A SYNTHESIS OF (*E,E*) SUSPENSOLIDE

by

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A Synthesis of (E,E) Suspensolide

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ABSTRACT

The aim of the current work was to explore the addition of various metallometallic reagents to allenes and alkynes in an attempt to control regio - and stereoselection. The goal was to use the dimetallic species generated in these reactions in the synthesis of tri-substituted alkenes. As an illustration of the synthetic potential of these processes a convergent preparation of (*E,E*) suspensolide, or 3(*E*),8(*E*)-4,8-dimethyl-decadienolide, the most recently isolated sex pheromone from the Caribbean fruit fly, *Anastrepha suspensa,* was undertaken.

The molecule has three functional groups that make metallometallation attractive as a process for its elaboration. First, there are **two** tri-substituted alkenes, secondly an allylic alcohol and thirdly a homoallylic alcohol is present. Thus, a variety of allene and alkyne metallometallations, as well as carboalumination and cupration reactions were studied.

It was found that stannylzincation of a protected alkynyl alcohol produced one trisubstituted alkene moiety and the allylic alcohol while the second alkene was generated by methylalumination of an additional alkyne. The required homoallylic alcohol was produced *via* alanate opening of ethylene oxide. The alanate was produced in the methylalumination reaction. The two synthons generated from these processes were subsequently coupled utilizing higher order cuprate chemistry. The required carboxylic acid residue was produced *via* oxidation of the homoallylic alcohol to an aldehyde, and thence to the acid. The protecting group of the remaining allylic alcohol was removed and the resulting dienic hydroxyacid lactonized using the Mitsunobu procedure to yield suspensolide.

DEDICATION

I would like to dedicate this work to the most important people in my life.

Shirley, Cynthia, Laura, Sherry, Heather, Petra and to the memories of James and Mary.

ACKNOWLEDGEMENTS

Grateful thanks go to my Supervisor, Dr. Oehlschlager, who has allowed me the freedom to explore my own ideas, and to his group that has shared with me their valuable experiences.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Anal calcd	Analytical calculated
bp	Boiling point
br	Broad
ca	Approximately
cat	Catalyst
CI	Chemical impact
Cp	Cyclopentadienyl
DEAD	Diethyl azodicarboxylate
DIBAlH	Diisobutylaluminum hydride
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
EI	Electron impact
eq	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
GC	Gas chromatography
HMPA	Hexamethylphosphoramide
HOAc	Acetic acid

hr	Hour
iso	Isothermal
LAH	Lithium aluminum hydride
LDA	Lithium diisopropyl amide
M	Molar
Me	Methyl
MEK	Methyl ethyl ketone
min	Minute
MPLC	Medium performance liquid chromatography
MS	Mass spectrometry
n	Normal
NBS	*N*-bromosuccinamide
NMR	Nuclear magnetic resonance
o	Ortho
p	Para
PDC	Pyridinium dichromate
Ph	Phenyl
p-TsOH	Para-toluenesulfonic acid
rbf	Round bottom flask
rt	Room temperature
satd	Saturated

t	Tertiary
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin layer chromatography
UV	Ultra violet

With respect to Infra red Spectroscopy:

s	Strong intensity
m	Medium intensity
w	Weak intensity

With respect to NMR:

d	Doublet
m	Multiplet
p	Pentet
q	Quartet
s	Singlet
sex	Sextet
t	Triplet

Combinations of the above letters are formed. Example: dt = doublet of triplets.

A SYNTHESIS OF (*E,E*) SUSPENSOLIDE

INTRODUCTION

Since the first reported isolation of a pheromone was bombykol, **1**, from the silkworm moth *Bombyx mori*, in 1959[1] the use of pheromones for monitoring and biorational control has become an exciting and dynamic field. To date, hundreds of pheromones have been isolated, characterized and synthesized including (-)- invictolide **2** from the red imported fire ant,[2] and periplanone-B **3** from the American cockroach[3] (Figure 1).

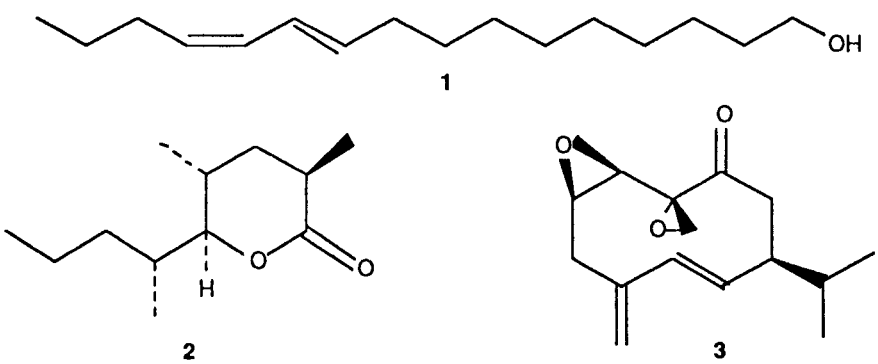


Figure 1. Examples of pheromones from isolation and synthesis.

More recently, the Mexican fruit fly, *Anastrepha ludens*, and the closely related Caribbean fruit fly, *Anastrepha suspensa*, have received attention as two economically important pests of fruit for which monitoring and control strategies are currently being sought. The Mexican species destroys 10 % of the citrus and an additional 5 % of other annual food crops in Mexico.[4] Although normally economically damaging only in Mexico, this fly has been detected in citrus groves in the Southwestern United States.[4] The Caribbean fly has enjoyed a continual habitat in Florida since 1965,[5] destroying the fruits of at least 84 species of plants.[6] Its most important host is guava,[6] although it also attacks common citrus fruits,[5] peaches[5] and tropical almonds.[5] Current methods of controlling these flies suffer from several disadvantages. The use of the common fumigant ethylene dibromide, while effective in killing *Anestrepha* larvae, has been curtailed due to health hazards.[7] Attracting and capturing the insects with protein lures,[4] such as alkaline enzymatic casein hydrolysates that slowly produce ammonia,[8] are inefficient and species non-specific. Attraction of flies to

previously captured adults decreases dramatically once sexually mature males are introduced into the test area.[9]

In view of the problems with current methods of monitoring and control, development of management strategies for these flies using their pheromones is of significant interest. To date, compounds (**4** - **8**) (Figure 2) have been isolated from volatiles of the Mexican species, and (**4** - **9**) from the Caribbean fly. Compound **9** is the most recently isolated and has been assigned the name suspensolide[10] for 3(*E*),8(*E*)-4,8-dimethyl-decadienolide. This pheromone, as well as anastrephin **4**, epianastrephin **5**, 3(*Z*),6(*Z*)-nonadienol **6**, 3(*Z*)-nonenol **7**, and bisabolene **8**, is produced by calling males and all are required in combination to attract virgin females.[9]

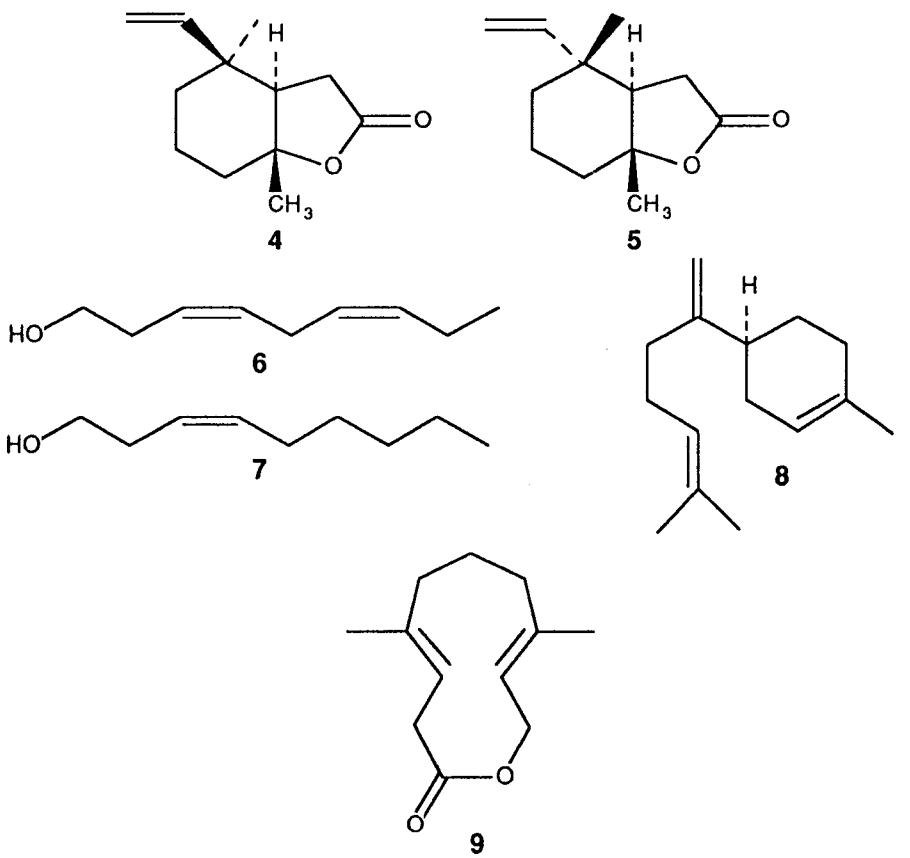


Figure 2. *Anastrepha* volatile pheromone components.

The synthesis of **9** can easily be envisioned by cyclization of the corresponding hydroxy-acid **10**. In fact, **9** has been prepared twice previous to

this work using this concept.[11,12] As well, this methodology also allows for the synthesis of compounds **4** and **5** *via* Lewis acid catalyzed ring formation (Figure 3).[13]

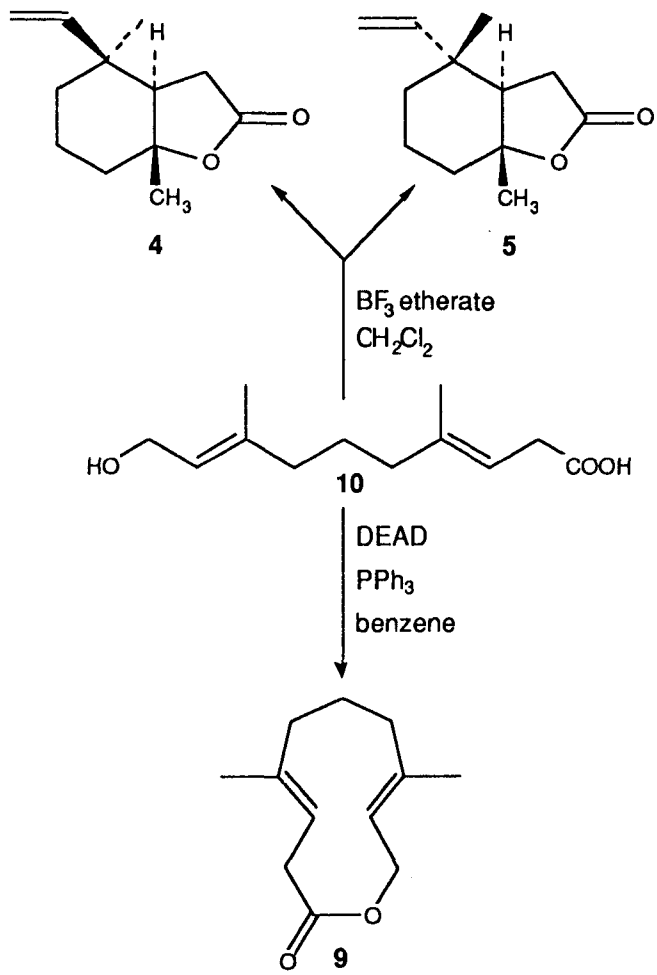


Figure 3. Different uses of hydroxy-acid **10.**

Previous syntheses of **10** involved long sequences with many protection-deprotection sequences and produced unfavorable stereoisomer *E/Z* ratios. The purpose of the author's synthesis was to therefore explore other, more efficient and stereospecific synthetic routes to suspensolide. The strategy in the present synthesis was to focus on the construction of the two *E* trisubstituted alkene moieties. Specifically, both have methyl groups appended. The three methods examined for construction of these fragments were bismetallation of allenes and alkynes, processes whereby two metals are added across the unsaturation. As

well, carbometallation of alkynes, where a metal and an alkyl residue are simultaneously added was explored.

A survey of the literature revealed that a variety of bisorganometallic reagents add to allenes and alkynes stereo and regiospecifically, and that these reagents often tolerate such functional groups as OAc, Br, OTHP, OH, and CN.[14] Control of regiochemistry is important since if the allene is unsymmetrical, such additions can lead to 6 products (Figure 4).

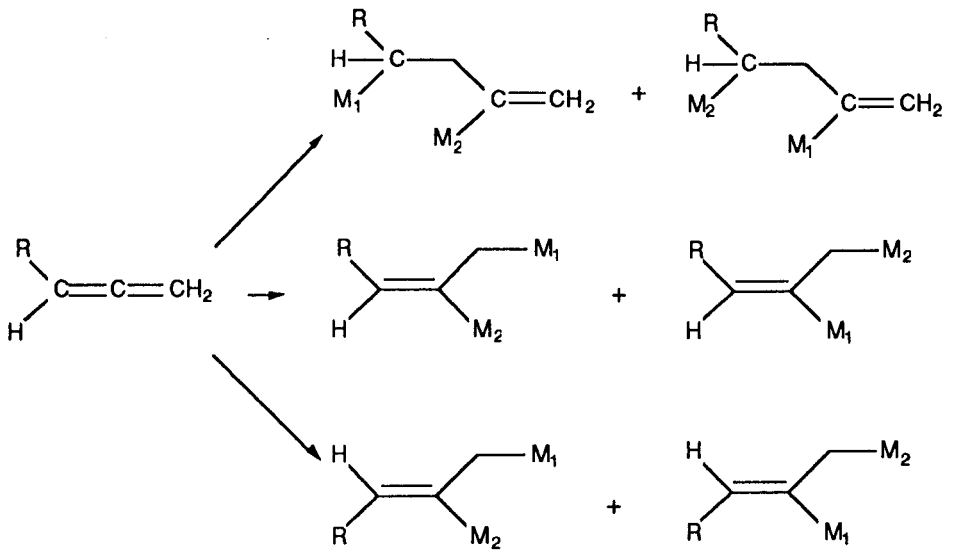


Figure 4. The six possible adducts from allene metallometallation.

The control of regiochemistry has been systematically studied by several groups. For example, Mitchell, *et al*,[15] have added **11** to **12** (Figure 5) in the presence of catalytic amounts of $Pd(PPh_3)_4$ to form **13** and **14** in equal amounts.

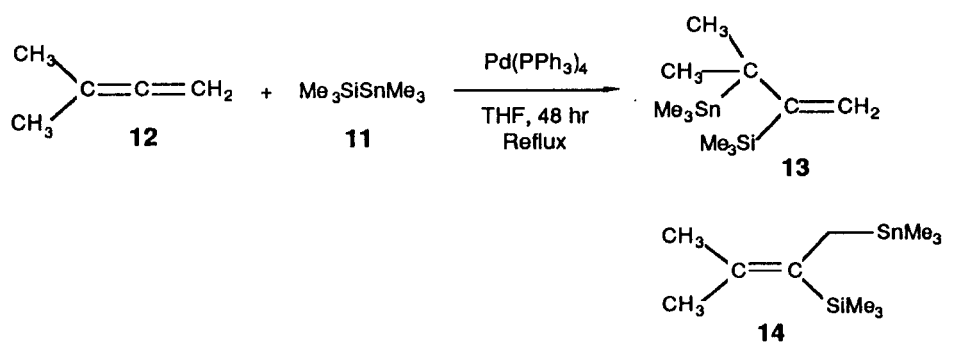


Figure 5. Mitchell *et al* results of palladium catalysis of **11** to **12**.

The authors claim that the initial mixture can be altered to consist of 80 % of **14** by heating to 90 °C for 15 hours with 1 mol % $Pd(PPh_3)_4$. The differential reactivity of the carbon metal bonds of these species lies in transmetallation of the tin followed by electrophilic capture, then allows silicon removal with *n*-Bu_4NF.

Fleming and co-workers[16] have reported the reaction of various allenes with **16** (Figure 6). This reagent was prepared *via* the reaction of 2 eq of phenyldimethylsilyl lithium with copper(I) cyanide. These authors claim *syn* addition across the least substituted unsaturation, to yield vinylcuprate **17** and allyl cuprate **18**. The C-Cu bonds of these adducts reacted preferentially with electrophiles to yield **19** and **20**.

