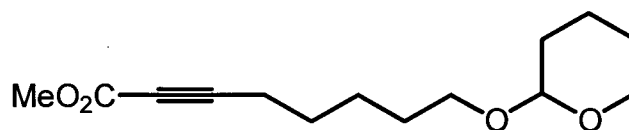
7-(2-Tetrahydropyranyloxy)-1-heptyne (**115**) (0.37 g, 1.9 mmol) was converted to **116** following the procedure outlined in Section 3.21. The crude yellow oil was purified by flash chromatography, eluting with 12% ethyl acetate / pet. ether to afford 0.44 g (92%) of **116** as a colourless oil. Kugelrohr distillation (115-120 °C / 0.05 mm Hg) from K_2CO_3 afforded analytically pure **116**.

IR (neat): 2940, 2866, 2236, 1716, 1436, 1258, 1132, 1120, 1074, 1031 cm^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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 (CI(+), ammonia) *m/z* (relative intensity): 272 (M$^+$+NH$_4$, 100), 255 (M$^+$+1, 10), 188 (30), 102 (30), 85 (20);

HRMS (CI(+), methane) *m/z* calcd for $C_{14}H_{23}O_4$ (M$^+$+1): 255.1596, found: 255.1588;

Anal. Calcd for $C_{14}H_{22}O_4$: 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^{-1};

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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 (EI) *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 (EI) *m/z* calcd for $C_9H_{14}O_3$: 170.0943, found: 170.0942;

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.30; H, 8.19.

3.61 Methyl (*E*)-3-bromo-8-hydroxy-2-octenoate (118)
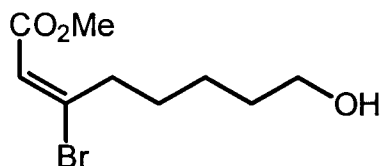
Methyl 8-hydroxy-2-octynoate (**117**) (0.26 g, 1.5 mmol) was converted to **118** following the procedure outlined in Section 3.36. The crude material was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (120 °C / 0.3 mm Hg) to afford 0.15 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 24.71, 28.07, 32.37, 37.55, 51.52, 62.69, 122.83, 150.41, 164.75;

LRMS (CI(+), ammonia) *m/z* (relative intensity): 270 (^{81}Br, M$^+$+NH$_4$, 100), 268 (^{79}Br, M$^+$+NH$_4$, 98), 253 (^{81}Br, M$^+$+1, 26), 251 (^{79}Br, M$^+$+1, 25), 190 (70), 173 (50);

HRMS (CI(+), methane) *m/z* calcd for $C_9H_{16}O_3{}^{81}$Br (M$^+$+1): 253.0264, found: 253.0268; *m/z* calcd for $C_9H_{16}O_3{}^{79}$Br (M$^+$+1): 253.0283, found: 251.0282;

Anal. Calcd for $C_9H_{15}O_3Br$: C, 43.05; H, 6.02. Found: C, 43.48; H, 6.25.

3.62 Methyl (Z)-3-bromo-8-hydroxy-2-octenoate (119)
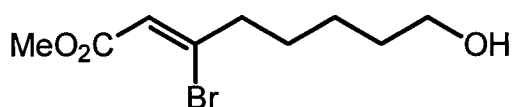
See Section 3.61.

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

^{1}H NMR (400 MHz, CDCl$_3$) δ: 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 24.60, 27.74, 32.29, 43.43, 51.51, 62.59, 119.10, 142.36, 164.64;

LRMS (CI(+), 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 (CI(+), 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)
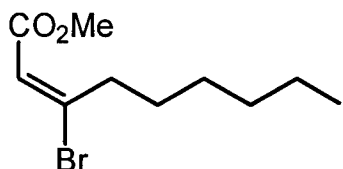
Methyl (E)-3-bromo-8-hydroxy-2-octenoate (118) (0.08 g, 0.3 mmol) was converted to 120 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 5% diethy ether / pet. ether followed by Kugelrohr distillation (150 °C / 0.2 mm Hg) to 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$_3$) δ: 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$_3$) δ: 6.53, 27.17, 29.37, 33.06, 37.32, 51.56, 123.02, 149.97, 164.67;

LRMS (CI(+), 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 (CI(+), methane)

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

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

Anal. Calcd for C$_9$H$_{14}$O$_2$BrI: C, 29.94; H, 3.91. Found: C, 30.11; H, 3.85.

3.64 Methyl (Z)-3-bromo-8-iodo-2-octenoate (121)
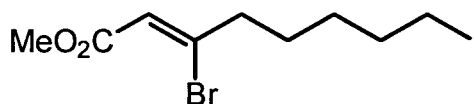
Methyl (Z)-3-bromo-8-hydroxy-2-octenoate (119) (0.09 g, 0.4 mmol) was converted to 121 following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 7% diethy ether / pet. ether followed by Kugelrohr distillation (150 °C / 0.05 mm Hg) to 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$_3$) δ: 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$_3$) δ: 6.30, 26.89, 29.22, 33.04, 43.21, 51.53, 119.28, 141.96, 164.55;

LRMS (CI(+), ammonia) *m/z* (relative intensity): 380 (^{81}Br, M$^+$+NH$_4$, 4), 378 (^{79}Br,

M$^+$+NH$_4$, 4), 363 (^{81}Br, M$^+$+1, 72), 361 (^{79}Br, M$^+$+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 (CI(+), methane)

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

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

Anal. Calcd for C$_9$H$_{14}$O$_2$BrI: C, 29.94; H, 3.91. Found: C, 30.22; H, 3.86.

3.65 Methyl (cyclohexylidene)acetate (122)
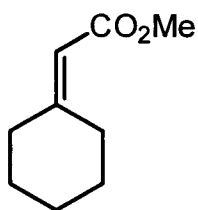
Methyl (*Z*)-3-bromo-8-iodo-2-octenoate (**121**) (60.4 mg, 0.167 mmol) was converted to **122** following the procedure outlined in Section 3.40. The procedure was amended by allowing 40 minutes of irradiation. The concentrated crude material was purified by radial chromatography, eluting with 4% diethyl 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$_3$) δ: 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 (EI) *m/z* (relative intensity): 154 (M$^+$, 100), 151 (26), 123 (33), 122 (20), 95 (40), 81 (21);

HRMS (EI) *m/z* calcd for C$_9$H$_{14}$O$_2$: 154.0994, found: 154.1001.

3.66 Methyl (E)-(2-methylcyclohexylidene)acetate (123)
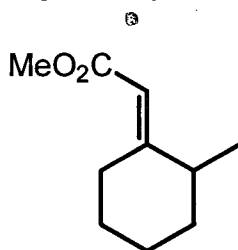
Methyl (E)-3-bromo-8-iodo-2-nonenoate (**125**) (108.6 mg, 0.290 mmol) was converted to **123** following the procedure outlined in Section 3.40. The procedure was amended by allowing 40 minutes of irradiation. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl 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$_3$) δ: 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)
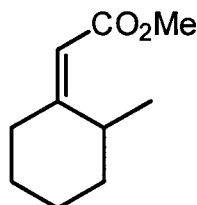
Methyl (Z)-3,8-diiodo-2-nonenoate (**155**) (91.4 mg, 0.217 mmol) was converted to **124** following the procedure outlined in Section 3.40. The procedure was amended by allowing 40 minutes of irradiation. The concentrated crude material was purified by radial chromatography, eluting with 3% diethyl 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$_3$) δ: 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-tetrahydropyranyloxy)hexane (128)
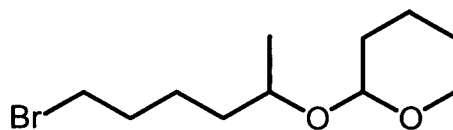
Bromine (3.1 mL, 60 mmol) was added to an ice cooled solution of triphenylphosphine (15.7 g, 60.0 mmol) in 170 mL of dry methylene chloride. To the resulting white precipitate was added 6-hydroxy-1-hexene (125) (5.00 g, 50.0 mmol) and the mixture was stirred at room temperature overnight. The reaction 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 NaBH$_4$ 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 NaHCO$_3$ 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$_3$) δ: 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 (CI(+), 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-Tetrahydropyranyloxy)-1-octyne (129)
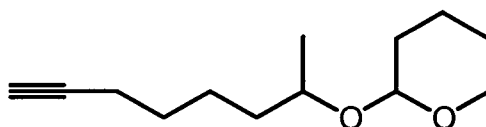
1-Bromo-5-(2-tetrahydropyranyloxy)hexane (**128**) (5.85 g, 22.1 mmol) was converted to **129** following the procedure outlined in Section 3.43. The crude material was purified by flash chromatography, eluting with 15% diethyl ether / pet. ether to afford 3.43 g (74%) of **129** as a colourless oil. 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$_3$) δ: 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 (CI(+), isobutane) *m/z* calcd for $C_{13}H_{23}O_2$ (M^++1): 211.1698, found: 211.1698;

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.17; H, 10.77.