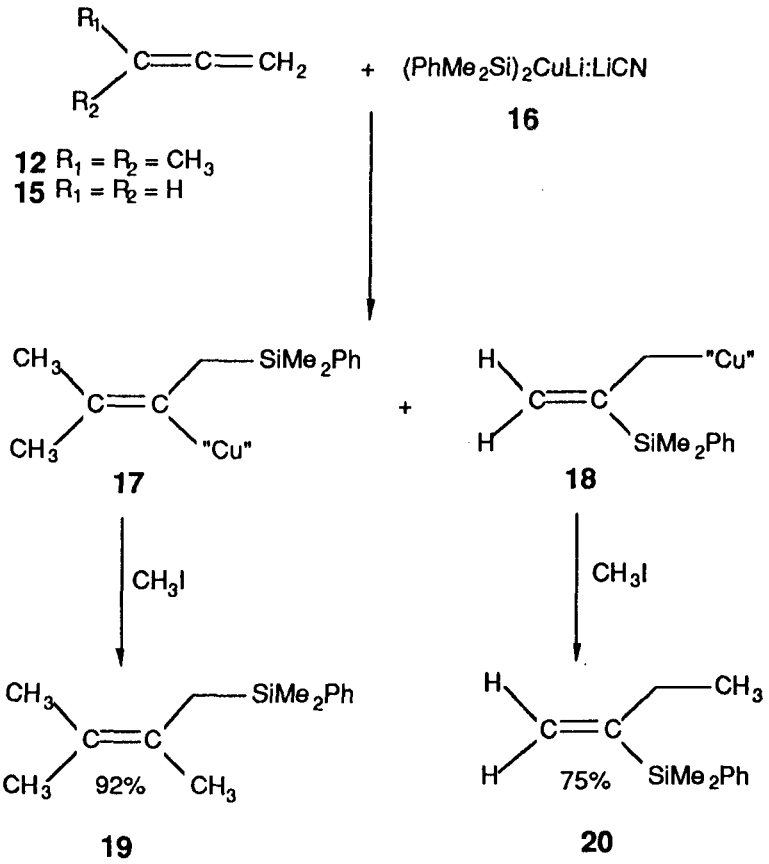


Figure 6. Fleming *et al* results of *syn* addition to various allenes.

Oshima and co-workers[17] have systematically studied additions of various bisorganometallics to **21** (Figure 7). Depending on the composition of the dimetalloid, either vinylsilanes **22** or allylsilanes **23** were formed. As well, using the conditions leading to **22** with different electrophiles shows how the *E* to *Z* ratio may be manipulated. Although the authors offer no explanation for the *E/Z* ratios observed, it is possible that the organocopper intermediate is undergoing fast *E/Z* isomerization. Electrophilic capture of the C-Cu bond with Me_3SiCl favours the intermediate affording the *E* isomer, while capture with MeCl favours the *Z* isomer.

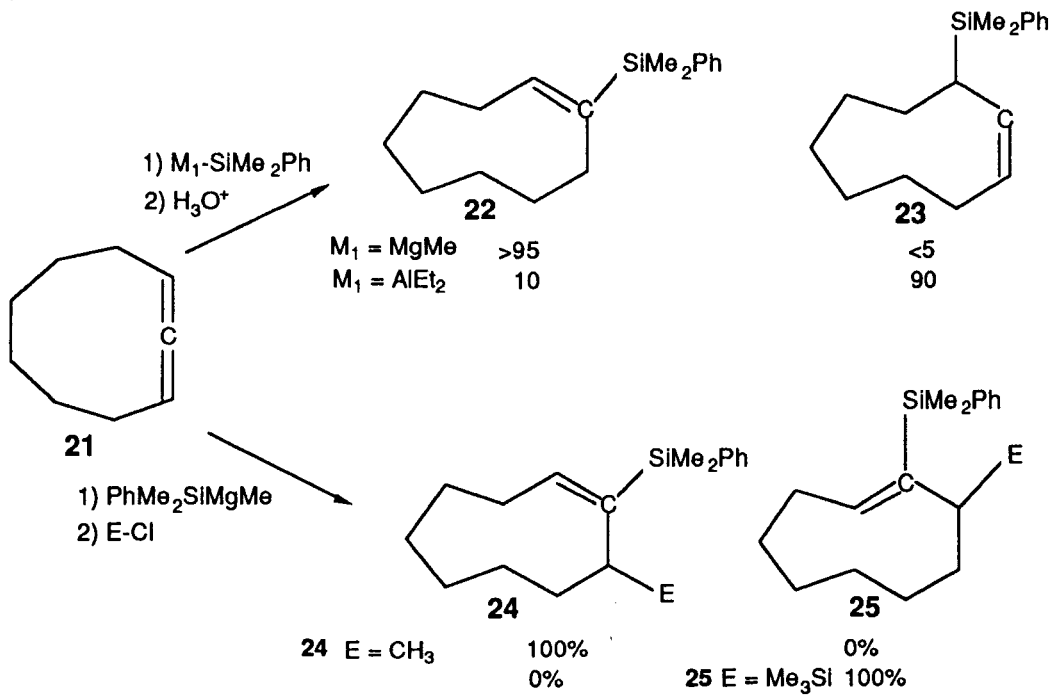


Figure 7. Oshima *et al* systematic study of bisorganometallic additions to **21**.

The use of symmetrical diorganometallic reagents avoids the problem of regioselectivity. Killing and Mitchell[18] report the low temperature addition of hexamethylditin to substituted allenes (Figure 8) such as **26** affording the vinyl-allyl distannes **27** and **29**. It was noted that at higher temperatures, **27** rearranges to **28** and **29**. All three products were not stable to distillation and decomposed to allenes and hexamethylditin. Based on these observations, it was suggested that distannylation was a reversible process. Although no mechanistic studies were conducted, the rearrangements were postulated to proceed *via* π-allyl complexes **30** and/or **31**.

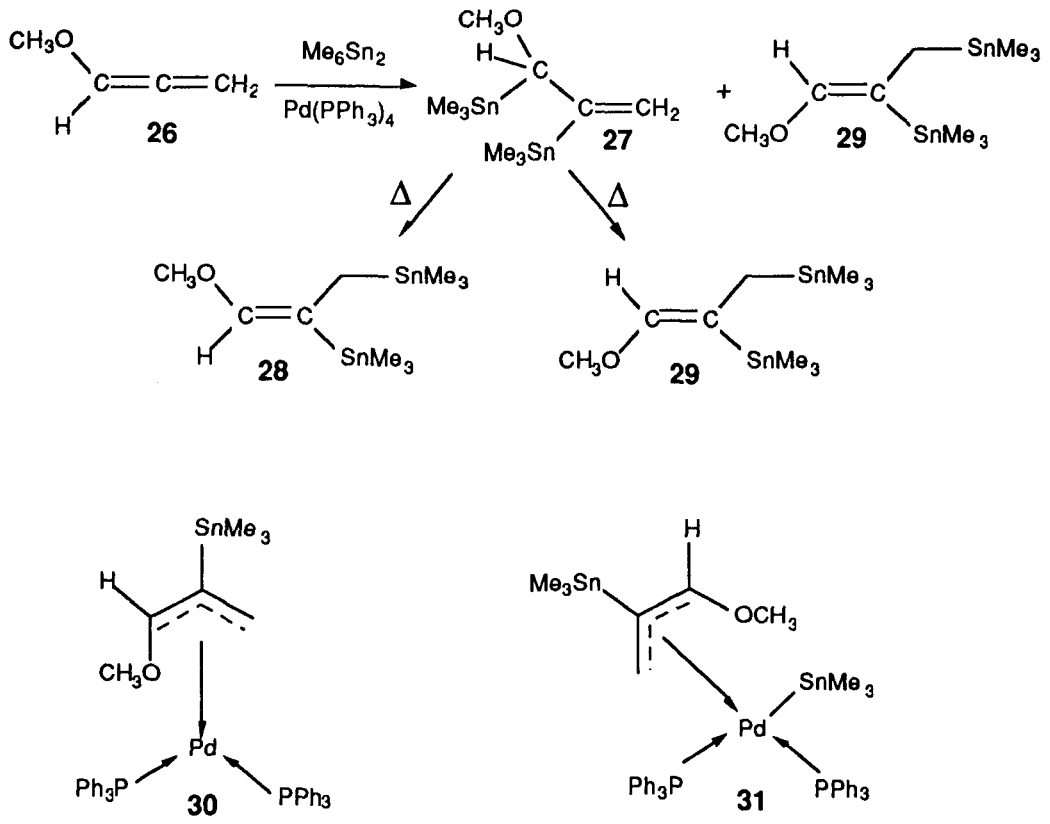


Figure 8. Mitchell and Killing's hexamethylditin additions to substituted allenes.

While numerous studies on allenes have been performed, the majority of metallometallations, however, have been conducted on 1-alkynes. While potentially synthetic useful processes, these reactions are generally influenced by three problems. First, they usually require at least a two-fold excess of reagent to consume the alkyne. This excess reagent leads to organometallic by-products which are difficult to remove from the reaction products, unless the alkyne contains a polar functional group. Second, regiochemical selectively is marginal for many metallometalloids toward 1-alkynes. Third, it is postulated that many of these reactions are reversible, leading to equilibrium mixtures of adducts. However, the problems associated with allenes (Figure 4) are reduced in the case of alkynes, which usually yield only two *cis* addition products.

In the case of copper catalyzed stannylation processes, it is considered that the initial reaction of lithium stannate anions with the copper salt occurs to produce a stannylcopper species (a, Figure 9). Coordination of this with the

alkyne (b) is followed by the regiodeterminate step of addition of the copper species to the alkyne (f). The second metal then coordinates with the copper-alkyne adduct (d) and reductive elimination regenerates a catalytically active stannyl-copper species (e). The second metal can be present at the beginning of the reaction to form a stannylmetal species, or can be introduced after the initial stannyl-cupration.[19]

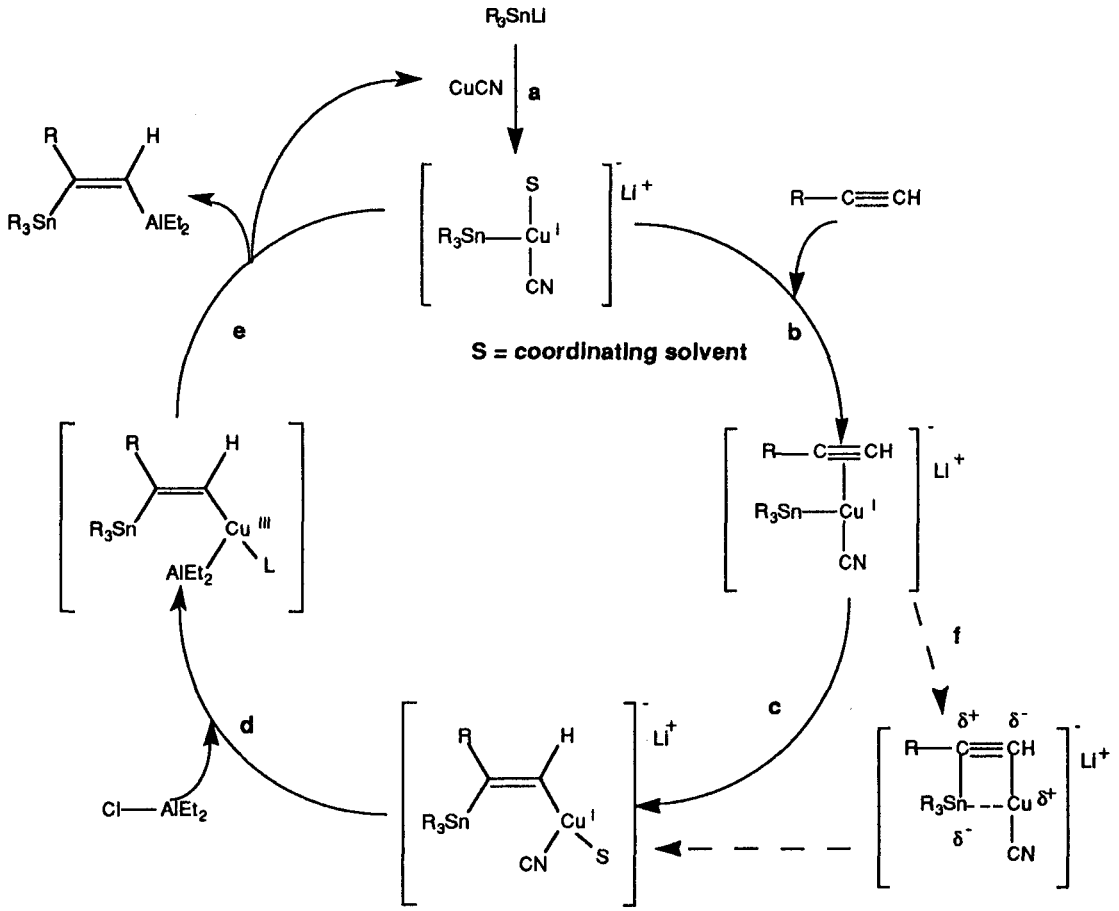


Figure 9. Sharma and Oehlschlager's proposed catalytic mechanism of stannylmetallation.

Oshima[20] and co-workers have reported a systematic study of silylzinc and silylalumination additions of a wide variety of mono and di-substituted alkynes (Figure 10).

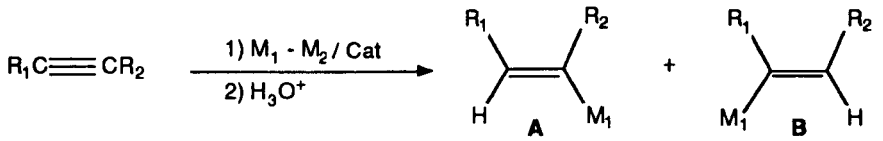


Figure 10. Oshima *et al* silylzinc and silylaluminum addition results.

	R_1	R_2	M_1 - M_2	Catalyst	Yield	A	B
1.	*n*-$C_{10}H_{21}$	H	$Ph_3SiZnEt_2Li$	CuI	90	100	0
2.	*n*-$C_{10}H_{21}$	H	$PhMe_2SiZn$*t*-Bu_2Li	CuCN	92	1	99
3.	$THPOCH_2CH_2$	H	$(PhMe_2Si)_3ZnMgMe$	CuCN	97	100	0
4.	$THPOCH_2CH_2$	H	$PhMe_2SiZn$*t*-Bu_2Li	CuCN	87	1	99
5.	$HOCH_2$	CH_3	$PhMe_2SiZnEt_2Li$	CuCN	5	100	0
6.	$THPOCH_2CH_2$	*n*-C_3H_7	$(PhMe_2Si)_3ZnLi$	CuCN	96	50	50
7.	*t*-$BuMe_2SiOCH_2CH_2$	CH_3	$PhMe_2SiZnEt_2Li$	CuCN	62	83	17

The results show that the choice of metallometalloid as well as the alkyne functionality can alter regioselectivity. For example, entries 3 and 4 reveal the structure of the metallometalloid reagent can reverse regioselectivity. Another study by Sharma and Oehlschlager[21] has reported that it is possible to reverse the regioselectivity of copper(I) catalyzed stannylalumination of 1-alkynes by use of HMPA as a co-solvent. The reasons are not clear, but the authors suggest that it could stem from reversible stannylcupration coupled with a decreased rate of attack of the vinylcopper intermediate **32** in the highly coordinating solvent (Figure 11).

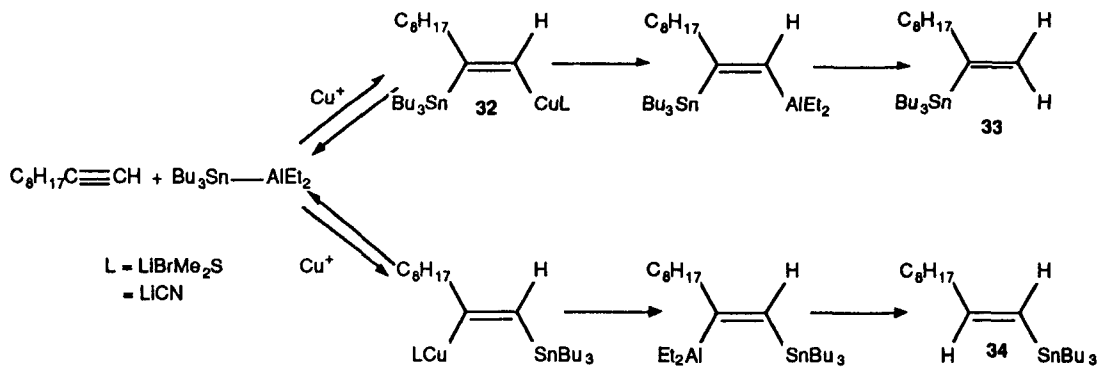


Figure 11. Sharma and Oehlschlager's regioselection of stannylalumination reversal.

Evidence for this came from time course quenching experiments. It was found that 2-stannylalkene **33** formed initially, but 1-stannylalkene **34** accumulated at the expense of **33** if the reaction was conducted at a higher temperature. Use of HMPA increased the proportion of **34** presumably from Al-HMPA chelation of the intermediate leading to **33**, thereby slowing its formation.

A third organometallic method for trisubstituted olefin synthesis involves the simultaneous transfer of an alkyl residue and a metal to an alkyne. Traditionally, this synthetic strategy involves either Cu or Al, but other metals such as Zn[22] and Pd[23] have been used. Copper has proven superior to aluminum owing to a wider variety of tolerated transferable alkyl groups and lack of β-elimination. As well, copper-based reagents are not as sensitive to heteroatoms, allowing for unprotected polar groups. However, aluminum reagents generally afford higher regioselectivity and are not as O_2 sensitive as the organocuprates. The reactions are easier, and the reagents are not as thermally sensitive. Both resulting vinyl metals may be transmetallated by a wide variety of metal salts of controllable reactivity.

In contrast to the usual alkyne metallometallation, both internal and terminal acetylenes may be carboaluminated. For example, Al-Hassan[24] (Figure 12) has prepared *tris*-(4-ethylphenyl) aluminum **35** by reaction of 3 equivalents of 4-ethylphenylmagnesium bromide with $AlCl_3$. This reagent carboaluminated diphenylacetylene **36** to give a vinylalane **37** which was brominated with NBS to yield broparestrol **38**, an estrogenic compound in 68 % yield.

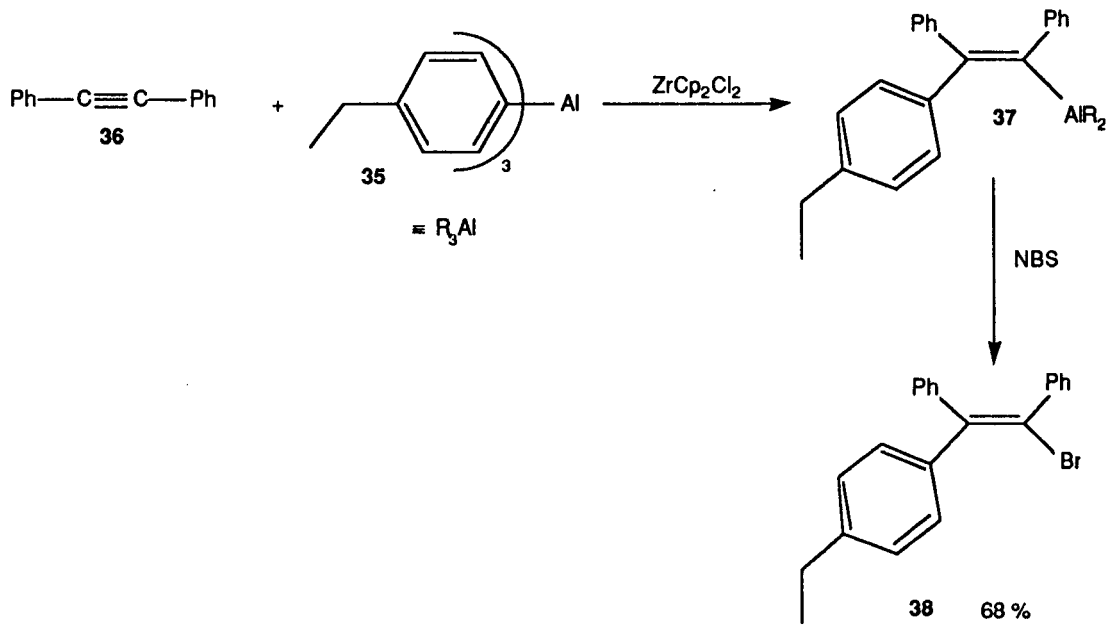
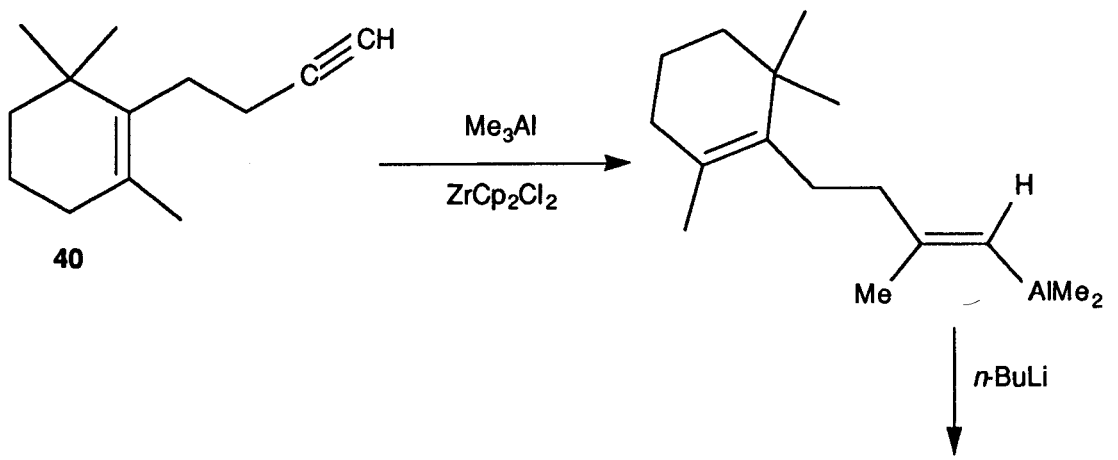


Figure 12. Al-Hassan's synthesis of broparestrol **38**.

Negishi[25] *et al* (Figure 13) has prepared monocyclofarnesol **39** demonstrating the methyl allylic alcohol trisubstituted alkene system, found in terpenoids and natural products, can be easily elaborated from a 1-alkyne *via* the carboalumination route. This system is difficult to prepare *via* traditional synthesis such as the Wittig reaction.[26] The synthesis was performed by methylalumination of alkyne **40** followed by *n*-BuLi to form an alanate **41** which was reacted with paraformaldehyde to afford **39** in 75 % yield.



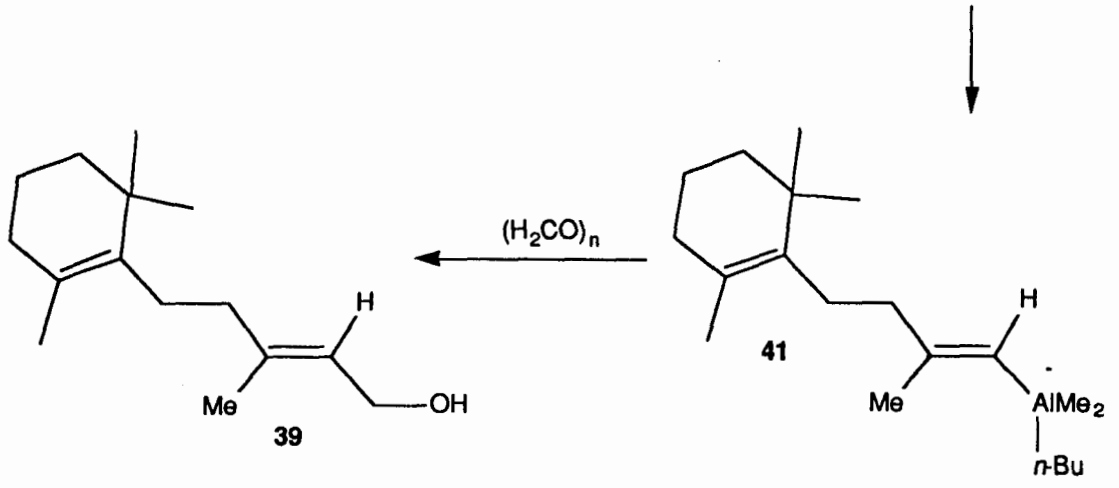


Figure 13. Negishi *et al* preparation of monocyclofarnesol **39**.

Finally, a number of (*E*)-methyl-3-alkene-1-ols **44** and **45** (Figure 14) were produced by carboalumination of alkynes **42** and **43**. The corresponding alanates were treated with epoxides to afford good yields of the alcohols.[27]

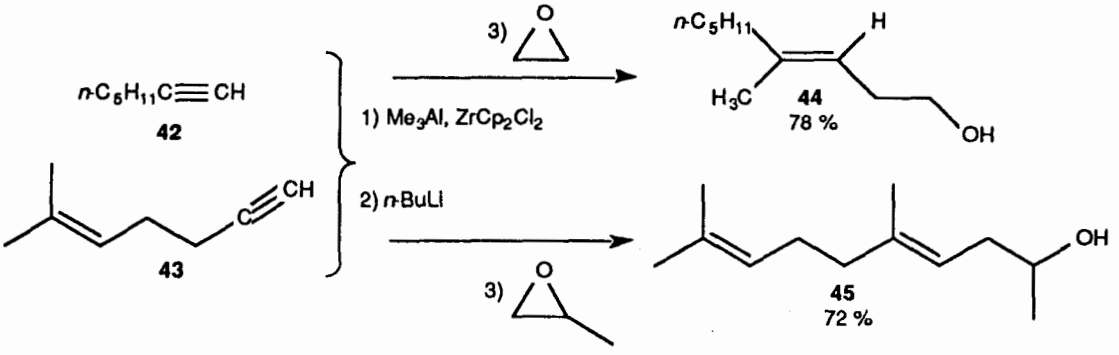
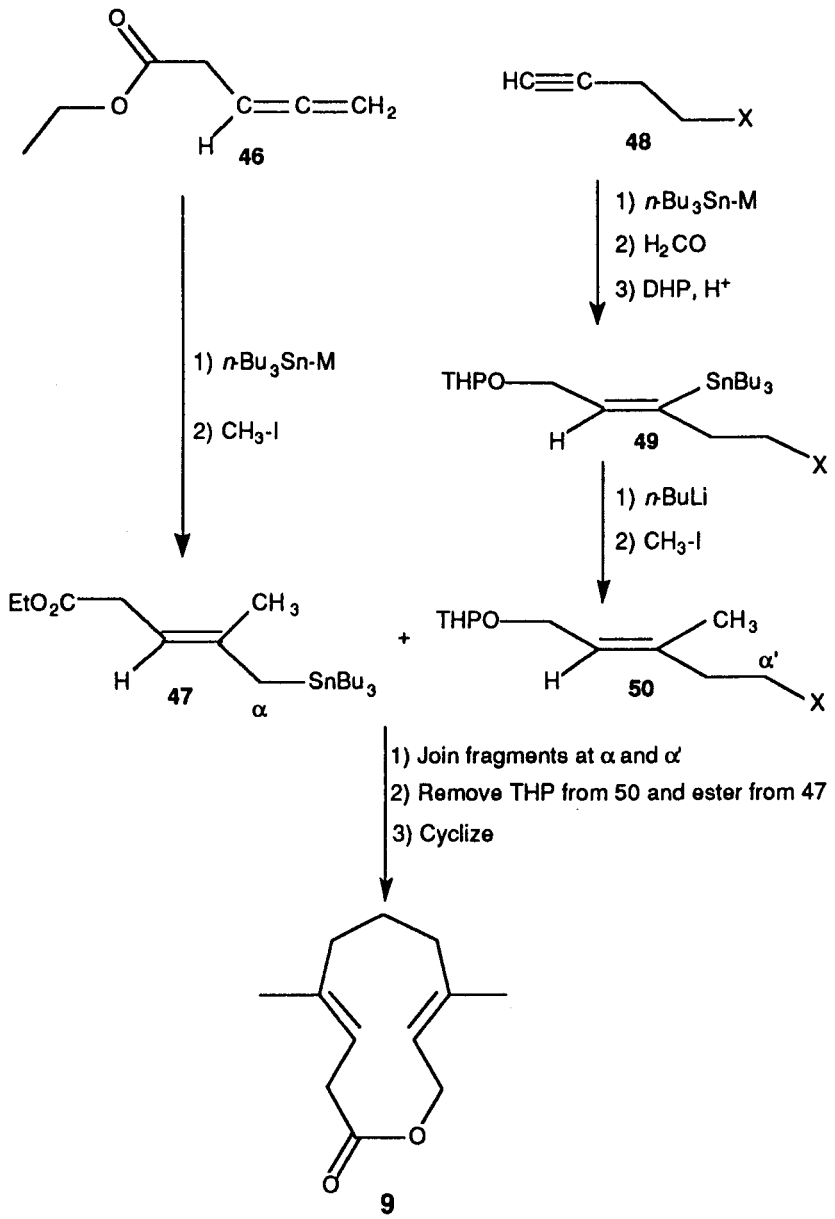


Figure 14. Carboalumination producing (*E*)-methyl-3-alkene-1-ols.

RESULTS AND DISCUSSION

Based on the literature survey, it seemed possible to find conditions under which almost any metallometallation could be performed with regiochemical and stereochemical control. It was attractive to start with a synthon that contained a carboxylic acid equivalent, to avoid steps involving oxidation. Thus, according to Approach 1, metallometallation of allenic ester **46**, followed by capture of the vinyl cuprate with methyl iodide would yield allyl tin **47**. A convergent pathway employing similar reactions with alkynyl bromide **48** or chloride, followed by capture of the vinyl cuprate with formaldehyde, or some other transmetallated species such as magnesium, would yield the desired allylic alcohol fragment. Protection of this synthon as the tetrahydropyranyl ether would afford **49**. Transmetallation of **49** with *n*-BuLi followed with methyl iodide capture would yield synthon **50**. Coupling of **47** and **50** at their α and α' positions respectively would yield a carboxyl and alcohol di-protected fragment that could be easily de-protected and cyclized to the target **9**.



Approach 1.

Bismetallations on allenic ester **46** using either *n*-Bu_3Sn-9-*B*-Methoxy-BBNLi **51** /CuBr•DMS (cat), *n*-$Bu_3SnCuCNLi$ **53**, $(n\text{-}Bu_3Sn)_2CuCNLi_2$ **54** or *n*-Bu_3Sn-(2-thienyl)-$CuCNLi_2$ **55** all followed by methyl iodide gave *E/Z* mixtures of **57** as shown in Figure 15. Tri-*n*-butyl tin hydride **58** was the source of tin in all cases. A preparation of 2-thienyl-(tri-*n*-butylstannane) **59** was performed to check for its formation as a side product. As well, attempted carboalumination

yielded only tertiary alcohol **60** from the attack of two methyls to the ester carbonyl.

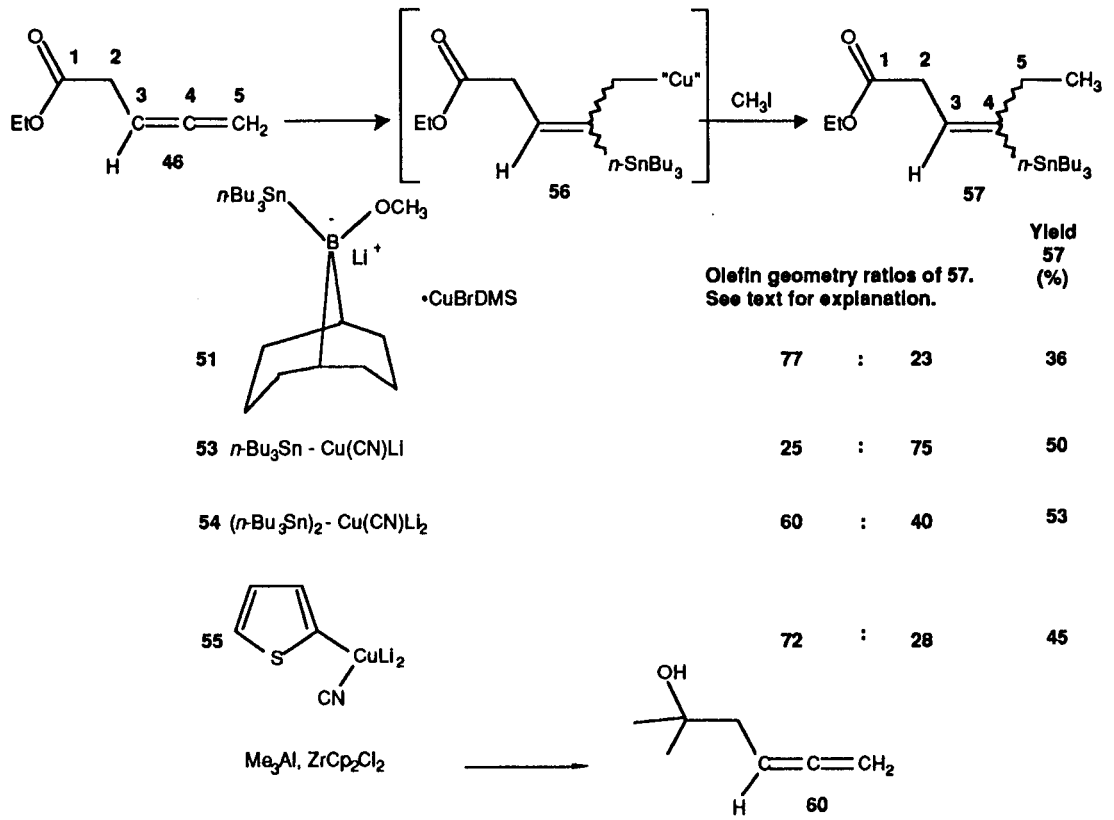


Figure 15. Allene **46** bismetallation results.

Separation of **57** into pure *E* and *Z* components proved to be impossible, although the olefin mixture itself was separated from the other reaction products. A number of flash chromatography attempts, MPLC trials, preparative GC and preparative TLC all failed to provide geometrically pure samples. Evidence for the formation of adduct **57** as an *E/Z* ratio came from anaylsis of the ^{1}H NMR vinyl region and mass spectral data. Addition of the tributylstannyl group was to carbon 4, since the $J_{Sn\text{-}H}$ were consistant with this product.[41] (J_{cis} = 64 Hz, J_{trans} = 140 Hz). According to GC/MS, only 2 products were formed, and their ratios were calculated assuming equal responce factors. Since the required product could not be obtained, this approach was abandoned.