3.70 Methyl 8-(2-tetrahydropyranyloxy)-2-nonynoate (130)
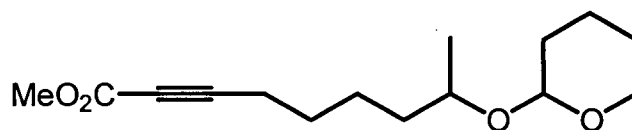
7-(2-Tetrahydropyranyloxy)-1-octyne (**129**) (1.32 g, 62.9 mmol) was converted to **130** following the procedure outlined in Section 3.21. The crude material was purified by flash chromatography, eluting with 15% diethyl ether / pet. ether to afford 1.59 g (95%) of **130** as a colourless oil. Kugelrohr distillation (140 °C / 0.1 mm Hg) afforded analytically pure **130**.

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

^{1}H NMR (200 MHz, CDCl$_3$) δ: 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^++NH_4, 100), 269 (M^++1, 8), 185 (22), 102 (21);

HRMS (CI(+), isobutane) *m/z* calcd for $C_{15}H_{25}O_4$ (M^++1): 269.1753, found: 269.1754;

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.49; H, 9.11.

3.71 Methyl 8-hydroxy-2-nonynoate (131)
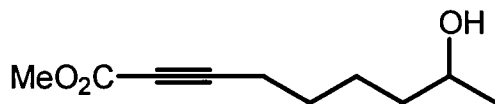
Methyl 8-(2-tetrahydropyranyloxy)-2-nonynoate (**130**) (1.59 g, 6.26 mmol) was converted to **131** following the procedure outlined in Section 3.9. The crude material was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether to

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};

^{1}H NMR (200 MHz, CDCl$_3$) 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 C$_{10}$H$_{16}$O$_3$: 184.1099, found: 184.1103;

Anal. Calcd for C$_{10}$H$_{16}$O$_3$: C, 65.19; H, 8.75. Found: C, 65.45; H, 8.96.

3.72   Methyl (*E*)-3-bromo-8-hydroxy-2-nonenoate (132)
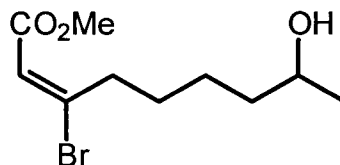
Methyl 8-hydroxy-2-nonynoate (**131**) (0.50 g, 2.9 mmol) was converted to **132** following the procedure outlined in Section 3.36. The crude yellow oil was purified by flash chromatography, eluting with 35% ethyl acetate / pet. ether followed by Kugelrohr distillation (160 °C / 0.2 mm Hg) to afford 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 100), 282 (^{79}Br, M$^+$+NH$_4$, 100), 267 (^{81}Br, M$^+$+1, 3), 265 (^{79}Br, M$^+$+1, 3), 167 (43);

HRMS (CI(+), isobutane)

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

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

Anal. Calcd for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46. Found: C, 45.30; H, 6.60.

3.73 Methyl (Z)-3-bromo-8-hydroxy-2-nonenoate (133)
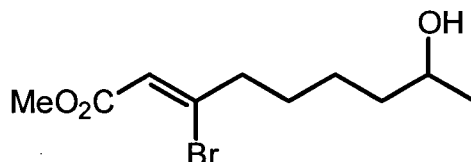
See Section 3.72.

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

^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.14 (d, J = 6.4 Hz, 3H), 1.23-1.48 (m, 4H), 1.59 (m, 3H), 2.54 (t, J = 7.3 Hz, 2H), 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 (CI(+), isobutane)

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

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

Anal. Calcd for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46. Found: C, 45.69; H, 6.66.

3.74 Methyl (E)-3-bromo-8-iodo-2-nonenoate (134)
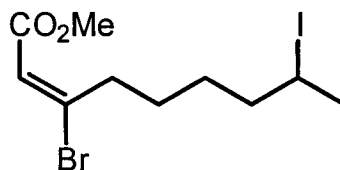
Methyl (E)-3-bromo-8-hydroxy-2-nonenoate (132) (0.13 g, 0.49 mmol) was converted to 134 following the procedure outlined in Section 3.53.   The crude

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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (CI(+), ammonia) *m/z* (relative intensity): 394 (^{81}Br, M$^+$+NH$_4$, 15), 392 (^{79}Br, M$^+$+NH$_4$, 17), 377 (^{81}Br, M$^+$+1, 20), 375 (^{79}Br, M$^+$+1, 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 (CI(+), methane)

m/z calcd for C$_{10}$H$_{17}$O$_2$^{81}BrI (M$^+$+1): 376.9437, found: 376.9432;

m/z calcd for C$_{10}$H$_{17}$O$_2$^{79}BrI (M$^+$+1): 374.9457, found: 374.9460;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$BrI: C, 28.46; H, 3.82. Found: C, 28.70; H, 3.79.

3.75 Methyl (Z)-3-bromo-8-iodo-2-nonenoate (135)
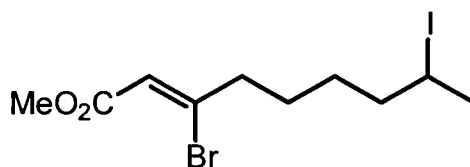
Methyl (Z)-3-bromo-8-hydroxy-2-nonenoate (**133**) (0.14 g, 0.53 mmol) was converted to **135** following the procedure outlined in Section 3.53. The crude colourless oil was purified by radial chromatography, eluting with 4% diethy ether / pet. ether to afford 0.12 g (75%) of **135** as a colourless 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};

^{1}H NMR (200 MHz, CDCl$_3$) 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 (CI(+), 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 (CI(+), methane)

m/z calcd for C$_{10}$H$_{17}$O$_2$^{81}BrI (M$^+$+1): 376.9437, found: 376.9430;

m/z calcd for C$_{10}$H$_{17}$O$_2$^{79}BrI (M$^+$+1): 374.9457, found: 374.9449;

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

3.76 Methyl (*E*)-7-(2-tetrahydropyranyloxy)-3-(tri(*n*-butyl)stannyl)-2-octenoate (140)
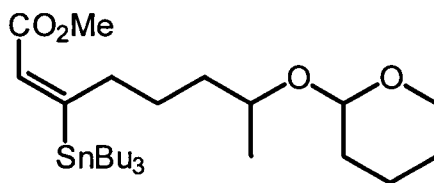
A solution of hexa(*n*-butyl)ditin (1.97 g, 3.90 mmol) in 26 mL of dry THF was cooled in an ice bath and *n*-butyllithium (2.50 mL of 1.54 M in hexanes, 3.90 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 20 minutes, and then cooled to -78 °C. Copper bromide-dimethyl sulfide 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-tetrahydropyranyloxy)-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};

^{1}H NMR (200 MHz, CDCl$_3$) 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, J$_{Sn-H}$ = 64 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 564 (^{120}Sn, M$^+$+NH$_4$, 18), 562 (^{118}Sn, M$^+$+NH$_4$, 13), 560 (^{116}Sn, M$^+$+NH$_4$, 7), 405 (100), 403 (75) 401 (40);

HRMS (CI(+), ammonia/methane)

m/z calcd for C$_{26}$H$_{54}$NO$_4$^{120}Sn (M$^+$+NH$_4$): 564.3075, found: 564.3066;

Anal. Calcd for C$_{26}$H$_{50}$O$_4$Sn: C, 57.26; H, 9.24. Found: C, 57.05; H, 9.20.

3.77 Methyl (E)-8-(2-tetrahydropyranyloxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (141)
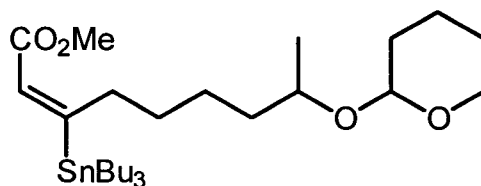
Methyl 8-(2-tetrahydropyranyloxy)-2-nonynoate (132) (0.65 g, 2.4 mmol) was converted to 141 following the procedure outlined in Section 3.76. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 1.27 g (93%) of 141 as a colourless oil. Kugelrohr distillation (200 °C / 0.05 mm Hg) afforded analytically pure 141.

IR (neat): 2936, 2854, 1720, 1592, 1452, 1165, 1136, 1026 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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, J$_{Sn-H}$ = 65 Hz, 1H);

LRMS (DCI(+), ammonia) m/z (relative intensity): 578 (^{120}Sn, M$^+$+NH$_4$, 100), 576 (^{118}Sn, M$^+$+NH$_4$, 69), 574 (^{116}Sn, M$^+$+NH$_4$, 34), 503 (43), 501 (31), 499 (18), 419 (91), 417 (65), 415 (36), 85 (27);

HRMS (CI(+), ammonia/methane)

m/z calcd for $C_{27}H_{56}NO_4{}^{120}Sn$ (M$^+$+NH$_4$): 578.3231, found: 578.3226;

Anal. Calcd for $C_{27}H_{52}O_4Sn$: C, 57.97; H, 9.37. Found: C, 58.45; H, 9.27.