Protection of the ester **46** as an ortho ester **61** failed probably due to hydrolysis of the acyclic product. Work-up on silica gel resulted in isolation of the

starting material **46** only. Conversion of ester **46** to the acid **62**, and protection as a 2-oxazoline **63** also failed (Figure 16).

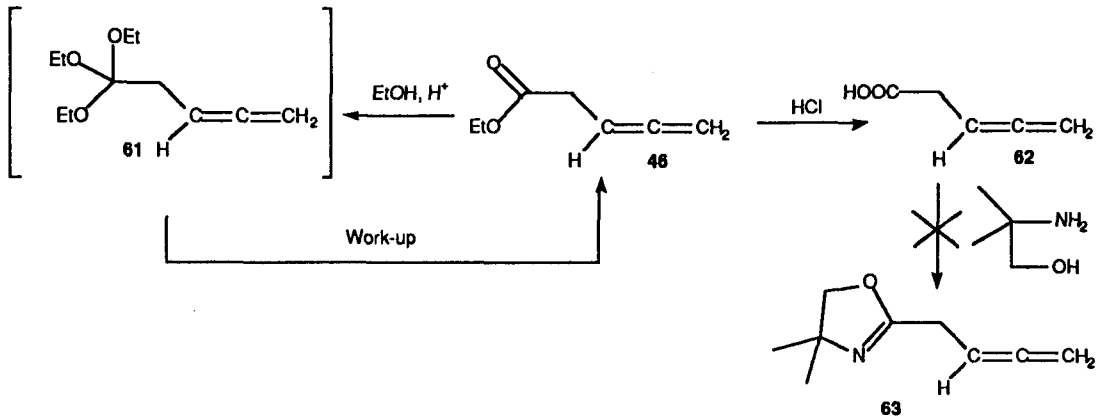
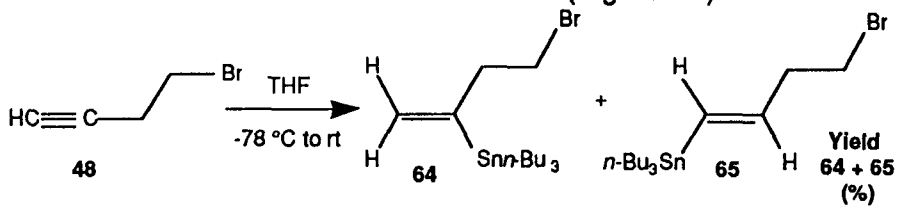


Figure 16. Attempts to protect allenic ester **46**.

The stannylcupration of alkynyl bromide **48** was also beset with problems of regio control and led to mixtures of **64** and **65** (Figure 17).



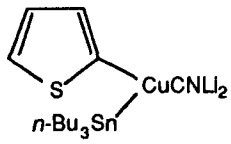
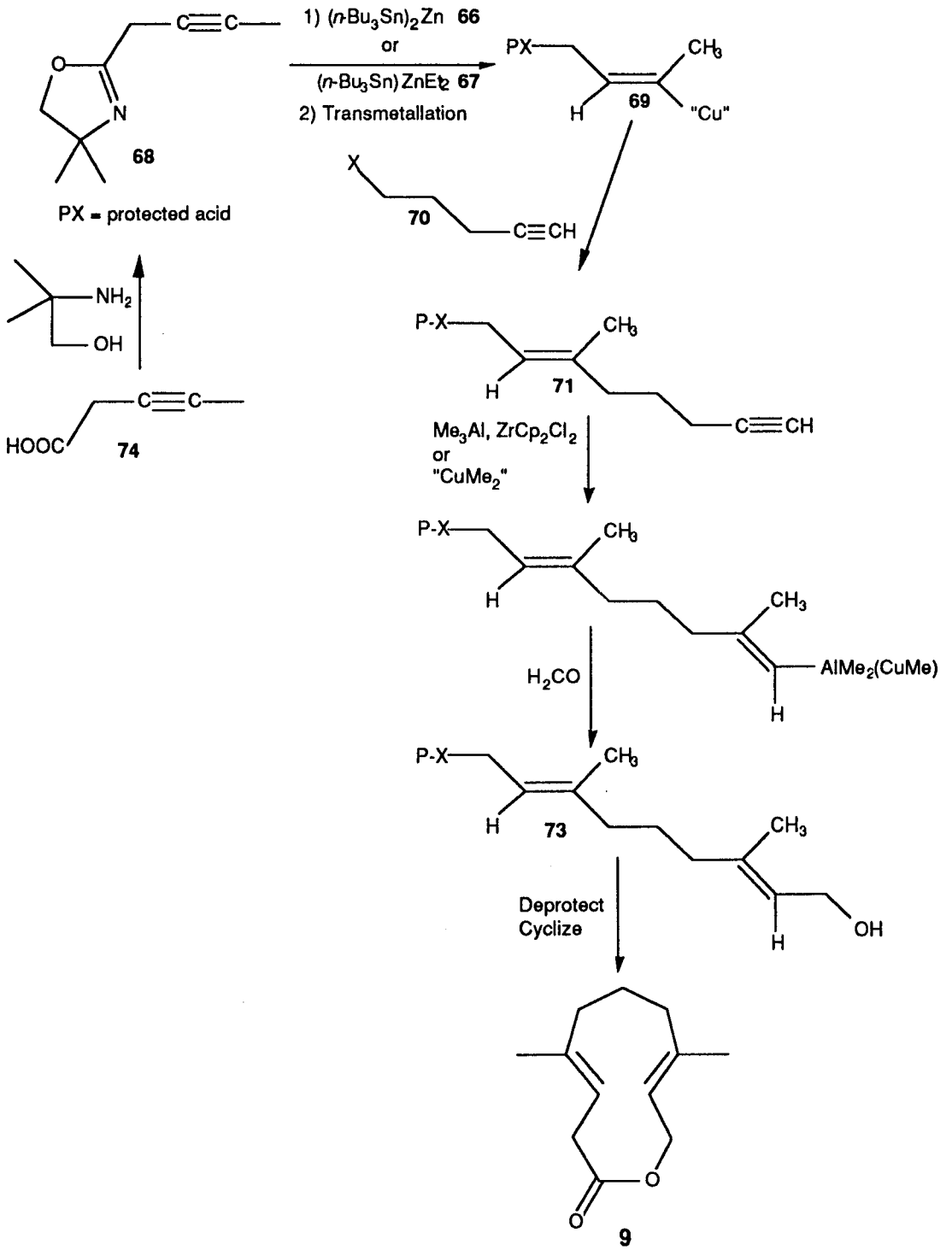
53	*n*-Bu_3SnCuCNLi	**55**	:	**45**	**72**
54	(*n*-$Bu_3Sn)_2$CuCNLi_2	**50**	:	**50**	**69**
55		**30**	:	**70**	**73**
53	*n*-Bu_3SnCuCNLi•SMe_2	**60**	:	**40**	**77**

Figure 17. Metallometallation of bromide **48** results.

Assignment of **64** and **65** was easier than in the case of **57** since the chemical shifts and coupling constants had been previously reported for similar structures.[19] As well, again only two products were formed according to GC/MS. Since the vinyl region in the ^{1}H NMR was more defined, it was possible to tell which of **64** or **65** was actually the major product. This made possible assignment of absolute ratios of products.

A different approach was taken to utilize heteroatom chelation as a regiochemical guide during addition (Approach 2). It was thought that using longer reaction times and two to three equivalents of stannylzinc reagents **66** and **67** with protected acid **68** would result in good yields of an addition product. The vinyl cuprate **69** was to be trapped with alkynyl synthon **70** to afford **71**. Carboalumination or cupration of **71**, followed by reaction with formaldehyde would yield the acid-protected product **73**. De-protection and cyclization would afford suspensolide **9**.

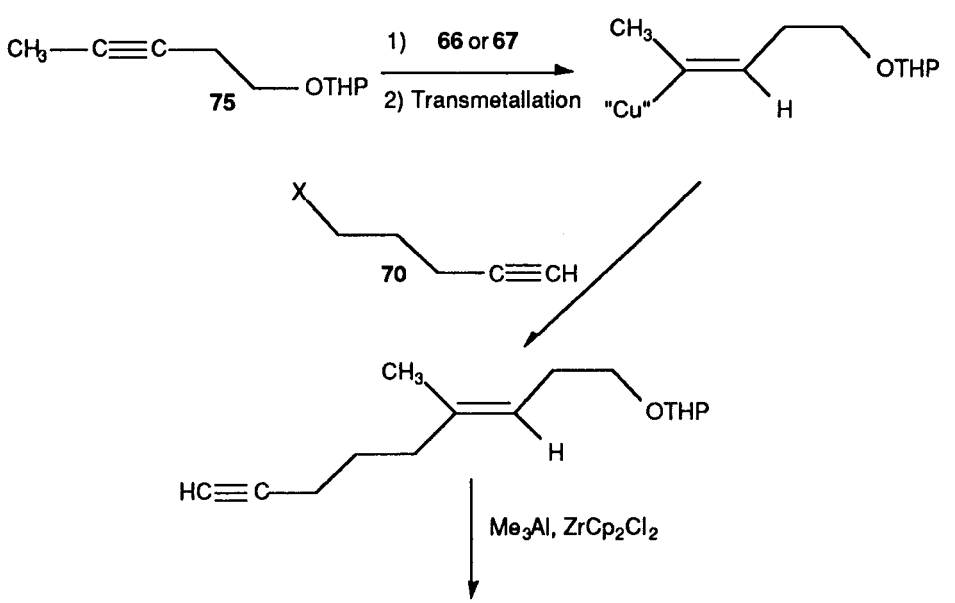

1) (n-Bu3Sn)2Zn 66
or
(n-Bu3Sn)ZnEt2 67
2) Transmetallation
68
PX = protected acid
69
"Cu"
70
71
74
Me3Al, ZrCp2Cl2
or
"CuMe2"
H2CO
AlMe2(CuMe)
73
Deprotect
Cyclize
9

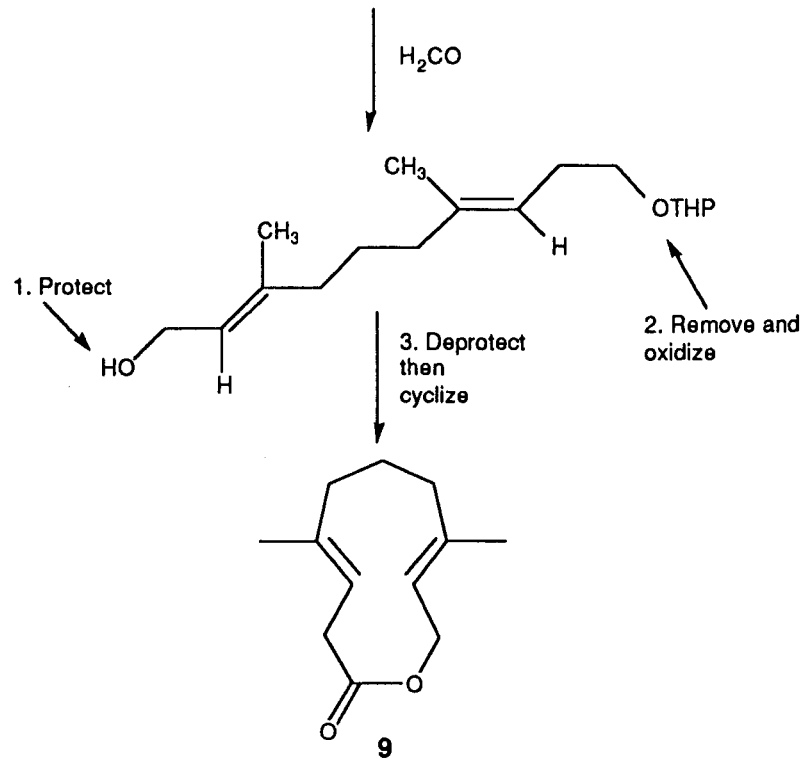
Approach 2.

Both (n-$Bu_3Sn)_2Zn$ **66** or n-$Bu_3SnZnEt_2$ (zincate formation **67**) failed to give an addition product, and in one case resulted in isolation of the corresponding carboxylic acid **74** from **68**!

Approach 3 centered on not using a carboxylic acid equivalent, but required oxidation of a primary homoallylic alcohol later in the sequence, this time originating from the alkynyl synthon **75**. Thus, as before, stannylzincation of **75** followed by transmetallation and iodo coupling would yield a homoallylic protected alcohol. The allylic alcohol was to be generated by vinyl aluminum reaction with formaldehyde. This strategy takes advantage of the symmetry of suspensolide. Without the lactone ether oxygen, it is a symmetrical ring.

For reasons that are not understood, attempts to stannylzincate alkyne **75** resulted in isolation of the starting materials.





Approach 3.

Use of tetrahydropyranyl protected alcohol **78** afforded the required vinyl stannane **77** in excellent regiochemical purity, using either the protected alcohol itself **78**, or by tin cuprate conjugate addition to ester **79**, followed by reduction of **80** to afford alcohol **81** and protection to yield **77** (Figure 17).

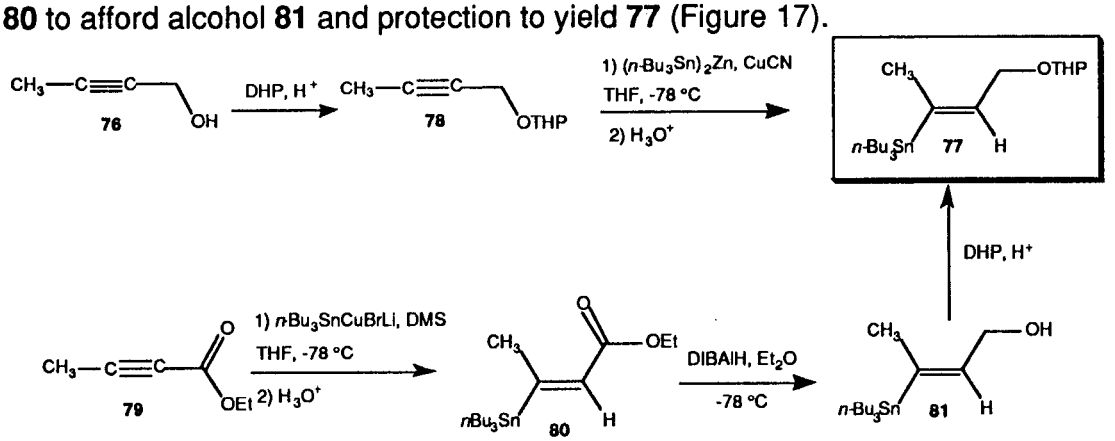
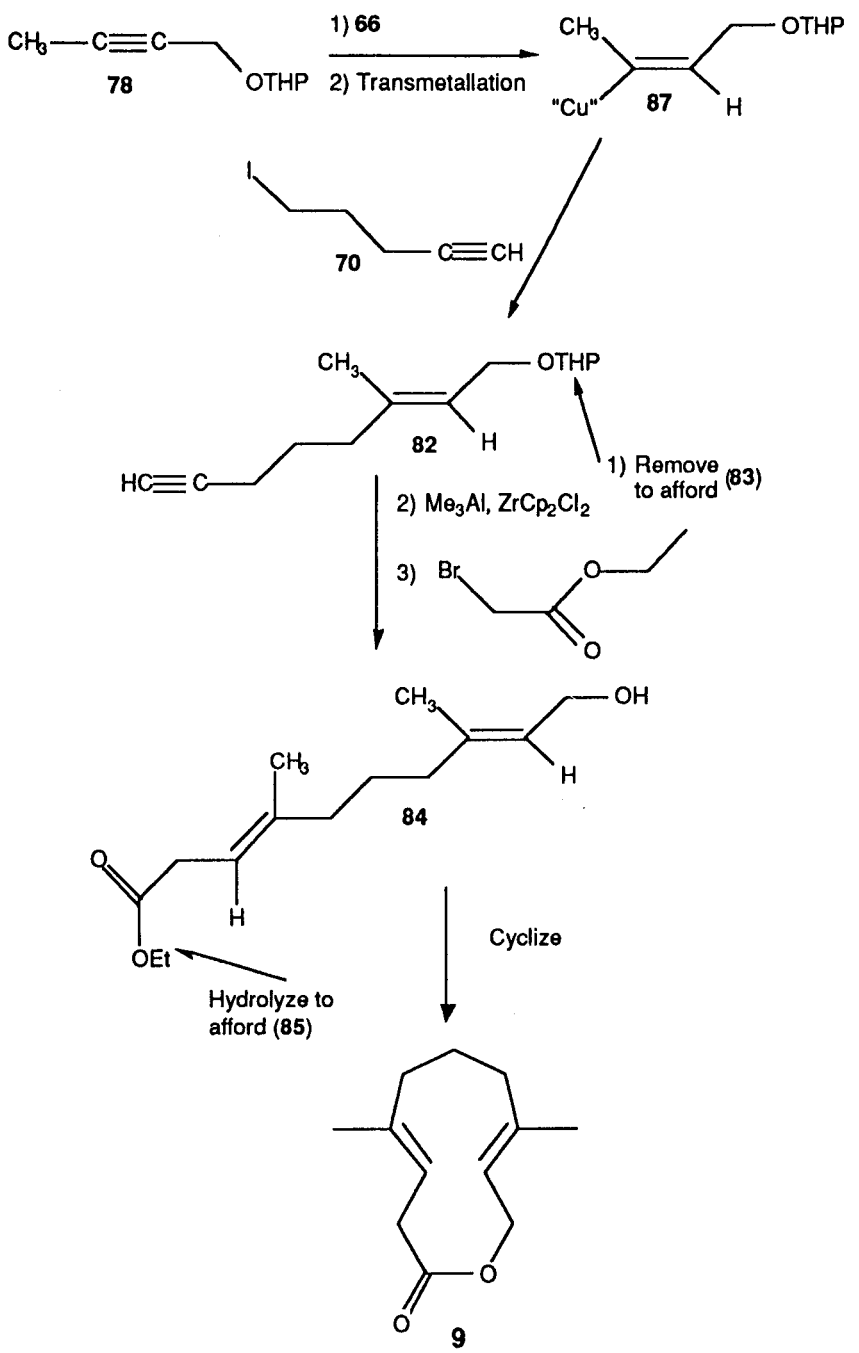


Figure 18. Two preparations of vinyl tin **77**.