3.78 Methyl (*E*)-7-hydroxy-3-(tri(*n*-butyl)stannyl)-2-octenoate (142)
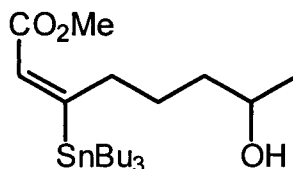
A solution of methyl (*E*)-7-(2-tetrahydropyranyloxy)-3-(tri(*n*-butyl)stannyl)-2-octenoate (**140**) (1.17 g, 2.15 mmol) and *p*-toluenesulfonic acid monohydrate in 11 mL of methanol was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and purified by flash chromatography, 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};

^{1}H NMR (200 MHz, CDCl$_3$) 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 (^{120}Sn, M$^+$+1, 91), 461 (^{118}Sn, M$^+$+1, 65), 459 (^{116}Sn, M$^+$+1, 35), 405 (100), 403 (73), 401 (41);

HRMS (CI(+), methane)

m/z calcd for $C_{21}H_{43}O_3{}^{118}Sn$ (M$^+$+1): 461.2228, found: 461.2225;

Anal. Calcd for $C_{21}H_{42}O_3Sn$: C, 54.68; H, 9.18. Found: C, 54.69; H, 9.20.

3.79 Methyl (E)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (143)
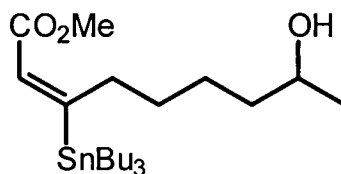
Methyl (E)-8-(2-tetrahydropyranyloxy)-3-(tri(n-butyl)stannyl)-2-nonenoate (141) (1.30 g, 2.39 mmol) was converted to 143 following the procedure outlined in Section 3.9. The crude material was purified by radial chromatography, eluting with 35% diethyl ether / pet. ether to afford 1.06 g (94%) of 143 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$_3$) δ: 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_{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 (CI(+), ammonia/methane)

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

Anal. Calcd for C$_{22}$H$_{44}$O$_3$Sn: C, 55.60; H, 9.33. Found: C, 55.72; H, 9.19.

3.80 Methyl (E)-7-iodo-3-(tri(n-butyl)stannyl)-2-octenoate (144)
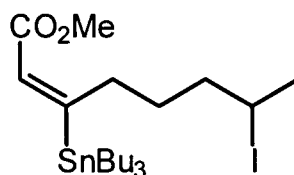
Methyl (E)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate (142) (0.30 g, 1.2 mmol) was converted to 144 following the procedure outlined in Section 3.53. The crude material was purified by radial chromatography, eluting with 2% diethyl ether / pet. ether

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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (CI(+), ammonia) m/z (relative intensity): 590 (^{120}Sn, M$^+$+NH$_4$, 40), 588 (^{118}Sn,

M$^+$+NH$_4$, 32), 586 (^{116}Sn, M$^+$+NH$_4$, 20) 573 (^{120}Sn, M$^+$+1, 30), 571 (^{118}Sn, M$^+$+1,
22), 569 (^{116}Sn, 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 (CI(+),ammonia/methane)

m/z calcd for C$_{21}$H$_{42}$O$_2$I^{120}Sn (M$^+$+1): 573.1252, found: 573.1246.

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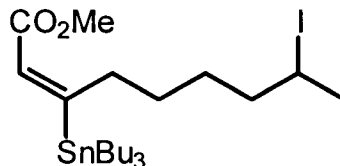
Methyl   (*E*)-8-(hydroxy)-3-(tri(*n*-butyl)stannyl)-2-nonenoate   **(143)**   (0.99 g, 2.1 mmol) was converted to **145** following the procedure outlined in Section 3.53. The crude material was purified by radial chromatography, eluting with 2% diethyl ether / pet. ether to afford 0.96 g (79%) of **145**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

IR (neat): 2928, 2855, 1709, 1597, 1434, 1197, 1173 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (^{120}Sn, M$^+$+NH$_4$, 54), 602 (^{118}Sn,

M$^+$+NH$_4$, 40), 600 (^{116}Sn, M$^+$+NH$_4$, 28), 587 (^{120}Sn, M$^+$+1, 65), 585 (^{118}Sn,

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 (CI(+), ammonia/methane)

m/z calcd for $C_{22}H_{44}O_2I^{120}Sn$ (M⁺+1): 587.1406, found: 587.1405.

3.82 Methyl (*Z*)-7-hydroxy-3-(tri(*n*-butyl)stannyl)-2-octenoate (146)
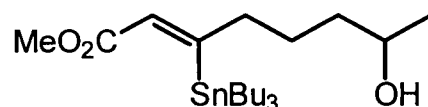
A solution of methyl (*E*)-7-hydroxy-3-(tri(*n*-butyl)stannyl)-2-octenoate (**142**) (0.50 g, 1.1 mmol), tri(*n*-butyl)tin hydride (0.15 mL, 0.54 mmol) and AIBN (catalytic amount) in 7.2 mL of benzene was refluxed for 2 hours. The rection mixture was concentrated in vacuo and purified by flash chromatography, 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;

¹H NMR (200 MHz, CDCl₃) δ: 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 (CI(+), methane)

m/z calcd for $C_{21}H_{43}O_3^{118}Sn$ (M⁺+1): 461.2228, found: 461.2214;

Anal. Calcd for $C_{21}H_{42}O_3Sn$: C, 54.68; H, 9.18. Found: C, 54.63; H, 9.15.

3.83 Methyl (*Z*)-8-(hydroxy)-3-(tri(*n*-butyl)stannyl)-2-nonenoate (147)
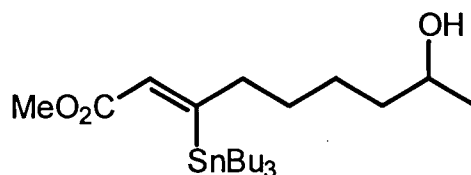
Methyl (E)-8-(hydroxy)-3-(tri(n-butyl)stannyl)-2-nonenoate **(143)** (1.06 g, 2.23 mmol) was converted to **147** following the procedure outlined in Section 3.82. The crude material was purified by radial chromatography, eluting with 25% diethyl ether / pet. ether to afford 0.99 g (93%) of **147** as 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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, J$_{Sn-H}$ = 108 Hz, 1H);

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

HRMS (CI(+), ammonia/methane)

m/z calcd for C$_{22}$H$_{45}$O$_3$^{120}Sn (M$^+$+1): 477.2391, found: 477.2388;

Anal. Calcd for C$_{22}$H$_{44}$O$_3$Sn: C, 55.60; H, 9.33. Found: C, 56.06; H, 9.51.

3.84 Methyl (Z)-7-iodo-3-(tri(n-butyl)stannyl)-2-octenoate (148)
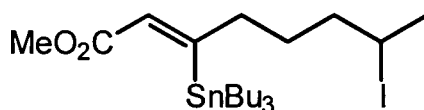
Methyl (Z)-7-hydroxy-3-(tri(n-butyl)stannyl)-2-octenoate **(146)** (0.78 g, 1.7 mmol) was converted to **148** following the procedure outlined in Section 3.53. The crude material was purified by radial chromatography, eluting with 1% diethyl ether / pet. ether to afford 0.86 g (89%) of **148** as a 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};

^{1}H NMR (200 MHz, CDCl$_3$) 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, J$_{Sn-H}$ = 106 Hz, 1H);

LRMS (DCI(+), ammonia) *m/z* (relative intensity): 590 (^{120}Sn, M$^+$+NH$_4$, 27), 588 (^{118}Sn, M$^+$+NH$_4$, 23), 586 (^{116}Sn, M$^+$+NH$_4$, 13) 573 (^{120}Sn, M$^+$+1, 5), 571 (^{118}Sn, M$^+$+1, 3), 569 (^{116}Sn, M$^+$+1, 1), 515 (100), 513 (75), 511 (38), 445 (30), 443 (21), 441 (14), 308 (50), 306 (38), 304 (22), 172 (82);

HRMS (CI(+), isobutane)

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

Anal. Calcd for C$_{21}$H$_{41}$O$_2$ISn: C, 44.16; H, 7.24. Found: C, 44.39; H, 7.18.

3.85   Methyl (*Z*)-8-iodo-3-(tri(*n*-butyl)stannyl)-2-nonenoate (149)
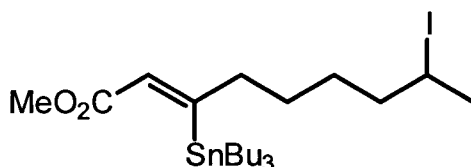
Methyl   (*Z*)-8-(hydroxy)-3-(tri(*n*-butyl)stannyl)-2-nonenoate   **(147)**   (0.99 g, 2.1 mmol) was converted to **149** following the procedure outlined in Section 3.53. The crude material was purified by flash chromatography, eluting with 1% diethyl ether / pet. ether to afford 0.91 g (75%) of **149** 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}H NMR (400 MHz, CDCl$_3$) δ: 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$_{Sn-H}$ = 108 Hz, 1H);

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

HRMS (CI(+), ammonia/methane)

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

Anal. Calcd for C$_{22}$H$_{43}$O$_2$ISn: C, 45.16; H, 7.41. Found: C, 45.31; H, 7.46.