Approach 4 shows the first sequence of steps that actually afforded suspensolide **9**, albeit in very poor (6 %) yield.

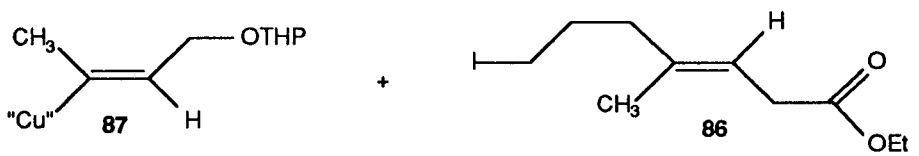


Approach 4.

The vinyl stannane **77** was transmetallated using *n*-BuLi. This was followed by addition of lithium-2-thienlycyanocuprate to produce the mixed higher-order cuprate **87**, to which was added iodo fragment **70** and HMPA.

Terminal alkyne **82** could not be carboaluminated, presumably due to Me_3Al chelation by the THP oxygens. Even a three-fold excess of Me_3Al and higher reaction temperatures did not afford the methylaluminated product. However, deprotection of the alcohol to afford **83** and reaction with excess Me_3Al, did afford the addition product. This was followed by the addition of 2 eq *n*-BuLi, and ethyl bromoacetate/HMPA to give a very poor yield of ester **84**. Aluminum to boron transmetallation of the vinyl alane did not improve the reaction with ethyl bromoacetate. The ester was saponified to **85** and cyclized to suspensolide **9**.

To avoid the problem that carboalumination of **82** failed it was undertaken first to build a carboaluminated synthon **86** then couple this. Approach 5 demonstrates that coupling vinyl cuprate **87** with iodo ester **86** yielded only alkene **88**. This probably results from the acidic proton in **86** (Figure 18).



Approach 5 .

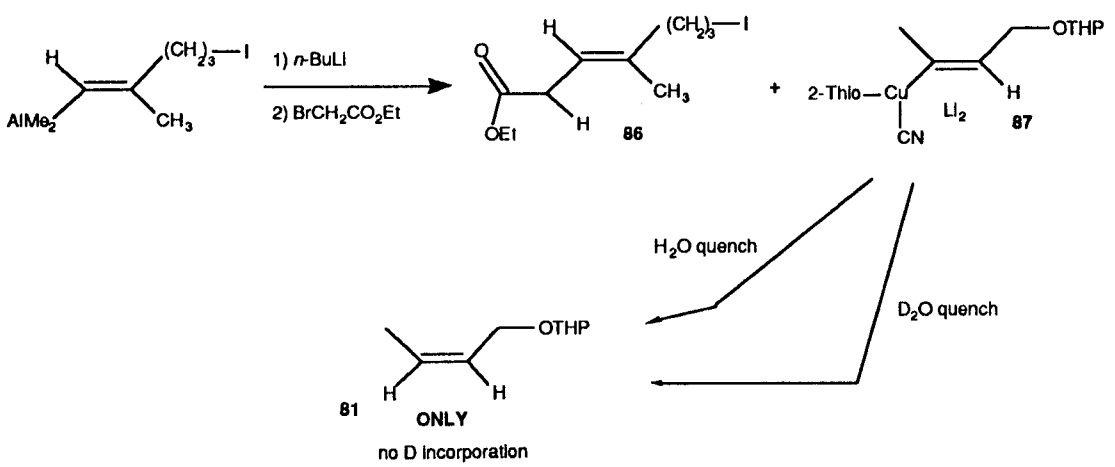
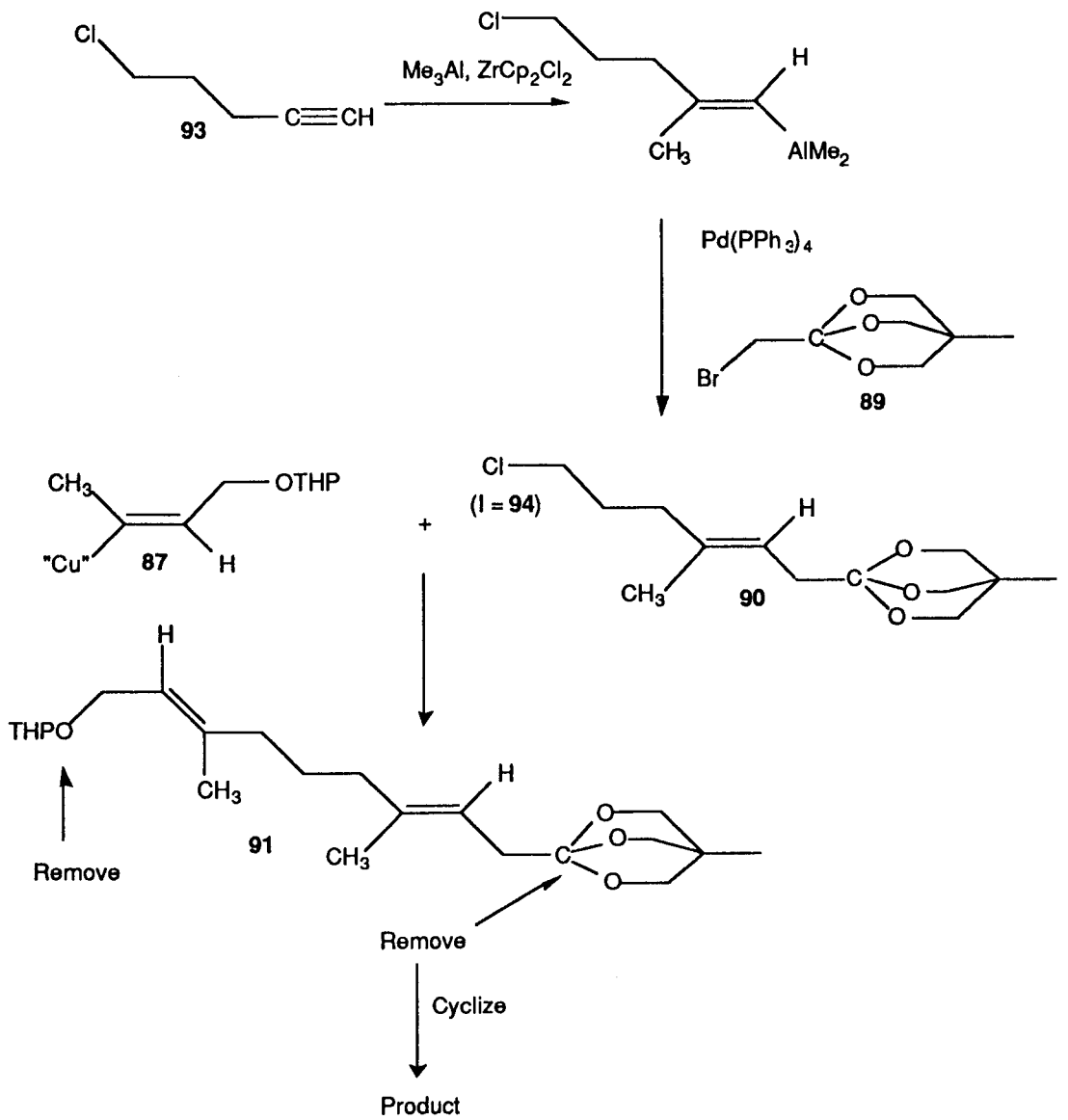


Figure 19. Test for cuprate **87** quenching mechanism.



Approach 6.

As well, in Approach 6 it was attempted to add a less acidic fragment **90** to the fragment **93** by carboalumination and palladium catalysis on the vinyl alane to produce **89.** This was to be coupled to cuprate **87** to afford **91** which was to be completely de-protected to the hydroxy-acid **85.** The product of alane self-coupling **92** (Figure 20) however, was isolated.

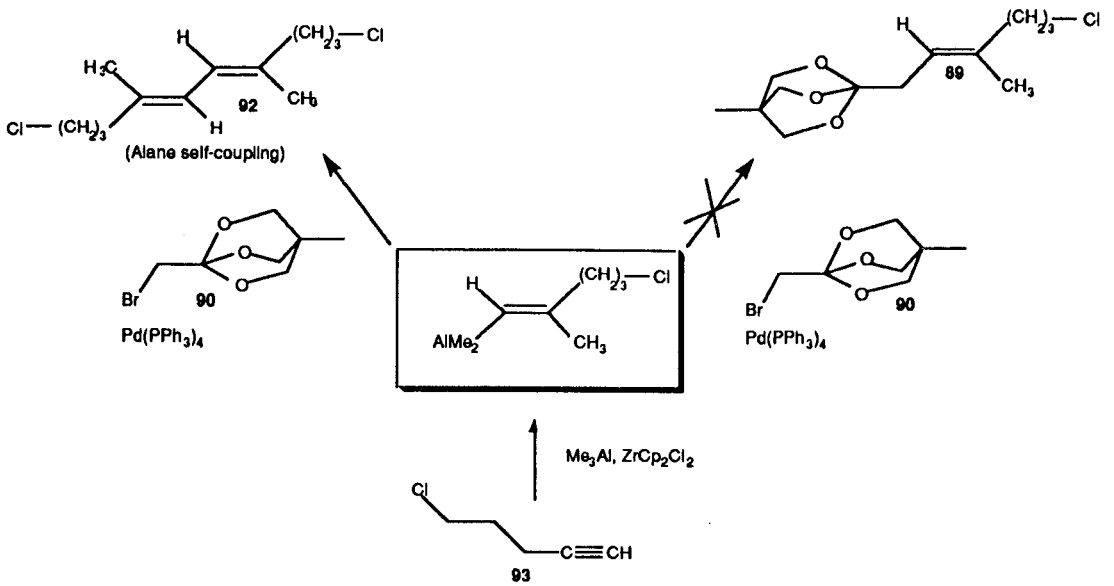


Figure 20. Alane self-coupling *vs* palladium coupling of **90.**

Approach 7 incorporated all these results for the best synthetic approach. Alkynyl iodide **70** was carboaluminated and the corresponding alanate reacted with ethylene oxide, affording alcohol **101**. This was protected as a tertiarybutyl dimethyl silyl ether **102**, and coupled to cuprate **87** to afford **100**. The silyl group was then removed to afford homoallylic alcohol **96**. Pyridinium dichromate **95** in DMF failed to oxidize **96** to the acid **97** or to the aldehyde **98**, and careful addition of Jones reagent **99** produced the di-acid **106**, probably from the sulfuric acid cleaving the THP group, followed by oxidation of both primary alcohols. Alcohol **96** was oxidized to aldehyde **98** by Swern oxidation, then to the acid **97** by pyridinium dichromate **95** in DMF. Attempts to oxidize **98** with Ag_2O did not produce **97**. The THP group of **97** was removed to yield **85**. Cyclization was performed with the high dilution apparatus in Figure 21. The hydroxy acid **85** was dissolved in THF and placed in addition funnel A. The refluxing THF enters chamber B through tube D and carries the substrate from tube C to the pot through tube E. The needle valve F controlled the flow rate through tube C. The tip of tube E was bent to prevent solvent from backing-up.

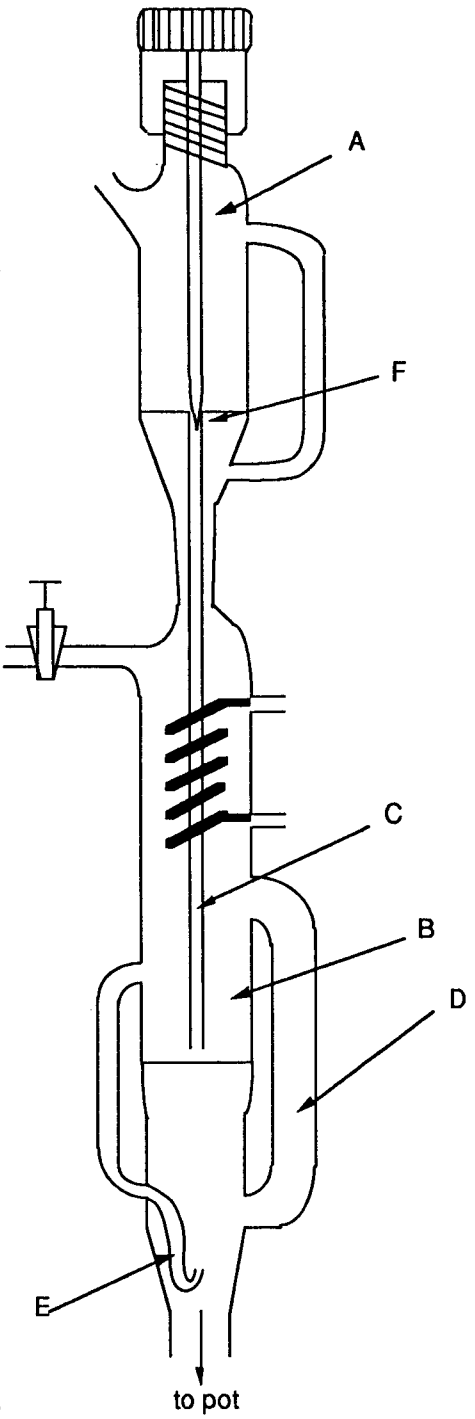
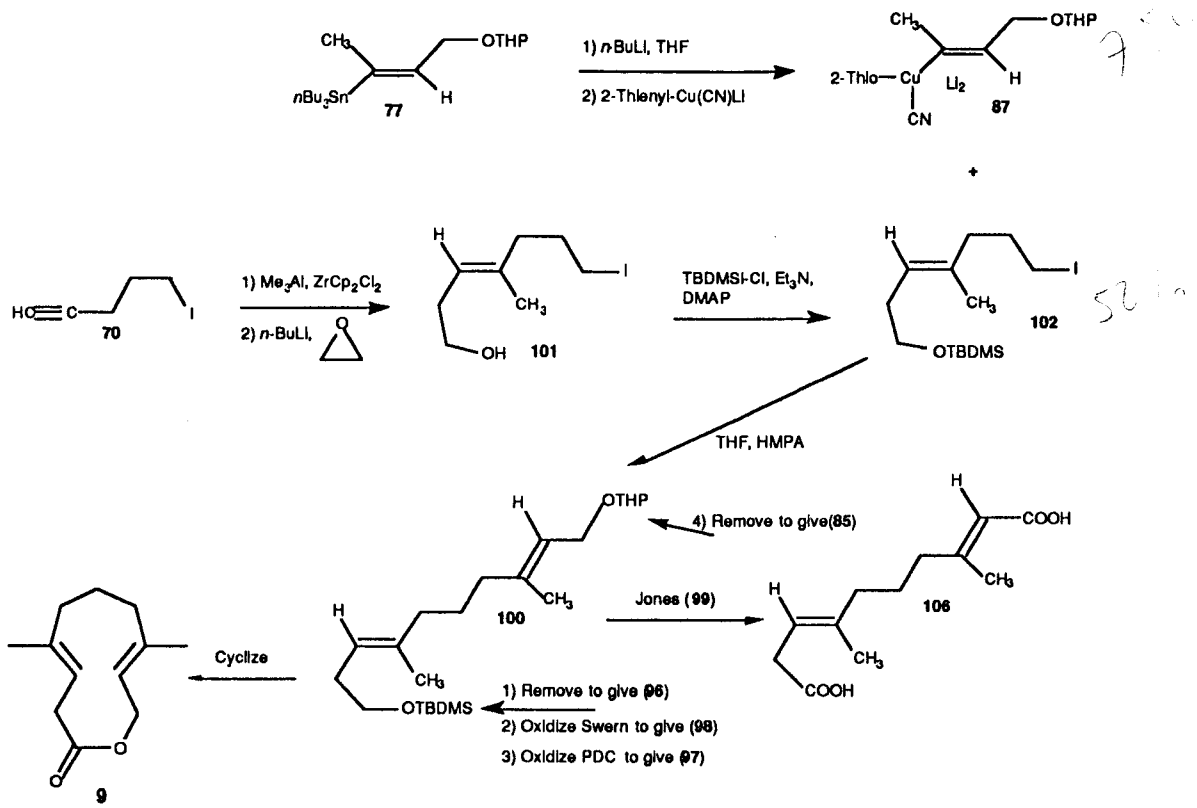


Figure 21. High dilution apparatus to perform lactonizations.