3.86   Methyl (*E*)-3,7-diiodo-2-octenoate (150)
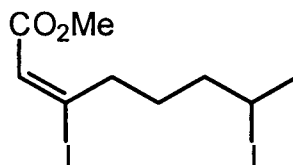
Iodine (0.08 g, 0.3 mmol) was added to a stirred solution of methyl (*E*)-3-(tri(*n*-butyl)stannyl)-7-iodo-2-octenoate (**144**) (0.19 g, 0.33 mmol) in 1.7 mL of dry methylene chloride.   After 1 hour the reaction mixture was diluted to 100 mL with ethyl acetate, washed with saturated Na$_2$S$_2$O$_3$ 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% diethy 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$_3$) δ: 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);

^{13}C NMR (50 MHz, CDCl$_3$) δ: 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 (CI(+), ammonia/methane)

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

Anal. Calcd for C$_9$H$_{14}$O$_2$I$_2$: C, 26.49; H, 3.46. Found: C, 26.71; H, 3.50.

3.87   Methyl (*E*)-3,8-diiodo-2-nonenoate (151)
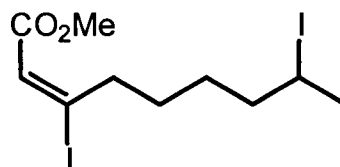
Methyl (*E*)- 8-iodo-3-(tri(*n*-butyl)stannyl)- 2-nonenoate (**145**) (0.14 g, 0.24 mmol) was converted to **151** following the procedure outlined in Section 3.86. The crude yellow oil was purified by flash chromatography, eluting with 2% diethyl ether / pet. ether to afford 0.10 g (100%) of **151** 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100), 295 (31);

HRMS (CI(+), ammonia/methane)

m/z calcd for C$_{10}$H$_{17}$O$_2$I$_2$ (M$^+$+1): 422.9318, found: 422.9301;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$I$_2$: C, 28.46; H, 3.82. Found: C, 28.70; H, 3.79.

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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (CI(+), ammonia) *m/z* (relative intensity): 298 (M$^+$+NH$_4$, 100), 281 (M$^+$+1, 20), 153 (25), 121 (30), 93 (65);

HRMS (CI(+), isobutane)

m/z calcd for $C_9H_{17}NO_2I$ (M$^+$+NH$_4$): 298.0304, found: 298.0305;

Anal. Calcd for $C_9H_{13}O_2I$: C, 38.59; H, 4.68. Found: C, 38.80; H, 4.58.

3.89 Methyl 8-iodo-2-nonynoate (153)
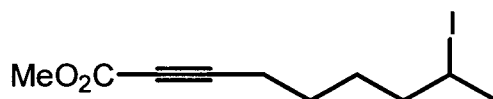
Methyl 8-hydroxy-2-nonynoate (133) (0.34 g, 1.9 mmol) was converted to 153 following the procedure outlined in Section 3.53. The crude material was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 0.52 g (96%) of 153 as a colourless oil. Kugelrohr distillation (140 °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$_3$) δ: 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 (CI(+), isobutane) *m/z* calcd for $C_{10}H_{16}O_2I$ (M$^+$+1): 295.0195, found: 295.0194;

Anal. Calcd for $C_{10}H_{15}O_2I$: C, 40.84; H, 5.14. Found: C, 41.09; H, 5.07.

3.90 Methyl (Z)-3,7-diiodo-2-octenoate (154)
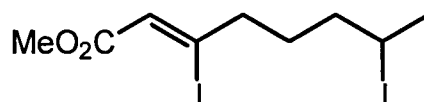
A solution of methyl 7-iodo-2-octynoate (152) (0.61 g, 2.1 mmol) and sodium iodide (0.51 g, 3.4 mmol) in acetic acid (0.80 mL, 14 mmol) was heated in 115 °C oil bath for 1.5 hours. The reaction mixture was diluted with diethyl ether, washed consecutively with water, saturated NaHCO$_3$ solution, saturated 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$_3$) δ: 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 (CI(+), 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) λ (ε): 332 (570), 250 (7000), 200 nm (9100);

Anal. Calcd for C$_9$H$_{14}$O$_2$I$_2$: C, 26.49; H, 3.46. Found: C, 26.80; H, 3.50.

3.91 Methyl (*Z*)-3,8-diiodo-2-nonenoate (155)
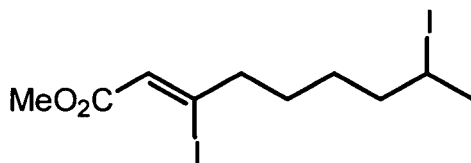
Methyl 8-iodo-2-nonynoate (**153**) (0.29 g, 1.0 mmol) was converted to **155** following the procedure outlined in Section 3.90. The crude yellow oil was purified by flash chromatography, eluting with 10% diethyl ether / pet. ether to afford 0.26 g (62%) of **155** as a colourless oil. Kugelrohr distillation (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$_3$) δ: 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$_3$) δ: 28.34, 28.92, 29.71, 42.43, 47.61, 51.58, 102.84, 121.43, 124.72, 164.81;

LRMS (DCl(+), 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)
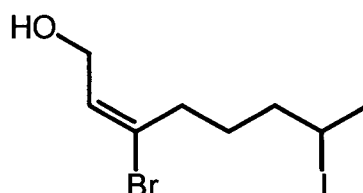
Diisobutylaluminum hydride (2.0 mL of 1.0 M solution in hexanes, 2.0 mmol), was added dropwise to a dry ice / acetone cooled solution of methyl (*E*)-3-bromo-7-iodo-2-octenoate (**108**) (0.33 g, 0.91 mmol) in 5.0 mL of dry methylene chloride. During the addition of the DIBAL, the initially colourless 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$_3$) δ: 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 (DCl(+), ammonia) *m/z* (relative intensity): 352 (^{81}Br, M$^+$+NH$_4$, 100), 350 (^{79}Br,

M$^+$+NH$_4$, 97), 334 (^{81}Br, M$^+$+1, 7), 332 (^{79}Br, M$^+$+1, 7);

HRMS (CI(+), ammonia/methane)

m/z calcd for C$_8$H$_{18}$NO^{81}BrI (M$^+$+NH$_4$): 351.9596, found: 351.9583;

m/z calcd for C$_8$H$_{18}$NO^{79}BrI (M$^+$+NH$_4$): 349.9617, found: 349.9614;

Anal. Calcd for C$_8$H$_{14}$OBrI: 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)
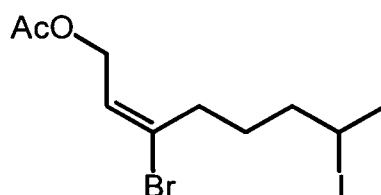
Pyridine (150 µl, 1.8 mmol) was added to a room temperature solution of (*E*)-3-bromo-7-iodo-2-octen-1-ol (**156**) (0.30 g, 0.90 mmol) and acetic anhydride (110 µl, 1.2 mmol) in 5.0 mL of dry methylene chloride. After 40 hours, TLC analysis indicated the reaction was completed. The reaction mixture 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$_3$) δ: 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 (DCl(+), ammonia) *m/z* (relative intensity): 394 (^{81}Br, M$^+$+NH$_4$, 100), 392 (^{79}Br,

M$^+$+NH$_4$, 87);

HRMS (CI(+), ammonia/methane)

m/z calcd for $C_{10}H_{20}NO_2{}^{81}BrI$ (M$^+$+NH$_4$): 393.9702, found: 393.9698;

m/z calcd for $C_{10}H_{20}NO_2{}^{79}BrI$ (M$^+$+NH$_4$): 391.9722, found: 391.9719;

Anal. Calcd for $C_{10}H_{16}O_2BrI$: C 32.03; H 4.30. Found: C 32.23; H 4.33.

3.94 (Z)-3-Bromo-7-iodo-2-octen-1-ol (158)
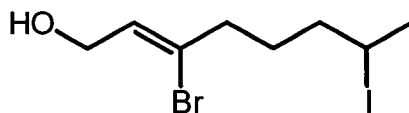
Methyl (Z)-3-bromo-7-iodo-2-octenoate (**109**) (2.67 g, 10.5 mmol) was converted to **158** following the procedure outlined in Section 3.92. The crude cloudy oil was purified by radial chromatography, eluting with 40% diethyl ether / pet. ether followed by Kugelrohr distillation (160 °C / 0.1 mm Hg) 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 100), 350 (^{79}Br, M$^+$+NH$_4$, 92), 334 (^{81}Br, M$^+$+1, 2), 332 (^{79}Br, M$^+$+1, 2);

HRMS (CI(+), ammonia/methane)

m/z calcd for $C_8H_{18}NO^{81}BrI$ (M$^+$+NH$_4$): 351.9596, found: 351.9591;

m/z calcd for $C_8H_{18}NO^{79}BrI$ (M$^+$+NH$_4$): 349.9617, found: 349.9624;

Anal. Calcd for $C_8H_{14}OBrI$: C 28.85, H 4.24. Found: C 29.03, H 4.12.

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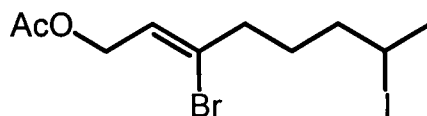
(*Z*)-3-Bromo-7-iodo-2-octen-1-ol (**158**) (0.43 g, 1.3 mmol) was converted to **159** following the procedure outlined in Section 3.93. The crude colourless oil was purified by radial chromatography, eluting with 10% diethyl ether / pet. ether followed by Kugelrohr distillation (180 °C / 0.1 mm Hg)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

IR (neat): 2936, 2864, 1742, 1660, 1442, 1374, 1237, 1031 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (^{81}Br, M$^+$+NH$_4$, 100), 392 (^{79}Br,
M$^+$+NH$_4$, 89);

HRMS (CI(+), ammonia/methane)

m/z calcd for C$_{10}$H$_{20}$NO$_2$^{81}BrI (M$^+$+NH$_4$): 393.9702, found: 393.9713;

m/z calcd for C$_{10}$H$_{20}$NO$_2$^{79}BrI (M$^+$+NH$_4$): 391.9722, found: 391.9728;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$BrI: 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)
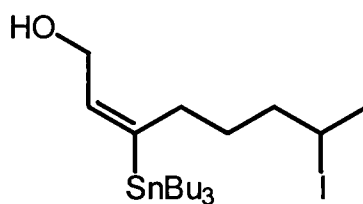
Methyl (*E*)-7-iodo-3-(tri(*n*-butyl)stannyl)-2-octenoate (**144**) (0.78 g, 1.4 mmol) was converted to **160** following the procedure outlined in Section 3.92. The crude cloudy oil was purified by radial chromatography, eluting with 25% diethyl ether / pet. ether to afford 0.69 g (93%) of **160** as 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$_3$) δ: 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 (EI) *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 (EI) *m/z* calcd for C$_{16}$H$_{32}$OI^{120}Sn (M$^+$-C$_4$H$_9$): 487.0520, found: 487.0524;

Anal. Calcd for C$_{20}$H$_{41}$OISn: C 44.23, H 7.61. Found: C 43.93, H 7.63.

3.97   (E)-1-Acetoxy-3,7-diiodo-2-octene (162)
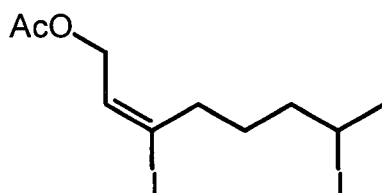
(E)-7-Iodo-3-(tri(n-butyl)stannyl)-2-octen-1-ol (160) (0.69 g, 1.3 mmol) was converted to (E)-1-acetoxy-7-iodo-3-(tri(n-butyl)stannyl)-2-octene (161) following the procedure outlined in Section 3.93. Purification by radial chromatography, eluting with 5% diethyl ether / pet. ether afforded 0.68 g (92%) 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$_3$) δ: 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);

HRMS (CI(+), ammonia/methane)

m/z calcd for $C_{10}H_{20}NO_2I_2$ (M^++NH_4): 439.9584, found: 439.9582;

Anal. Calcd for $C_{10}H_{16}O_2I_2$: C 28.46, H 3.82. Found: C 28.54, H 3.82.

3.98 (*Z*)-7-Iodo-3-(tri(*n*-butyl)stannyl)-2-octen-1-ol (163)
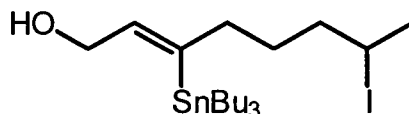
Methyl (*Z*)-7-iodo-3-(tri(*n*-butyl)stannyl)-2-octenoate (**148**) (0.86 g, 1.5 mmol) was converted to **163** following the procedure outlined in Section 3.92. The crude cloudy oil was purified by radial chromatography, eluting with 15% diethyl ether / pet. ether to afford 0.74 g (90%) of **163** as a colourless oil

IR (neat): 3347, 2922, 2853, 1455, 1377, 1004 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) 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, J$_{Sn-H}$ = 124 Hz, 1H);

LRMS (DCI(+), ammonia) *m/z* (relative intensity): 487 (^{120}Sn, M^+-C$_4$H$_9$, 44), 485 (^{118}Sn, M^+-C$_4$H$_9$, 39), 483 (^{116}Sn, M^+-C$_4$H$_9$, 23), 378 (100), 376 (68), 374 (39), 359 (77), 308 (100), 306 (78), 304 (43), 109 (82);

HRMS (CI(+), ammonia/methane)

m/z calcd for $C_{16}H_{32}OI^{120}Sn$ (M^+-C$_4$H$_9$): 487.0520, found: 487.0512.

3.99 (*Z*)-1-Acetoxy-3,7-diiodo-2-octene (165)
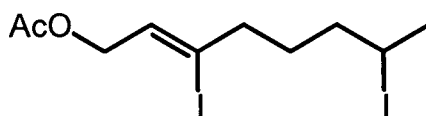
(*Z*)-7-Iodo-3-(tri(*n*-butyl)stannyl)-2-octen-1-ol (**163**) (0.74 g, 1.4 mmol) was converted to (*Z*)-1-acetoxy-7-iodo-3-(tri(*n*-butyl)stannyl)-2-octene (**164**) following the procedure outlined in Section 3.93. Purification by radial chromatography, eluting with

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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 100);

HRMS (CI(+), ammonia/methane)

m/z calcd for C$_{10}$H$_{20}$NO$_2$I$_2$ (M$^+$+NH$_4$): 439.9584, found: 439.9588;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$I$_2$: C 28.46; H 3.82. Found: C 28.77; H 3.86.

3.100 (*E*)-2-(2-Methylcyclopentylidene)ethanol (166)
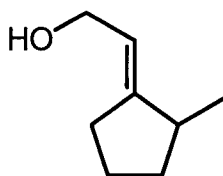
Method A. Via cyclization of compound **156**.

(*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 Na$_2$SO$_4$ solution. The

white precipitate was filtered, the organic layer was separated and was washed with $NaHCO_3$ 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (CI(+), isobutane) *m/z* (relative intensity): 127 (M$^+$+1, 0.7), 126 (M$^+$, 4), 125 (5), 109 (100), 82 (26), 67 (28);

HRMS (CI(+), isobutane) *m/z* calcd for C$_8$H$_{15}$O (M$^+$+1): 127.11229, found: 127.11253;

Anal. Calcd for C$_8$H$_{14}$O: C,75.77; H, 11.31. Found: C, 76.14; H, 11.18.

3.101 (Z)-2-(2-Methylcyclopentylidene)ethanol (167)
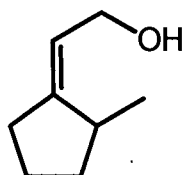
Method A. Via cyclization of compound **163**.

(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};

^{1}H NMR (400 MHz, CDCl$_3$) 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 (CI(+), isobutane) m/z (relative intensity): 127 (M$^+$+1, 0.5), 126 (M$^+$, 2), 125 (3), 109 (100);

HRMS (CI(+), isobutane) m/z calcd for C$_8$H$_{15}$O (M$^+$+1): 127.1122, found: 127.1120;

Anal. Calcd for C$_8$H$_{14}$O: C, 76.14; H, 11.18. Found: C, 75.98; H, 11.43.

3.102 (*E*)-1-(2-Acetoxyethylidene)-2-methylcyclopentane (168)
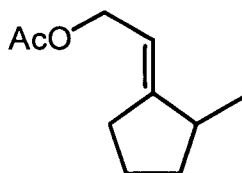
Method A. Via cyclization of compound **162**.

(*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, NaHCO$_3$ 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};

^{1}H NMR (400 MHz, CDCl$_3$) 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$^+$+NH$_4$, 11), 109 (100), 108 (57), 78 (35);

HRMS (CI(+), methane) *m/z* calcd for C$_{10}$H$_{17}$O$_2$ (M$^+$+1): 169.1228, found: 169.1229;

Anal. Calcd for C$_{10}$H$_{16}$O$_2$: C, 71.39; H, 9.59. Found: C, 71.13; H, 9.62.

3.103 (Z)-1-(2-Acetoxyethylidene)-2-methylcyclopentane (169)
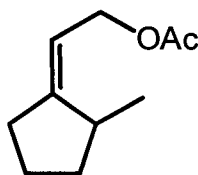
Method A. Via cyclization of compound **165**.

(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 (CDCl$_3$): 2959, 2871, 1729, 1242, 1024 cm^{-1};

¹H NMR (400 MHz, CDCl₃) δ: 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.

2   Paneth, F.; Hofeditz, W. *Chem. Ber.* **1929**, *62*, 1335.

3   Hey, D.H.; Waters, W.A. *Chem. Rev.* **1937**, *21*, 169.

4   Kharasch, M.S.; Margolis, E.T.; Mayo, F.R. *J. Org. Chem.* **1937**, *2*, 393.

5   Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, 1986.

6   Hart, D.J. *Science* **1984**, *223*, 883.

7   Laird, E.R.; Jorgensen, W.L. *J. Org. Chem.* **1990**, *55*, 9.

8   Curran, D.P. In *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B.M.; Fleming, I., Ed.; Pergamon, Oxford, 1991: Chapter 4.1.