Approach 7.

Since test reactions showed that the chloride analogue **93** of iodo fragment **70** did not couple to cuprate **87**, a series of experiments were conducted to see how fragment **102** could be best prepared (Figure 22). Since chlorides are not light sensitive, the iodide **102** could be prepared from the commercially available chloride **93** at a number of junctures in the synthesis.

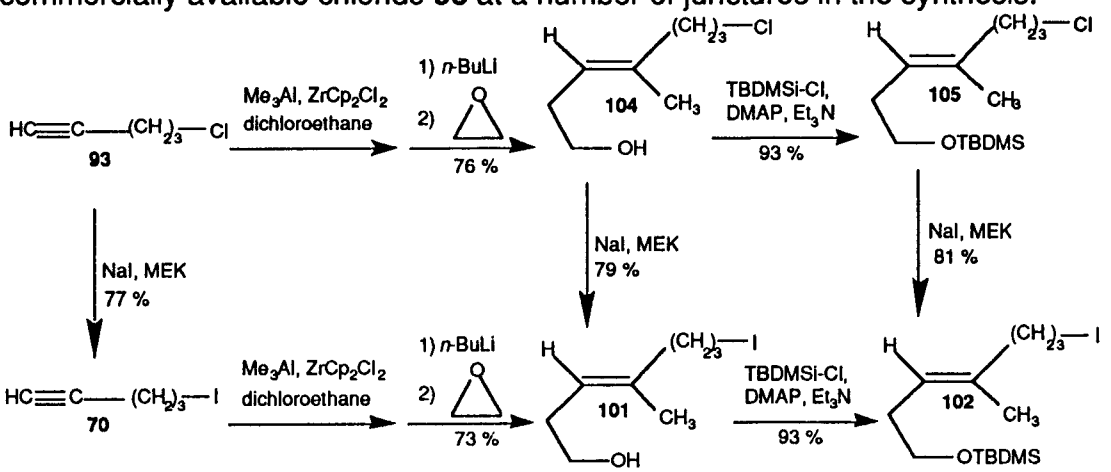


Figure 22. Synthetic routes for the preparation of iodo **102**.

The *E* stereochemistry was assigned to all the alkenes in Figure 22 based on the ^{13}C chemical shifts of the vinyl methyls. Numerous literature examples[28,29,30,31] show that shifts of *ca* 17 ppm correspond to *E* stereochemistry, while shifts of *ca* 24 ppm correspond to the *Z* isomer.

CONCLUSIONS

The organometallic syntheses of suspensolide **9** were not trivial. While various studies of allene and alkyne metallometallations have been reported, the additions of various stannyl metalloids to allenic ester **46** and to alkynyl bromide **48** were not deemed to be valuable synthetic routes to suspensolide **9**. The uncontrollable product ratios, lack of reproducibility and often large proportions of unreacted substrate often encountered generated many problems in separation and purification. This was unacceptable from a synthetic point of view.

Although some mechanistic work has been conducted, to elucidate the problems encountered, no obvious solutions were found.

In contrast, however, successful stannylzincation on alkyne **78** was performed with excellent yield and regioselectivity. It is thought that the α-OTHP may help to control regioselectivity in this addition. The failure of homologue **75** to undergo this addition may support this observation.

The facile conversion of alkyl chlorides to their corresponding iodides proved useful for higher order cuprate coupling. Since the chloride did not couple in the cases studied, the generation of the synthons capable of coupling was shown to be facile at several steps along the synthetic pathway.

The coupling of a synthon containing a carboxylic equivalent proved difficult, as in one case the acidic α-protons caused cuprate quenching. In an other case, an ortho ester preparation failed, leading to a rather interesting diene **92**.

A number of oxidation processes were studied to determine the best approach to produce the acid **97** from the homoallylic alcohol **96**. It was found that a two-stage conversion by way of the aldehyde **98** was the best.

Finally, the synthesis of the lactone **9** was low-yielding. The reasons for this are one of dimer *vs* ring formation. Even using high dilution conditions, the yield was no more than (11 %).

EXPERIMENTAL

General:

THF and diethyl ether were freshly distilled from potassium benzophenone ketyl under argon before use. Molecular sieves (4 Å) were activated by heating overnight to *ca* 200 °C under vacuum. 1,2-Dichloroethane was distilled from P_2O_5 and stored over molecular sieves. HMPA was distilled from CaH_2 and stored in the dark over molecular sieves. CH_2Cl_2 was freshly distilled from CaH_2. Methanol was dried *via* Mg/I_2 and stored over molecular sieves. Pentane was distilled from P_2O_5 and stored over molecular sieves. DMF was stored over molecular sieves. Methyl iodide was distilled from P_2O_5 and stored in the dark over pure elemental copper. Di-isopropyl amine was dried from CaH_2 and stored over KOH. Ethyl bromoacetate was purified by distillation from $MgSO_4$ (bp = 40 °C @ 5 mm•Hg). 2-Amino-2-methyl-1-propanol was distilled from $MgSO_4$ (bp = 163 °C @ 760 mm•Hg) and stored over molecular sieves. All other commercial chemicals were analytical grade, and unless otherwise mentioned, were used without further purification.

Glassware, stirbars and syringes for organometallic reactions were dried at least 8 hr at 155 °C, assembled hot, and cooled under argon. Air and water sensitive reagents were handled in a nitrogen atmosphere bag. Liquid transfers were performed either by syringe (lightly oiled to assure good sealing) or by a double-tipped needle (canula).

Reactions below room temperature were conducted by placing the flask in a vacuum sealed Dewar. The cryogen for -78 °C was acetone/dry ice. Additions of liquids to the flask were dripped slowly down the sides to minimize internal temperature gradients.

GC aliquots were withdrawn by syringe and placed in a tube with 1.5 M HCl. Ether was added and mixed for at least 1 min. The etheral layer was passed into a new tube through a bed of celite/magnesium sulfate before analysis.

TLC and preparative TLC samples were analyzed on commercial Merck 5554 aluminum plates. Detection was either by short-wave UV, iodine, or a mixture of ceric sulfate (1 %), molybdic acid (1.4 %) in 10 % H_2SO_4 and charred on a hot plate.

Flash chromatography by the procedure of Still *et al*[32] was followed and the silica used for all columns was Merck Art. 9385 230 - 400 mesh ASTM.

Mass spectral analyses were performed using a Hewlett Packard 5985B using either electron impact (70 eV) or isobutane as the ionizing source.

^1H and ^{13}C NMR were obtained on either a Bruker WM 400 or Bruker SW 100 and all values are reported in δ. Alkenes resulting from the metallometallations of allene **46** or alkyne **48** were analyzed by the chemical shift of the ^1H NMR vinyl region[31]. Ratios of adducts were calculated from GC/MS integration data.

IR were recorded on either a Perkin Elmer 599B or a Bomem 120 using NaCl cells and were calibrated to polystyrene.

GCs used were Hewlett Packard 5880 A series equipped with a 7.5 m DB-1 column (GC1), or Hewlett Packard 5890 with a 15 m DB-1 column (GC2). Both columns had film thicknesses of 0.25 μm and inside diameters of 0.25 mm. Flame ionization detectors were used. The retention times are listed according to the following programs, all at 20 °C per minute:

$GC1_{T1}$ = 50 °C(1) to 250 °C, $GC1_{T2}$ = 60 °C (1) to 250 °C, $GC1_{T3}$ = 40 iso.

$GC2_{T1}$ = 45 °C(3) to 250 °C, $GC2_{T2}$ = 45°C (1) to 250 °C, $GC2_{T3}$ = 40 iso., $GC2_{T4}$ = 50 °C(1) to 250 °C; $GC2_{T5}$ = 60 °C (1) to 250 °C.

The author wishes to thank the following people for valuable chemical donations. Dr. M. Singh for 1-Bromomethyl-4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octane orthoester, Dr. S. Sharma for 1-(*O*-Tetrahydropyranyl)-5-hexyne, and Dr. R. Heath for (*E,E*) suspensolide and a mixture of *Anastrepha* volatile components.

Preparation of Ethyl 3,4-pentadienoate (46).[33]

To a mixture of triethylorthoacetate (96.51 g, 600 mmol) and propionic acid (2 mL) in a 2-necked rbf equipped with a dropping funnel and a distillation unit immersed into an oil bath was added propargyl alcohol (*ca* 4 g). The bath was raised to 140 °C and the propargyl alcohol was continually added noting the ethanol being distilled off at 60 - 76 °C. When all the propargyl alcohol was added (22.21 g, 400 mmol) and no more ethanol was being produced, the oil temperature was raised to 180 °C for 30 min.

The mixture was acidified with 2 M HCl and extracted with 3 x 150 mL ether, dried over $MgSO_4$, filtered through Celite and concentrated. Distillation afforded 30 g (59 %) allenic ester. bp = 155 °C @ 760 mm•Hg; $GC1_{T3}$ = 1.5 min; $GC2_{T1}$ = 5.4 min; ρ = 0.98 g/mL; IR neat, cm^{-1} (intensity) 2950 (s), 1965 (s), 1740 (s), 1450 (m), 1420 (m), 1378 (m), 1045 (s), 865 (s); ^1H NMR ($CDCl_3$) δ 1.13 (3H, t, J = 7 Hz), 3.05 (2H, dt, J = 7 Hz, 3 Hz), 4.15 (2H, q, J = 7 Hz), 4.77 (2H, dt, J = 6 Hz, 3 Hz), 5.28 (1H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.91, 33.99, 60.53, 75.42, 83.32, 171.08, 209.19; MS/EI, m/z, (%) 126 (trace), 98 (100), 81 (22), 70 (42), 53 (51); MS/CI (isobutane), m/z, (%) 129 (100), 99 (78), 85 (8), 71 (6). The volatility of the compound did not allow for satisfactory elemental analysis.

Preparation of Tri-(*n*-butyl)-tin hydride (58).[34]

To tri-*n*-butyl chloride (42.36 g, 130.1 mmol) in ether (150 mL) at 0 °C was added over 1 min LAH (5 g,132 mmol). The reaction was stirred for 1 hr under argon and was carefully quenched with cold H_2O. The slurry was extracted with 3 x 100 mL pentane which was dried over $MgSO_4$, filtered through Celite and concentrated *in vacuo*. The mixture was distilled to afford 31.70 g (83.7 %) **58** as a colorless liquid. bp = 71 °C @ 0.05 mm•Hg; $GC1_{T1}$ = 3.7 min; ρ = 1.08 g/mL; IR neat, cm^{-1} (intensity) 2980 (s), 2950 (s), 2895 (m), 2880 (m), 1830 (s), 1573 (m), 1385 (w), 1085 (w); ^1H NMR ($CDCl_3$) δ 0.89 (9H, t, J = 12 Hz), 0.93 (6H, sex, J = 6 Hz), 1.32 (6H, p, J = 7 Hz), 1.51 (6H, dt, J = 18 Hz, 6 Hz), 4.62 (1H, t, J = 88 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.60, 17.54, 26.85, 27.86; MS/EI, m/z, (%) 235 (20), 233 (15), 179 (80), 177 (100), 121 (70), 119 (52); MS/CI, CH_4, m/z, (%) 291 (50), 289 (38), 235 (100), 233 (79); MS/CI, isobutane, m/z, (%) 291 (100), 289

(79), 235 (40), 233 (32); Anal calcd for $C_{12}H_{28}Sn$: C = 49.52, H = 9.7, Sn = 40.78; Found: C = 49.36, H = 10.1.

Preparation of 9-*B*-methoxy-bicyclo[3.3.1]nonane (52).[35]

To 9-BBN (60 mL, 0.5 M in THF, 30 mmol) at 0 °C was added over 10 min CH_3OH (*ca* 10 mL, *ca* 240 mmol) and stirred for 1 hr at 0 °C and 2 hr at rt. The excess CH_3OH was removed under vacuum and the residue distilled to afford 2.08 g (46 %) **52** as a colorless liquid. bp = 55 °C @ 2.2 mm•Hg.

Preparation of Lithium-[tri-*n*-butylstannyl-9-methoxyboronate bicyclo[3.3.1]nonane] (51).[14]

Typically, to di-isopropyl amine (1.4 mL, 10 mmol) in THF (10 mL) at -78 °C was added slowly *n*-BuLi (4 mL, 10 mmol) and stirred for 30 min, then *n*-Bu_3SnH **58** (2.91 g, 10 mmol) was added and the reaction stirred for another 30 min. This was transferred *via* canula into another flask containing 9-*B*-methoxy BBN **52** (1.52 g, 10 mmol) in THF (10 mL) at -78 °C and the resulting solution stirred 30 min.

Preparation of Lithium-[tri-*n*-butylstannyl-cyanocuprate] (53).

Typically, tri-*n*-butyltin lithium was prepared by reaction of **58** with LDA as above, then copper cyanide (1 eq) was added and stirred for 15 min.

Preparation of Dilithio-[*bis*-(tri-*n*-butylstannyl)-cyanocuprate] (54).

Typically, tri-*n*-butyltin lithium was prepared as above, and CuCN (0.5 eq) was added.

Preparation of Lithium-(2-thienyl)-cyanocuprate. [36]

To triply distilled thiophene (bp = 83 - 84 °C @ 760 mm•Hg) (5 mL, 62.5 mmol) in THF (25 mL) at -78 °C was slowly added *n*-BuLi (26 mL, 62.5 mmol) over 30 min. The solution became turbid and yellow and was stirred for an additional 30 min at -60 °C. This solution was then transferred *via* canula to a flask containing CuCN (5.6 g, 62.5 mmol) suspended in THF (65 mL) also at -60 °C. The contents were transferred back and forth *via* canula between the 2 flasks until the mixture was a homogeneous dark grey.

Preparation of Dilithio-[tri-*n*-butylstannyl-2-(thienyl)-cyanocuprate] (55).

Typically, tri-*n*-butylstannyl lithium was prepared as above, followed by lithium 2-thienyl cyanocuprate (1 eq).

Preparation of 2-Thienyl-tri-*n*-butylstannane (59).

To a 50 mL rbf containing lithium 2-thienylcyanocuprate (20 mL, 5 mmol, 0.25 M) at -78 °C was slowly added neat tributyl tin chloride (1.1 mL, 4.05 mmol). Reaction formed an instant precipitate of LiCl. Stirring was continued for 1 hr, then quenched with $NH_4Cl/H_2O/CH_3OH$ at 0 °C and extracted with 3 x 50 mL ether. The combined ether extract was dried with $MgSO_4$, filtered through Celite and passed through a short bed of flash silica (100 % hexanes) to afford 1.39 g (92 %) **59**. $GC1_{T1}$ = 6.3 min; IR neat, cm^{-1} (intensity) 3100 (w), 2990 (s), 2970 (s), 2890 (s), 2880 (s), 1470 (m), 1390 (w), 1220 (m), 1085 (w), 960 (w), 710 (m); ^1H NMR ($CDCl_3$) δ 0.94 (9H, t, J = 7 Hz), 1.15 (6H, m), 1.38 (6H, sex, J = 7 Hz), 1.61 (6H, p, J = 7 Hz), 7.23 (1H, m), 7.30 (1H, m), 7.68 (1H, m); MS/EI, m/z, (%) 374 (trace), 317 (75), 315 (55), 261 (60), 259 (40), 203 (100), 201 (700), 177 (20), 175 (14); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 10.79, 13.63, 27.24, 28.95, 127.79, 130.54, 135.14, 135.70; Anal calcd for $C_{16}H_{30}SSn$: C = 51.49, H = 8.12, S = 8.59, Sn = 31.80; Found: C = 51.51, H = 8.13.

Preparation of 3,4-Pentadienoic acid (62).

To allenic ester **46** (2.3 g, 18.2 mmol) was added 1 M HCl (40 mL) and the reaction was refluxed for 30 min and extracted with 3 x 100 mL ether. The ether was dried over $MgSO_4$, filtered through Celite and concentrated to afford 1.6 g (89.3 %) **58** as an almost colorless oil. $GC1_{T3}$ = 1.7 min; $GC2_{T1}$ = 5.8 min; IR oil, cm^{-1} (intensity) 3450 - 2800 (br, s), 2280 (m), 1970 (w), 1730 (s), 925 (s), 750 (s), 670 (m); ^1H NMR ($CDCl_3$) δ 3.11 (2H, dt, J = 7.6 Hz, 5.6 Hz), 4.79 (2H, dt, J = 6.8 Hz, 5.6 Hz), 5.25 (1H, p, J = 7.2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 34.00, 76.08, 82.70, 82.90, 177.5; MS/CI (isobutane), m/z, (%) 99 (100); Anal calcd for $C_5H_6O_2$: C = 61.22, H = 6.16, O = 32.62; Found: C = 61.19 , H =6.12.

Preparation of a mixture of 3(*E*)-Ethyl 4-(tri-*n*-butylstannyl)-hexanoate and 3(*Z*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate (57).