9   Beckwith, A.L.J; Ingold, K.U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic, New York, 1980: Vol. 1, p. 162.

10 Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R.A., Ed.; Plenum, New York, 1982; Vol. 2, Chapter 3.

11 Caronna, T.; Citterio, A.; Ghirardini, M.; Minisci, F. *Tetrahedron*, **1977**, *33*, 793.

12 Baban, J.A.; Roberts, B.P. *J. Chem. Soc., Perkin Trans.* 2 **1981**, 161.

13 Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753.

14 Riemenschneider, K.; Drechsel-Grau, E.; Boldt, P. *Tetrahedron Lett.* **1979**, 185.

15 Curran, D.P. In *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry;* Trost, B.M.; Fleming, I., Ed.; Pergamon: Oxford, 1991; Chapter 4.2.

16 Beckwith, A.L.J. *Tetrahedron* **1981**, *37*, 3073.

17 Beckwith, A.L.J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472.

18 Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron Lett.* **1985**, *26*, 373.

19 Houk, K.N.; Spellmeyer, D.C. *J. Org. Chem.* **1987**, *52*, 959.

20 Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* **1980**, 482.

21 (a) Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* **1985**, *41*, 3925; (b) Beckwith, A.L.J.; Meijs, G.F. *J. Chem. Soc., Perkin Trans.* 2 **1979**, 1535.

22 (a) RajanBabu, T.V.; Fukanaga, T.; Reddy, G.S. *J. Am. Chem. Soc.* **1989**, 111, 1759; (b) RajanBabu, T.V.; Fukanaga, T. *J. Am. Chem. Soc.* **1989**, *111*, 296.

23   Jackson, R.A. *J. Organomet. Chem.* **1979**, *166*, 17.

24   Carlsson, D.J.; Ingold, K.U. *J. Am. Chem. Soc.* **1968**, *90*, 7047.

25   Beckwith, A.L.J.; Pigou, P.E. *Aust. J. Chem.* **1986**, *39*, 1151.

26   Ingold, K.U.; Lusztyk, J.; Scaiano, J.C. *J. Am. Chem. Soc.* **1984**, *106*, 343.

27   Stork, G.; Sher, P.M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

28   (a) Curran, D.P. *Synthesis* **1988**, *9*, 417;   (b) Curran, D.P. *Synthesis*, **1988**, *9*, 489.

29   Simpkins, N.S. In Encyclopedia of Reagents for Organic Synthesis; Paquette, L.A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 1, p. 229.

30   Brown, H.C. *Boranes in Organic Chemistry*; Cornell University: London, 1972; p. 433.

31   Ichinose, Y.; Nozaki, K.; Wakamatsu, K.; Oshima, K. *Tetrahedron Lett.* **1987**, *28*, 3709.

32   (a) Curran, D.P.; Rakiewicz, D.M. *Tetrahedron*, **1985**, *41*, 3943;   (b) Curran, D.P.; Rakiewicz, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 1448;   (c) Curran, D.P.; Chen, M.H. *Tetrahedron Lett.* **1985**, *26*, 4991;   (d) Curran, D.P.; Kuo, SC. *J. Am. Chem. Soc.* **1986**, *108*, 1106;   (e) Curran, D.P.; Jasperse, C.P. *J. Am. Chem. Soc.* **1990**, *112*, 5601.

33   Ohnuki, T.; Yoshida, M.; Simamura, O. *Chem. Lett.* **1972**, 797.

34   Kuivila, H.G.; Sommer, R. *J. Am. Chem. Soc.* **1967**, *89*, 5616.

35   Wedegaertner, D.K.; Kopchik, R.M.; Kampmeier, J.A. *J. Am. Chem. Soc.* **1971**, *93*, 6890.

36   Ohnuki, T.; Yoshida, M.; Simamura, O.; Fukuyama, M. *Chem. Lett.* **1972**, 999.

37   Bennett, J.E.; Howard, J.A. *Chem. Phys. Lett.* **1971**, *9*, 460.

38   (a) Fessenden, R.W.; Schuler, R.H. *J. Chem. Phys.* **1963**, *39*, 2147;   (b) Cochran, E.L.; Adrian, F.J.; Bowers, V.A. *J. Chem. Phys.* **1964**, *40*, 213.

39   Singer, L.A.; Kong, N.P. *J. Am. Chem. Soc.* **1966**, *88*, 5219.

40   Munt, S.P.; Thomas, E.J. *J. Chem.Soc., Chem. Comm.* **1989**, 480.

41   Baldwin, J.E.; Kelly, D.R. *J. Chem. Soc., Chem. Commun.* **1985**, 682.

42   (a) Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1985**, *26*, 4975;   (b) Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1986**, *27*, 3479;   (c) Russell, G.A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622.

43   Harris, F.L.; Weiler, L. *Tetrahedron Lett.* **1987**, *28*, 2941.

44   Lowinger, T.B. Ph.D. Thesis, University of British Columbia, July 1991.

45   Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681.

46   Sonnet, P.E. *Tetrahedron* **1980**, *36*, 557.

47   Rokach, J.; Young, R.N.; Kakushima, M. *Tetrahedron Lett.* **1981**, *22*, 979.

48   Ferreri, C.; Ballestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* **1993**, *34*, 5147.

49   Chatgilialoglu, C.; Ballestri, M.; Ferreri, C.; Vecchi, D. *J. Org. Chem.* **1995**, *60*, 3826.

50   Lowinger, T.B.; Weiler, L. *J. Org. Chem.* **1992**, *57*, 6099.

51   Lolkema, L.D.M.; Hiemstra, H.; Ghouch, A.A.A.; Speckamp, W.N. *Tetrahedron Lett.* **1991**, *32*, 1491.

52   (a) Bohme, H.; Krack, W. *Liebigs Ann. Chem.* **1977**, 51; (b) Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1983**, *24*, 1711.

53   (a) Booth, H.; Dixon, J.M.; Khedhair, K.A. *Tetrahedron* **1992**, *48*, 6161; (b) Jensen, F.R.; Bushweller, C.H.; Beck, B.H. *J. Am. Chem. Soc.* **1969**, *91*, 344; (c) Eliel, E.L.; Reese, M.C. *J. Am. Chem. Soc.* **1968**, *90*, 1560; (d) Tichy, M.; Sipos, F.; Sicher, J. *Coll. Czech. Chem. Commun.* **1966**, *31*, 2889.

54   (a) Booth, H.; Everett, J.R. *J. Chem. Soc., Perkin Trans 2* **1980**, 255; (b) Hirsch, J.A. *Topics Stereochem.* **1967**, *1*, 199.

55   Eliel, E.L.; Hargrave, K.D.; Pietrusiewicz, K.M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635.

56   Arya, P.; Samson, C.; Lesage, M.; Griller, D. *J. Org. Chem.* **1990**, *55*, 6248.

57   Yadav, V.K.; Fallis, A.G. *Tetrahedron Lett.* **1988**, *29*, 897.

58   Burke, S.D.; Jung, K.W. *Tetrahedron Lett.* **1994**, *35*, 5837.

59   Huval, C.C.; Singleton, D.A. *Tetrahedron Lett.* **1993**, *34*, 3041.

60   Curran, D.P., Chang, C-T. *Tetrahedron Lett.* **1987**, *28*, 2477.

61   Curran, D.P. ; Chang, C-T. *J. Org. Chem.* **1989**, *54*, 3140.

62   (a) Cornish, C.A.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2585; (b) Cannon, G.W.; Ellis, R.L.; Leal, J.R. *Org. Synth.* **1951**, *31*, 74.

63   (a) Menapace, L.W.; Kuivila, H.G. *J. Am. Chem. Soc.* **1964**, *86*, 3047; (b) Carlsson, D.J.; Ingold, K.U. *J. Am. Chem. Soc.* **1968**, *90*, 7047.

64   Corey, E.J.; Pyne, S.G.; Su, W.G. *Tetrahedron Lett.* **1983**, *24*, 4883.

65   Kang, S.K.; Kim, W.S.; Moon, B.H. *Synthesis* **1985**, 1161.

66   Brown, H.C.; Geoghegan, P.Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522.

67   Hanessian, S.; Dhanoa, D.S.; Beaulieu, P.L. *Can. J. Chem.* **1987**, *65*, 1859.

68   Piers, E; Chong, J.M.; Morton, H.E. *Tetrahedron* **1989**, *45*, 363.

69   Leusink, A.J.; Budding, H.A.; Marsman, J.W. *J. Organometal. Chem.* **1967**, *9*, 285.

70   Piers, E.; Wong, T.; Coish, P.D.; Rogers, C. *Can J. Chem.* **1994**, *72*, 1816.

71   Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals* 3rd.ed.; Pergamon: New York, 1988.