To **51** (10 mmol) in THF (30 mL) at -78 °C was added allene **46** (0.63 g, 5 mmol) followed immediately by CuBr•DMS (0.11 g, 0.5 mmol) and the resulting solution was stirred for 5 hr. This was followed by the addition of methyl iodide (1.42 g, 10 mmol) and the reaction was allowed to stir for an additional 4 hr. The reaction was quenched with 1.5 M HCl and extracted with 3 x 75 mL ether. The ether was dried with $MgSO_4$, filtered through Celite and concentrated *in vacuo*. Flash chromatography (15 % EtOAc/hexanes) afforded 0.77 g (36 %) **57** as a 77:23 geometric ratio. $GC1_{T2}$ = 7.1 min, 7.2 min. MS/EI, m/z, (%) both isomers 375 (45), 373 (40), 291 (20), 235 (70), 233 (60), 179 (90), 177 (100), 175 (60), 137 (10), 135 (10), 123 (10), 121 (40), 119 (30), 55 (10), 41 (10). ^1H NMR ($CDCl_3$) δ 0.76 - 0.97 (18H, m), 1.12 (6H, m), 1.20 - 1.42 (8H, m), 1.48 (2H, m), 1.57 (3H, t, J = 4 Hz), 4.12 (2H, q, J = 4 Hz), 5.79 (1H dt, J = 18 Hz, 60 Hz), 5.92 (1H, dt, J = 18 Hz, 140 Hz).

Alternate preparation of a mixture of 3(*E*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate and 3(*Z*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate (57).

To **53** (10 mmol) in THF (30 mL) at -78 °C was added allene **46** (0.63 g, 5 mmol) and the reaction was allowed to stir for 1 hr. Then, methyl iodide (1.42 g, 10 mmol) was added and the reaction was allowed to stir for an additional 4 hr. Quenching and purification were identical as above to afford 1.87 g (50 %) **57** as a 25:75 geometric ratio.

Alternate preparation of a mixture of 3(*E*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate and 3(*Z*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate (57).

To **54** (4 mmol) at -78 °C in THF (15 mL) was added allene **46** (0.25 g, 2 mmol) and the resulting solution was stirred for 1 hr. This was followed by methyl iodide (1 mL, 16.1 mmol) and allowed to stir for 6 hr. This was followed by an identical amount of methyl iodide and was allowed to stir overnight. Quenching and purification were identical as above to afford 0.45 g (53 %) **57** as a 60:40 geometric ratio.

Alternate preparation of a mixture of 3(*E*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate and 3(*Z*)-Ethyl 4-(tri-*n*-butylstannyl)-hexenoate (57).

To **55** (10 mmol) at -78 °C in THF (50 mL) was added allene **46** (0.63 g, 5 mmol) and the resulting solution was stirred for 1 hr. This was followed by methyl iodide (1 mL, 16.1 mmol) and allowed to stir overnight. Quenching and purification were identical as above to afford 0.97 g (45 %) **57** as a 72:28 geometric ratio.

Attempted preparation of 1,1,1-Triethoxy-3,4-pentadiene (61).

To allenic ester **46** (1.18 g, 9.35 mmol) in benzene (25 mL) were added a few crystals *p*-toluene sulfonic acid, ethanol (10 mL), and 4 Å molecular sieves (5 g). Reaction was refluxed overnight resulting in the destruction of the sieve matrix. Complete consumption of **46** according to $GC2_{T1}$ afforded a new peak at 5.7 min. Mixture was filtered through Celite and placed on silica gel. Elution with 30 % EtOAc/hexanes resulted only in starting allenic ester **46** recovery according to $GC2_{T1}$.

Preparation of 1(*E*),2(*E*)-5-Methyl-hexadien-5-ol (60).

This product was isolated from an attempt to add Me_3Al to allenic ester **46**, but yielded **60** as a result of the addition of 2 methyls attacking at the ester carbon. The procedure was identical to **101**. Reaction was purified on flash chromatography (10 % EtOAc/hexanes) to afford 85.6 % **60**. $GC2_{T1}$ = 4.1 min; IR neat, cm^{-1} (intensity) 3680 - 3080 (br, s), 2960 (s), 1945 (s), 1460 (m), 1370 (m), 1130 (m), 835 (s); ^1H NMR ($CDCl_3$) δ 1.19 (6H, s), 1.92 - 2.02 (1H, br), 2.14 (2H, dt, J = 7 Hz, 4 Hz), 4.64 (2H, dt, J = 7 Hz, 5 Hz), 5.10 (1H, p, J = 7 Hz); MS/EI, m/z, (%) 112 (trace), 97 (15), 77 (8), 59 (100), 43 (30); MS/CI, isobutane, m/z, (%) 95 (100); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 28.65, 28.71, 42.83, 70.72, 73.86, 85.42; Anal calcd for $C_7H_{12}O_2$: C = 74.94, H = 10.80, O = 14.26; Found: C = 74.82, H = 10.69.

Preparation of 4-Bromo-1-butyne (48).

On a 200 mL rbf containing PBr_3 (40.9 g, 151 mmol) was placed a pressure equalized dropping funnel containing pyridine (11.29 g, 143 mmol) and

homopropargyl alcohol (3-butyne-1-ol) (20 g, 285 mmol). The flask was supported in an ultrasonic bath containing ice and the contents of the funnel were slowly added over 1 hr. Frequent swirling was necessary as the reaction became very thick, which was diluted with *o*-xylene (30 mL). After an additional 1 hr swirling/sonicating the mixture was distilled at atmospheric pressure using a 25.4 cm Vigereux column to yield 27.3 g (71 %) **48**. bp = 118 °C @ 760 mm•Hg; $GC2_{T3}$ = 2.2 min; ρ = 1.50 g/mL; IR neat, cm^{-1} (intensity) 3308 (s), 2950 (w), 1425 (w), 1280 (s), 1225 (m), 903 (w); ^1H NMR ($CDCl_3$) δ 2.11 (1H, t, J = 3 Hz), 2.78 (2H, dt, J = 5 Hz, 3 Hz), 3.45 (2H, t, J = 3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 22.78, 29.11, 70.30, 80.92; MS/EI, m/z, neat, cm^{-1} (%) 134 (100), 132 (95), 95 (18), 93 (22), 81 (17), 79 (16), 53 (50). The volatility of the compound did not allow for satisfactory combustion analysis.

Preparation of a mixture of 1(*E*)-4-Bromo-1-(tri-*n*-butylstannyl)-butene (65) and 4-Bromo-2-(tri-*n*-butylstannyl)-butene (64).

To **53** (4 mmol) in THF (15 mL) at -78°C was added bromide **48** (0.36 mL, 4 mmol) and stirred for 1 hr. The reaction was quenched into 50 mL satd NH_4Cl/MeOH (1:1) and extracted with 3 x 50 mL ether. The ether was dried with $MgSO_4$, filtered through Celite and concentrated *in vacuo*. Flash chromatography (5 % EtOAc/hexanes) afforded 1.22 g (72 %) of **64** and **65** as a 55:45 ratio.$GC1_{T2}$ = 6.0 min (**64**), 6.3 min; (**65**).MS/EI, m/z, (%) both isomers 369 (30), 367 (50), 365 (40), 313 (50), 311 (70), 309 (60), 257 (60), 255 (70), 253 (55), 201 (75), 199 (100), 197 (80), 179 (25), 177 (30), 175 (20), 121 (30), 119 (25), 55 (20), 44 (20); ^1H NMR ($CDCl_3$) δ 0.75 - 0.83 (15H, m), 1.25 - 1.33 (6H, m), 1.42 - 1.55 (6H, m), 1.96 (2H, t, J = 4 Hz), 2.42 (2H, dt, J = 4 Hz, 18 Hz), (**64**) (vinyl region) 5.11 (1H, ddt, J = 1 Hz, 3 Hz, 65 Hz), 5.70 (1H, ddt, J = 1.5 Hz, 3 Hz, 140 Hz); (**65**) (vinyl region) 5.99 (1H, ddt, J = 2 Hz, 18 Hz, 60 Hz), 6.02 (1H, ddt, J = 6 Hz, 18 Hz, 47 Hz).

Alternate preparation of a mixture of 1(*E*)-4-Bromo-1-(tri-*n*-butylstannyl)-butene (65) and 4-Bromo-2-(tri-*n*-butylstannyl)-butene (64).

To **54** (4 mmol) in THF (15 mL) at -78°C was added bromide **48** (0.36 mL, 4 mmol) and stirred for 1 hr. Quenching and purification were as above to afford 1.17 g (69 %) **64** and **65** as a 50:50 ratio.

Alternate preparation of a mixture of 1(*E*)-4-Bromo-1-(tri-*n*-butylstannyl)-butene (65) and 4-Bromo-2-(tri-*n*-butylstannyl)-butene (64).

To **55** (4 mmol) in THF (15 mL) at -78°C was added bromide **48** (0.36 mL, 4 mmol) and stirred for 1 hr. Quenching and purification were as above to afford 1.24 g (73 %) **64** and **65** as a 30:70 ratio.

Alternate preparation of a mixture of 1(*E*)-4-Bromo-1-(tri-*n*-butylstannyl)-butene (65) and 4-Bromo-2-(tri-*n*-butylstannyl)-butene (64).

To **53** (4 mmol) in THF (15 mL) at -78°C was added DMS (0.25 g, 4 mmol) and stirred for 1 hr. This was followed by the addition of bromide **48** (0.36 mL, 4 mmol) and stirred for 18 hr. Quenching and purification were as above to afford 1.31 g (77 %) **64** and **65** as a 60:40 ratio.

Preparation of Jones oxidation reagent (99).[37]

To CrO_3 (26.7 g, 267 mmol) dissolved in H_2O (77 mL) at 0 °C was CAREFULLY and SLOWLY added, in *ca* 5 mL increments, with swirling, concentrated H_2SO_4 (23 mL).

Preparation of 3-Pentynoic acid (74).

To 3-pentyn-1-ol (8 g, 95.09 mmol) in acetone (500 mL) at 0 °C was added Jones reagent **99** (47 mL, 206 mmol) over 20 min to produce a brown solution with green precipate. Reaction was stirred/swirled for an additional 30 min when excess isopropyl alcohol was added resulting in homogeneity.

Most of the acetone was carefully (FOAMS) removed *in vacuo* and the residue was filtered through Celite into a separatory funnel and extracted with 3 x 100 mL pentane. The pentane was washed with 3 x 100 mL H_2O and extracted twice with satd Na_2CO_3 solution. The aqueous phase was acidified to pH=1 with 1 M HCl and extracted with 3 x 100 mL ether. The ether was washed with 2 x 100 mL H_2O, dried over $MgSO_4$, filtered through Celite and concentrated *in vacuo* to afford 4.3 g (39.3 %) white solid. mp = 102 °C; $GC1_{T1}$ = 1.4 min; IR nujol, cm^{-1} (intensity) 3500 - 2500 (br, s), 1725 (m), 1470 (s), 1385 (s), 1250 (w); ^1H NMR ($CDCl_3$) δ 1.82 (3H, t, J = 3 Hz), 3.30 (2H, q, J = 3 Hz), 8.8 - 9.2 (1H, broad); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 3.50, 25.84, 69.70, 80.00, 175.20; MS/EI, m/z, (%) 98

(100), 53 (40); Anal calcd for $C_5H_6O_2$: C = 61.21, H = 6.18, O = 32.61; Found: C =60.92 , H = 5.91.

Preparation of 5-Iodo-1-pentyne (70).[38]

To 5-chloro-1-pentyne **93** (12.54 g, 122 mmol, $GC2_{T2}$ = 1.8 min) in methyl ethyl ketone (100 mL) was added NaI (27.5 g, 183 mmol, 1.5 eq) in *ca* 5 g portions (quite exothermic). Reaction was refluxed in the dark for 24 hr. Precipitation of NaCl occured during this time.

Most of the solvent was removed *in vacuo* and the residue was filtered through Celite into a separatory funnel and partioned between 100 mL H_2O. The H_2O was extracted with 3 x 100 mL of ether. The ether was concentrated and the residue distilled to afford 18.08 g (77 %) **70**. bp = 90 °C @ 30 mm•Hg; $GC2_{T2}$ = 3.3 min; ρ = 1.60 g/mL; IR neat, cm^{-1} (intensity) 3315 (s), 2950 (w), 1440 (m), 1230 (s), 1180 (m); ^1H NMR ($CDCl_3$) δ 2.00 (3H, m), 2.33 (2H, m), 3.32 (2H, t, J = 6 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 4.98, 19.32, 31.68, 69.40, 82.06; MS/EI, *m/z*, (%) 194 (60), 67 (100); Anal calcd for C_5H_7I: C = 30.95, H = 3.64, I = 65.41; Found: C =30.69 , H = 3.49.

Preparation of 1-(*O*-Tetrahydropyranyl)-3-pentyne (75).[39]

To 3-pentyn-1-ol (6.93 g, 82.74 mmol) was added 3,4-dihydro-2*H*-pyran (7.38 g, 87.7 mmol) and a few crystals of *p*-toluenesolfonic acid. Reaction was stirred overnight, decolorized with charcoal, and concentrated i*n vacuo* 6 hr affording 11.9 g (86 %) pure **75**. $GC1_{T1}$ = 2.7 min; $GC2_{T4}$ = 6.5 min; bp = 130 °C @ 20 mm•Hg; IR neat, cm^{-1} (intensity) 2950 (s), 2890 (s), 1450 (s), 1360 (s), 1290 (m), 1270 (m), 1210 (s), 1030 (s), 970 (s), 920 (s), 880 (s), 825 (m); ^1H NMR ($CDCl_3$) δ 1.50 - 1.62 (6H, m), 1.78 (3H, t, J = 5 Hz), 2.43 (2H, m), 3.50 (2H, m), 3.75 (1H, m), 4.90 (1H, m), 4.62 (1H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 3.03, 19.19, 19.92, 25.25, 30.35, 61.80, 65.90, 75.65, 76.10, 96.40; MS/EI, m/z, (%), 167 (5), 153 (16), 140 (18), 126 (33), 115 (15), 101 (10), 85 (100), 67 (65), 41 (28); Anal calcd for $C_{10}H_{16}O_2$: C = 71.38, H = 9.60, O = 19.02; Found: C =71.00, H =9.45.

Preparation of 1-(*O*-Tetrahydropyranyl)-2-butyne (78).[39]

To neat alcohol **76** (15.8 g, 225 mmol) was added a few crystals of *p*-toluenesulfonic acid and 3,4 dihydro-2*H*-pyran (20.9 g, 247 mmol, 1.1 eq) was added in *ca* 5 g increments (quite exothermic). CH_2Cl_2 (5 mL) was used to rinse the walls of the flask. The reaction was stirred for 1 hr and was distilled to afford 27.06 g (82 %) **78**. The vacuum distillation did not proceed smoothly even in the presence of efficient stirring. bp = 65 - 67 °C @ 0.35 mm•Hg; $GC1_{T1}$ = 2.2 min; $GC2_{T2}$ = 3.5 min; ρ = 1.01 g/mL; IR neat, cm^{-1} (intensity) 2960 (s), 2895 (s), 1450 (m), 1355 (m), 1210 (s), 1125 (s), 1030 (s), 915 (m), 880 (m); ^1H NMR ($CDCl_3$) δ 1.50 - 1.83 (6H, m), 1.85 (3H, t, J = 3 Hz), 3.53 (2H, m), 3.83 (1H, m), 4.17 (1H, dq, J = 15 Hz, 3 Hz), 4.82 (1H, t, J = 3 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 18.91, 19.37, 25.22, 30.10, 50.79, 54.37, 61.67, 81.76, 96.48; MS/EI, m/z, (%) 153 (4), 111 (18), 101 (42), 85 (62), 67 (25), 53 (100), 41 (41); Anal calcd for $C_9H_{14}O_2$: C = 70.10, H = 9.15 O = 20.75; Found C = 69.92, H = 8.95.

Preparation of 3(*E*)-Ethyl 3-methyl-3-(tri-*n*-butlystannyl)-butenoate (80).[40]

To di-isopropyl amine (13.86 g, 137 mmol) in THF (400 mL) at -78 °C was slowly added *n*-BuLi (57 mL, 137 mmol, 2.5 M) and stirred for 30 min followed by tri-*n*-butyl tin hydride **58** (40 g, 137 mmol) and stirred for an additional 1 hr. $CuBr•SMe_2$ (30.97 g, 151 mmol, 1.1 eq) was then added carefully in *ca* 5 g portions at which point the reaction was dark green. After a further 1 hr of stirring, ethyl 3-butynoate (16.9 g, 150 mmol) was added and stirred for an additional 1 hr.

The reaction was quenched with 1.5 M HCl and extracted with 3 x 100 mL ether, dried over $MgSO_4$, filtered through Celite and concentrated *in vacuo*. Flash chromatography on silica pre-treated with *ca* 4 mL Et_3N in hexanes was performed collecting 1-500 mL fraction (which contained Bu_4Sn and $(Bu_4Sn)_2$), and then 20 % EtOAc/hexanes into another 600 mL fraction to afford 40 g (72 %) **80**. $GC1_{T1}$ = 7.0 min; IR neat, cm^{-1} (intensity) 2990 (s), 2970 (s), 1725 (s), 1610 (m), 1480 (m), 1350 (m), 1270 (m), 1180 (s), 1050 (m), 880 (m); ^1H NMR ($CDCl_3$) δ 0.86 (9H, t, J = 7.2 Hz), 0.93 (6H, m), 1.28 (9H, m), 1.45 (6H, m), 2.37 (3H, dd, J = 36 Hz, 3 Hz), 4.12 (2H, qd, J = 6.8 Hz, 0.8 Hz), 5.93 (1H, tqd, J = 65 Hz, 3 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 9.4, 13.5, 14.3, 22.2, 27.2, 28.8, 59.4, 128.2,

164.3, 168.8; MS/CI, isobutane, m/z, (%) 405 (100), 403 (78), 347 (15), 345 (11), 291 (trace); Anal calcd for $C_{18}H_{36}O_2Sn$: C = 53.62, H = 9.00, O = 7.94, Sn = 29.44; Found C = 53.27, H = 8.91.