72   Kofron, W.G.; Baclawski, L.M.J. *J. Org. Chem.* **1976**, *41*, 1879.

73   Kuivila, H.G.; Beumel, O.F. *J. Am. Chem. Soc.* **1961**, *83*, 1246.

74   House, H.O.; Chu, C.Y.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem.* **1975**, 1460.

75   Still, W.C.; Kahn, M.; Mirta, A. *J. Org.Chem.* **1978**, *43*, 2923.

36

37

40

integral

1.0000 4.0914 2.0437 7.5169

(ppm)

% Transmittance

Wave number (cm−1)

41

CO₂Me

OTHP

42

CO₂Me

OTHP

43

CO$_2$Me

OH

44

Integral

4.7188

1.0000
1.8686

(ppm)

7   6   5   4   3   2   1   0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm−1)

CO$_2$Me

OH

45

integral

5.1164

2.0000

3.1472

7   6   5   4   3   2   1   0

(ppm)

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm−1)

PhS⌒CO₂Me

47

Cl
|
PhS—CH—CO₂Me

48

MeO$_2$C

CO$_2$Me

49

% Transmittance

Wave number (cm—1)

50

MeO₂C

CO₂Me

51

% Transmittance

Wave number (cm−1)

MeO$_2$C

CO$_2$Me

O

52

% Transmittance

Wave number (cm−1)

53

55

56

57

Integral: 4.8870, 1.0000, 4.6272, 2.1284, 0.6583, 9.4043, 5.7396

(ppm)

% Transmittance

Wave number (cm−1)

58

CO₂Me

59

63

MeO$_2$C — / = / — O — / — OH
SnBu$_3$ SPh

CO$_2$Me

CO$_2$Me

O

PhS   Me

71

Integral 4.8488 1.9744 5.7861 2.0000 2.9603

8   7   6   5   4   3   2   1   0
(ppm)

72

MeO₂C

CO₂Me
Me

73

Wave number (cm−1)

CO$_2$Me

CO$_2$Me

Me

O

74

Integral

0.8000

2.0886

5.8182

2.0197

3.3943

(ppm)

7 6 5 4 3 2 1 0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200 2400 1600 800

Wave number (cm−1)

MeO$_2$C

CO$_2$Me

Me

O

75

CO₂Me
CO₂Me
Me
O

76

77

85

86

CO$_2$Me

OTHP

CO₂Me

OH

87

Integral

5.1612

2.0000

5.1691

7   6   5   4   3   2   1   0

(ppm)

100
90
80
70
60
50
40
30
20
10
0

% Transmittance

3200   2400   1600   800

Wave number (cm—1)

MeO₂C

Br

OH

88

Integral   0.6752   4.6902   2.0000   4.5253

(ppm)

% Transmittance

Wave number (cm−1)

89

MeO$_2$C

Br

Br

90

Integral

0.7415

7.1409

4.0000

7 6 5 4 3 2 1 0

(ppm)

100
90
80
70
60
50
40
30
20
10
0

% Transmittance

3200 2400 1600 800

Wave number (cm-1)

CO₂Me

Br

Br

91

Integral

1.0000

3.3165

2.2278

2.3431

4.3267

(ppm)

CO₂Me

92

Integral

1.0000

3.0641

1.9988

1.9964

4.5621

(ppm)

% Transmittance

Wave number (cm−1)

MeO$_2$C

93

Integral

0.9000 2.9901 2.9995 1.9435 1.1071 4.0165

7 6 5 4 3 2 1 0

(ppm)

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200 2400 1600 800

Wave number (cm−1)

94

CO₂Me

98

Integral

4.2916

2.1102
1.0000
4.3557

3.1868

(ppm)

% Transmittance

Wave number (cm−1)

99

% Transmittance

Wave number (cm−1)

100

Integral

1.8733 0.9241 4.8554 2.9311

(ppm)

101

Integral

1.0000   2.0190 1.0322   1.95.39   11.277   3.2231

(ppm)

% Transmittance

Wave number (cm−1)

CO$_2$Me

OTHP

102

Integral

1.0297
5.1880
1.0000
1.9201
10.437
3.1118

(ppm)

% Transmittance

Wave number (cm−1)

103

CO2Me

OH

Integral

3.7175 2.0000 5.1367 3.2004

(ppm)

% Transmittance

Wave number (cm−1)

104

105

MeO₂C

106

Integral

0.6955

1.0000

3.1158

2.2710

7.3405

(ppm)

% Transmittance

Wave number (cm−1)

CO2Me

Br

Br

107

108

109

MeO₂C

Br

I

110

111

Br⌒⌒⌒OTHP

114

Integral

1.0000 1.9327 3.9113 12.486

(ppm)

% Transmittance

Wave number (cm−1)

115

Integral

1.0000
2.0700
1.9905
2.0080
13.719

(ppm)
7 6 5 4 3 2 1 0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200 2400 1600 800

Wave number (cm−1)

CO$_2$Me

116

Integral

1.0000 5.0339 1.9985 1.9746 12.435

(ppm)

7 6 5 4 3 2 1 0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200 2400 1600 800

Wave number (cm−1)

117

Integral
5.3456
2.0743
1.0000
6.4612

(ppm)

% Transmittance

Wave number (cm−1)

118

119

Integral

0.8181

4.8537

2.0000

6.9169

7 6 5 4 3 2 1 0
(ppm)

MeO₂C

Br

I

120

Integral
0.7850
3.0000
4.3470
7.3293

(ppm)

% Transmittance

Wave number (cm−1)

121

CO2Me

122

Integral 0.8000 2.8857 1.9529 2.0238 6.2060

(ppm)

7 6 5 4 3 2 1 0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200 2400 1600 800

Wave number (cm—1)

128

129

CO₂Me

OTHP

130

Integral

(ppm)

% Transmittance

Wave number (cm−1)

CO$_2$Me

OH

131

Integral

4.0287 2.0000 7.5576 3.0323

(ppm)

% Transmittance

Wave number (cm−1)

MeO$_2$C

Br

OH

132

Integral

0.7626

3.6611

2.0000

6.7195

2.9117

7   6   5   4   3   2   1   0

(ppm)

100
90
80
70
60
50
40
30
20
10
0

% Transmittance

3200   2400   1600   800

Wave number (cm−1)

133

134

CO2Me

Br

I

135

Integral

0.8810

1.0000
3.1890

2.1666

4.4013

6.0576

(ppm)

7   6   5   4   3   2   1   0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm-1)

MeO$_2$C

SnBu$_3$

OTHP

140

Integral: 1.0000 0.9868 5.0312 0.9576 1.8915 40.229

(ppm)

% Transmittance

Wave number (cm−1)

141

142

MeO$_2$C

SnBu$_3$

OH

143

Integral   0.8500   3.8929   2.0169   35.673

(ppm)

% Transmittance

Wave number (cm−1)

144

MeO$_2$C

SnBu$_3$

I

145

Integral

0.9000

1.0387

3.5139

2.3190

28.311

14.989

7 6 5 4 3 2 1 0

(ppm)

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm—1)

146

147

148

149

MeO₂C

150

Integral 0.7212 1.0000 3.0072 2.2925 7.5625

(ppm)

% Transmittance

Wave number (cm−1)

MeO$_2$C

151

Integral

0.7320

1.0000

3.1354

2.2328

4.2978

5.6899

7   6   5   4   3   2   1   0

(ppm)

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm$-$1)

CO₂Me

152

Integral

1.0000 3.0759 2.0624 7.2272

(ppm)

% Transmittance

Wave number (cm−1)

CO$_2$Me

153

Integral

1.0000
3.0186
1.9258
9.2679

(ppm)

7   6   5   4   3   2   1   0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm−1)

154

CO₂Me

155

Integral

1.0000

1.0132

2.9793

2.0021

9.1881

(ppm)

% Transmittance

Wave number (cm−1)

156

157

Integral

0.7672   2.0891 1.0000   2.2016 10.020

(ppm)

7   6   5   4   3   2   1   0

% Transmittance

100
90
80
70
60
50
40
30
20
10
0

3200   2400   1600   800

Wave number (cm−1)

158

Integral
0.9000
2.8802
2.0691
8.5652

(ppm)

159

160

162
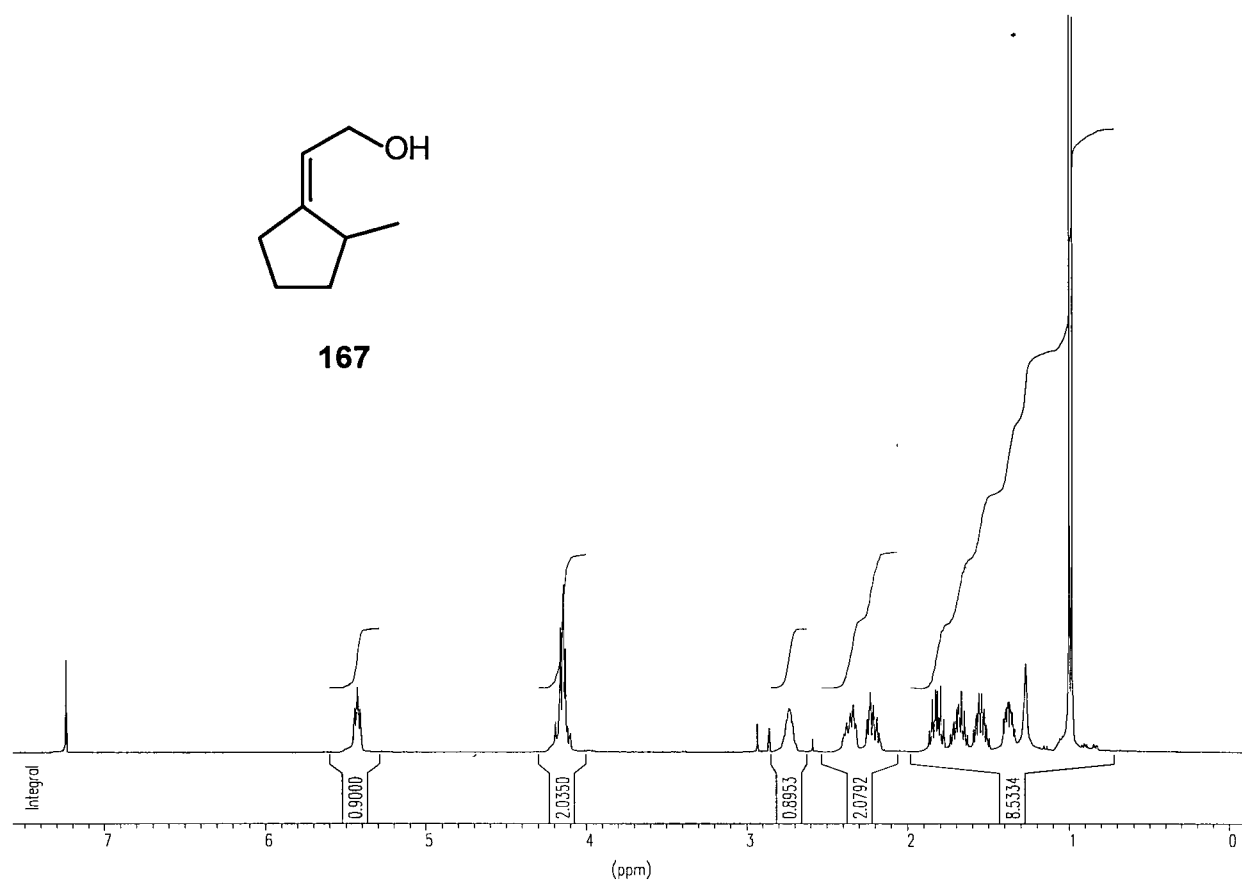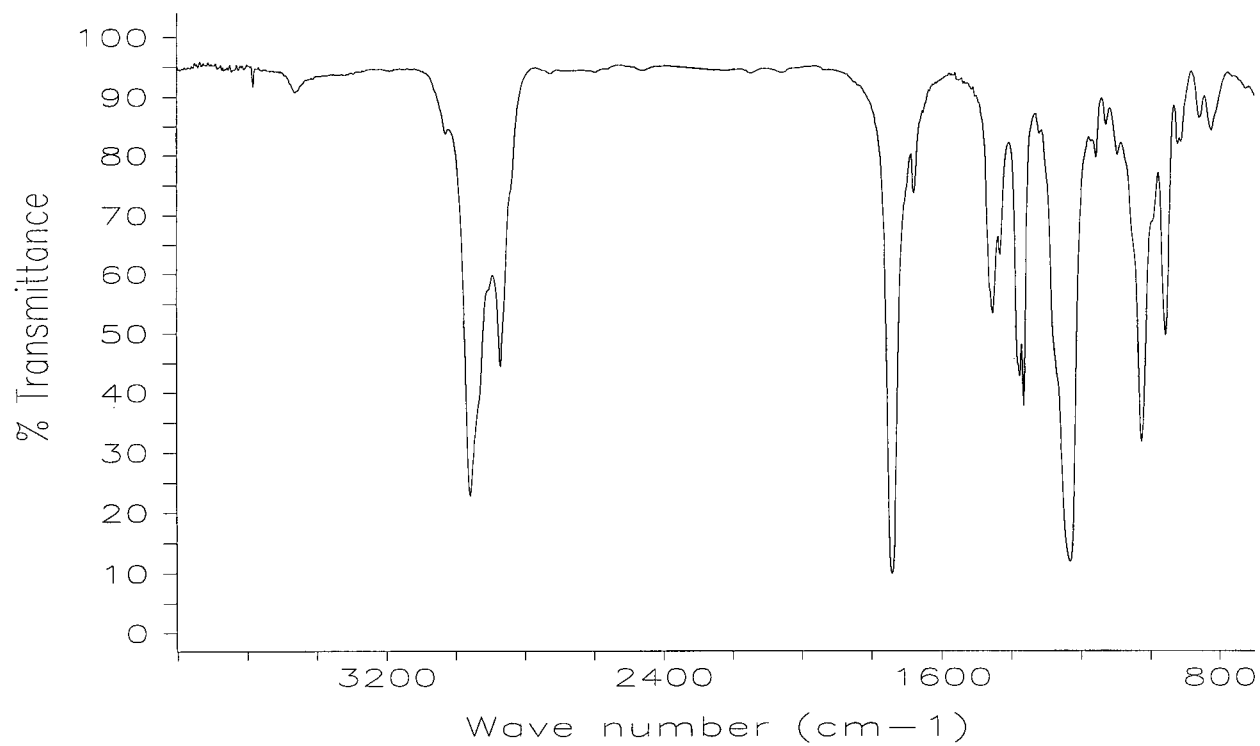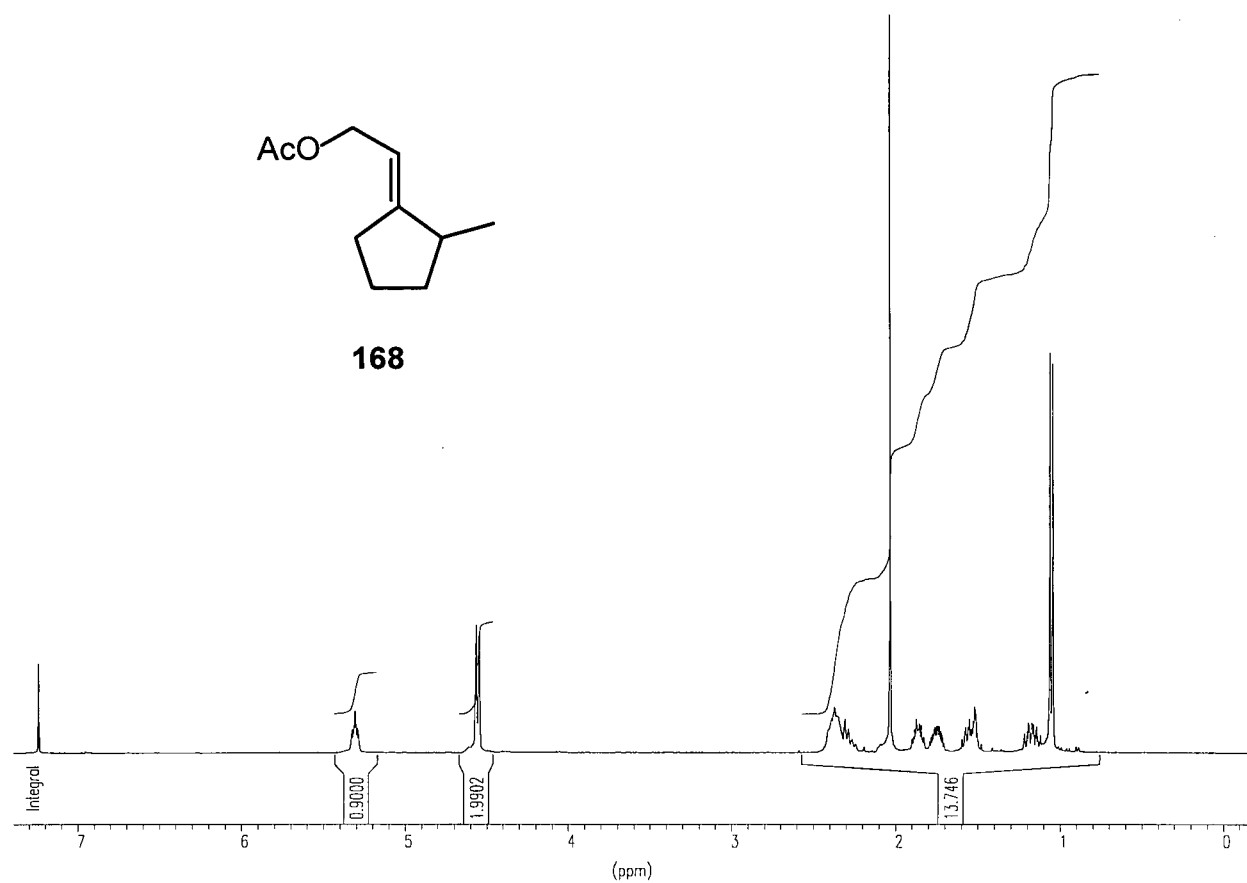

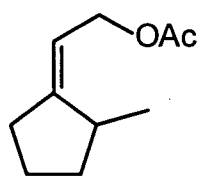Integral

0.7565

2.2547
1.0000

2.2796
10.698

(ppm)

% Transmittance

Wave number (cm−1)

163

165

166

167

168

169