Preparation of 3(*E*)-3-(Tri-*n*-butylstannyl)-3-methyl-butene-1-ol (81).

To vinyl stannyl ester **80** (39.24 g, 97.1 mmol) in ether (250 mL) at -78 °C was slowly added DIBAlH (235 mL, 235 mmol, 2.4 eq). The reaction was stirred for 1 hr and carefully quenched with aqueous tartaric acid. The mixture was transferred to a separatory funnel and the water drained. The ether was then washed with 3 x 50 mL 1 M NaOH solution, dried over $MgSO_4$, filtered through Celite and concentrated *in vacuo*.

The mixture was then placed on flash silica that had been pre-treated with *ca* 4 mL Et_3N in hexanes. 1-500 mL fraction of hexanes was collected, then a second 500 mL fraction of 50 % EtOAc/hexanes containing, after concentration, 20.69 g (60 %) **81**. $GC1_{T1}$ = 6.3 min; IR neat, cm^{-1} (intensity) 3600 - 3120 (br, s), 2990 (s), 2950 (s), 2900 (s), 1475 (s), 1390 (m), 1190 (m), 1060 (s), 1020 (w); ^1H NMR ($CDCl_3$) δ 0.89 (15H, m), 1.30 (6H, p, J = 7 Hz), 1.47 (6H, m), 2.38 (3H, dd, J = 45 Hz, 2 Hz), 4.23 (2H, d, J = 12 Hz), 5.73 (1H, dtq, J = 68 Hz, 12 Hz, 2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 8.77, 9.12, 13.69, 27.39, 29.13, 58.90, 69.80, 139.30; MS/EI, m/z, (%) 305 (100), 303 (70), 249 (75), 247 (50), 193 (75), 191 (50), 177 (25), 175 (18), 137 (45), 135 (35), 121 (25), 119 (17); Anal calcd for $C_{16}H_{34}OSn$: C = 53.21, H = 9.49, O = 4.43, Sn = 32.87; Found: C = 52.97, H = 9.11.

Preparation of 6(*E*)-6-Methyl-8-(*O*-tetrahydropyranyl)-ene-1-octyne (82).

To vinyl stannane **77** (1.40 g, 3.14 mmol) in THF (70 mL) at -78 °C was added *n*-BuLi (1.31 mL, 3.14 mmol, 2.4 M). The reaction was stirred for 2.5 hr then lithium 2-thienylcyanocuprate (6.28 mL, 3.15 mmol) was added. After 30 min with stirring, alkynyl iodide **70** (0.38 mL, 3.14 mmol) and HMPA (1.09 mL, 3.14 mmol) were added and the reaction stirred in the dark overnight.

The reaction was quenched with 1.5 M HCl and extracted with 3 x 100 mL ether. The ether was dried with $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. Flash chromatography (100 % hexanes) collecting 1-500 mL fraction (which contained Bu_4Sn) followed by 10 % EtOAc/hexanes afforded 0.5 g (72 %) **82.** $GC1_{T1}$ = 4.8 min; IR neat, cm^{-1} (intensity) 3320 (m), 2990 (m), 2960 (s), 1450

(m), 1210 (m), 1125 (s), 1030 (s), 920 (w), 880 (w); ^{1}H NMR ($CDCl_3$) δ 1.50 (6H, m), 1.70 (6H, m), 1.95 (1H, t, J = 2 Hz), 2.16 (3H, m), 3.50 (1H, m), 3.92 (1H, m), 4.05 (1H, ddd, J = 18 Hz, 5 Hz, 1 Hz), 4.20 (1H, ddd, J = 18 Hz, 7 Hz, 1 Hz), 4.63 (1H, t, J = 7 Hz), 5.37 (1H, tq, J = 14 Hz, 1 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 15.08, 17.84, 18.22, 19.46, 25.37, 30.60, 58.50, 62.16, 63.52, 65.69, 97.8, 98.8, 115.5, 121.3; MS/EI, m/z, (%) 221 (trace), 177 (10), 149 (27), 137 (40), 121 (35), 105 (15), 85 (100), 67 (48), 55 (38), 41 (85); Anal calcd for $C_{14}H_{22}O_2$: C = 75.62, H = 9.99, O = 14.39; Found: C = 75.59, H = 9.88.

Preparation of 6(*E*)-8-Hydroxy-6-methyl-ene-1-octyne (83).

To **82** (120 mg, 0.54 mmol) in CH_3OH (30 mL) was added a spatula tip of *p*-toluenesulfonic acid. The reaction was stirred for 3 hr, concentrated *in vacuo*, and mixed with ether (30 mL). The ether was washed with 2 x 20 mL satd Na_2CO_3, and the H_2O phase was re-extracted with 3 x 20 mL ether. The combined etheral phases were dried over $MgSO_4$, filtered through Celite, and concentrated to afford 60 mg (81 %) **83**. $GC1_{T1}$ = 1.9 min; IR neat, cm^{-1} (intensity) 3700 - 3100 (br, s), 3322 (s), 2940 (s), 2890 (s), 2140 (w), 1680 (m), 1440 (s), 1390 (s), 1010 (s), 880 (w); ^{1}H NMR ($CDCl_3$) δ 0.87 (2H, p, J = 7 Hz), 1.32 - 1.37 (1H, br), 1.67 (2H, t, J = 7 Hz), 1.94 (1H, t, J = 3 Hz), 2.13 (2H, t, J = 7 Hz), 2.16 (3H, td, J = 8 Hz, 2 Hz), 4.13 (2H, d, J = 5 Hz), 5.42 (1H, tq, J = 12 Hz, 2 Hz); ^{13}C {^{1}H} NMR ($CDCl_3$) δ 14.60, 16.50, 17.83, 26.37, 29.31, 38.26, 59.25, 68.37, 123.00; MS/EI, m/z, (%) 137 (trace), 123 (32), 105 (50), 95 (60), 79 (100), 71 (95), 53 (55), 41 (95); Anal calcd for $C_9H_{14}O$: C = 78.13, H = 10.23, O = 11.57; Found: C =77.96 , H =9.96.

Preparation of 3(*E*)-Ethyl 4-methyl-dodeceneoate.

This product was the result of a carboalumination test reaction, followed by alanate attack on ethyl bromoacetate.

To $ZrCp_2Cl_2$ (1.46 g, 5 mmol) in 1,2-dichloroethane (50 mL) was added Me_3Al (7.5 mL, 15 mmol) and the reaction stirred 15 min. To the lemon-yellow solution was added 1-decyne (95.3 mg, 5 mmol) and stirred overnight. The reaction was placed under vacuum for 2.5 hr and re-dissolved in 1,2-dichloroethane (60 mL) and cooled to -78 °C. Then, *n*-BuLi (2 mL, 5 mmol) followed with HMPA (1 mL) and ethyl bromoacetate (0.6 mL, 5 mmol) were

added, and stirred 1 hr. Reaction was quenched with 1.5 M HCl, extracted with 3 x 50 mL ether. The ether was dried with $MgSO_4$, filtered through Celite and concentrated. Flash chromatography (30 % EtOAc/hexanes) afforded 960 mg (80 %) colorless oil. $GC1_{T3}$ = 6.5 min; IR neat, cm^{-1} (intensity) 2940 (s), 2870 (s), 1745 (s), 1470 (m), 1375 (m), 1310 (m), 1040 (m), 735 (w); ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 6 Hz), 1.25 (14H, m), 1.62 (3H, m), 2.0 (3H, t, J = 7 Hz), 3.05 (2H, d, J = 8 Hz), 4.15 (2H, q, J = 6 Hz), 5.28 (1H, tq, J = 14 Hz, 1 Hz); MS/EI, m/z, (%) 240 (4), 155 (17), 142 (22), 110 (23), 96 (35), 69 (100), 55 (95), 41 (98); MS/CI, isobutane, m/z, (%) 241 (100); Anal calcd for $C_{15}H_{28}O_2$: C = 74.95, H = 11.74, O = 13.31; Found: C = 74.59, H = 11.91.

Purification of $ZnBr_2$.

Typically, $ZnBr_2$ (40 g) was mixed with thionyl chloride (150 mL) in a rbf equipped with a stirbar and an efficient reflux condensor. The slurry was refluxed under argon for 6 hr, with a gradual yellow colour appearing. Most of the thionyl chloride was removed by aspirator, and then placed under vacuum (N_2 in trap) overnight. The $ZnBr_2$ was a light tan powder.

Preparation of 2(*E*)-1-(*O*-Tetrahydropyranyl)-3-(tri-*n*-butlystannyl)-butene (77).

To (n-$Bu_3Sn)_2$ (16.8 mL, 33 mmol) in THF (200 mL) at -60 °C was slowly added over 20 min *n*-BuLi (13.6 mL, 33 mmol). The reaction suddenly turned tan yellow after *ca* 5 mL of *n*-BuLi was added and remained so. Reaction was stirred for an additional 30 min followed by rapid addition of $ZnBr_2$ (3.72 g, 16.5 mmol). Reaction became brilliant yellow as the $ZnBr_2$ dissolved, which often took 2 hr. Dissolution may be encouraged by warming to a maximum of -35 °C. The THP-protected alcohol **78** (1.855 g, 12.03 mmol) was then added at -78 °C followed by a few crystals of CuCN at which point the reaction turned orange for a moment. The reaction was stirred overnight and worked-up as follows.

50 mL 1.5 M HCl was added and the mixture was extracted with 3 x 100 mL of ether. The ether was dried over $MgSO_4$, filtered through Celite, and removed *in vacuo*. The entire mixture was placed on *ca* 250 g flash silica which had been previously pre-treated with *ca* 4 mL Et_3N in hexanes. One 600 mL fraction was collected which contained Bu_4Sn and $(Bu_4Sn)_2$, then elution was

conducted with 10 % EtOAc/hexanes to afford 3.39 g (63.2 %) pure vinyl stannane **77**. $GC1_{T1}$ = 8.2 min; ρ = 1.11 g/mL; IR neat, cm^{-1} (intensity) 2975 (s), 2940 (s), 1470 (w), 1460 (w), 1035 (m); ^1H NMR ($CDCl_3$) δ 1.00 (15H, m), 1.38 (12H, m), 1.62 (6H, m), 1.98 (3H, m), 3.47 (1H, m), 3.90 (1H, m), 4.33 (1H, m), 4.62 (1H, m) 4.78 (1H, m), 5.15 (1H, dtq, J = 70 Hz, 12 Hz, 2 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 9.15, 13.16, 19.44, 19.65, 25.54, 27.32, 29.11, 30.78, 62.32, 63.14, 97.89, 136.78, 142.94; MS/EI, m/z, (%) 389 (20), 387 (17), 305 (40), 302 (35), 177 (25), 175 (20), 121 (10), 119 (8), 85 (100); Anal calcd for $C_{21}H_{42}O_2Sn$: C = 56.65, H = 9.51, O = 7.19, Sn = 26.66; Found: C = 56.29, H = 9.22.

Alternate preparation of 2(*E*)-1-(*O*-Tetrahydropyranyl)-3-(tri-*n*-butlystannyl)-butene (77).

The product was converted from stannyl alcohol **81** to the THP protected derivative as in alkyne **78**, except almost 1 eq *p*-TsOH was required which, generated *ca* 10 % of the corresponding de-stannylated alkene **88**. The product was purified in a manner analogously by flash chromatography as in the procedure for to yield 78 % **77**.

Preparation of 3(*E*)-7-Iodo-4-methyl-hepten-1-ol (101).

To $ZrCp_2Cl_2$ (6.26 g, 21.4 mmol) in dry 1,2-dichloroethane (40 mL) was added Me_3Al (48.22 mL, 42.88 mmol) and the lemon yellow solution was stirred 30 min at rt. Iodo-alkyne **70** (4.16 g, 21.44 mmol) was then added slowly, and stirred in the dark for 24 hr. GC analysis ($GC1_{T1}$) showed complete consumption of the alkyne.

The mixture was then placed under vacuum for 6 hr to remove the 1,2-dichloroethane and excess Me_3Al. The contents were transferred *via* canula into another flask, using 3 x 40 mL pentane and cooled to -78 °C. This was followed followed by slow addition of *n*-BuLi (8.56 mL, 21.4 mmol). A thick yellow precipate made stirring difficult and frequent swirling was found to be necessary. After 30 min of stirring/swirling, a minimum amount of ethylene oxide was bubbled directly into the slurry immediately causing it to separate into clear yellow and yellow sludge layers. Stirring was continued for 30 min.

The reaction was carefully quenched with 1.5 M HCl and extracted with 3 x 100 mL ether. The ether was dried over $MgSO_4$, filtered through Celite and

removed *in vacuo*. Flash chromatography in the dark (20 % EtOAc/hexanes) afforded 4.01 g (73 %) **101**. $GC1_{T1}$ = 3.9 min; IR neat, cm^{-1} (intensity) 3690 - 3100 (br, s), 2950 (s), 1450 (m), 1390 (m), 1250 (m), 1230 (m), 1180 (m), 1055 (s), 890 (w); ^1H NMR ($CDCl_3$) δ 1.63 (3H, br, s), 1.95 (2H, m), 2.01 (1H, br), 2.08 (2H, p, J = 7 Hz), 2.25 (2H, q, J = 7 Hz), 3.14 (2H, t, J = 7 Hz), 3.62 (2H, t, J = 7 Hz), 5.19 (1H, tq, J = 7 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 6.33, 16.05, 31.51, 40.14, 44.70, 62.43, 121.47, 136.40; MS/CI, isobutane, m/z (%) 255 (100), 237 (45), 127 (5), 109 (30); Anal calcd for $C_8H_{15}IO$: C = 37.81, H = 5.95, I = 49.99, O = 6.3; Found C = 37.49, H = 5.44.

Alternate preparation of 3(*E*)-7-Iodo-4-methyl-hepten-1-ol (101).

The procedure was identical as that for **70**. Flash chromatography in the dark (20 % EtOAc/hexanes) afforded 79 % **101**.

Preparation of 3(*E*)-1-(*O*-Tertiarybutyldimethylsilyl)-7-Iodo-4-methyl-heptene (102).[41]

To iodo alcohol **101** (5 g, 19.5 mmol) was added tertiarybutyldimethylsilyl chloride (4.39 g, 29.2 mmol), Et_3N (3.04 g, 29.25 mmol), CH_2Cl_2 (30 mL) and a few crystals of 4-*N,N*-dimethylamino pyridine with stirring for 30 min at rt. The solvent was removed *in vacuo* and the residue redissolved in *ca* 100 mL ether in a separatory funnel. The ether was mixed with 1.5 M HCl until the pH was 1. The ether was dried over $MgSO_4$, filtered through Celite and removed *in vacuo.*

The product was purified by flash chromatography in the dark (10% EtOAc/hexanes) to afford 18.12 g (93 %) **102**. $GC1_{T1}$ = 5.8 min; IR (neat, cm^{-1}) 2980 (s), 2950 (s), 1475 (m), 1390 (w), 1275 (m), 1100 (s), 850 (s), 790 (m); ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 1.60 (3H, br), 1.91 (2H, m), 2.08 (2H, p, J = 7 Hz), 2.22 (2H, q, J = 7 Hz), 3.14 (2H, t, J = 7 Hz), 3.57 (2H, t, J = 7 Hz), 5.19 (1H, tq, J = 7 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ -5.25, 0.99, 6.3, 16.1, 25.96, 31.86, 40.11, 44.81, 62.92, 120.14, 136.11; MS/EI, m/z, (%) 369 (25), 353 (5), 311 (10), 293 (5), 275 (5), 249 (5), 237 (100), 227 (5), 109 (40); Anal calcd for $C_{14}H_{29}IOSi$: C = 45.65, H = 7.49, I = 34.45, O = 4.34, Si = 7.62; Found C = 45.19, H = 7.70.

Alternate preparation of 3(*E*)-1-(*O*-Tertiarybutyldimethylsilyl)-7-iodo-4-methyl-heptene (102).

Procedure was identical as for the preparation of **70**. Flash chromatography in the dark (10 % EtOAc/hexanes) afforded 81 % **102**.

Preparation of 3(*E*),8(*E*)-1-(*O*-Tertiarybutyldimethylsilyl)-10-(*O*-tetrahydropyranyl)-4,8-dimethyl-decadiene (100).

To vinyl stannane **77** (2.62 g, 5.9 mmol) in THF (150 mL) at -78 °C was added *n*-BuLi (2.71 mL, 6.0 mmol) with stirring for 2 hr. Then, lithium 2-thienylcyanocuprate (11.8 mL, 5.9 mmol, 0.5 M) was added with stirring for a further 1 hr. Iodoalkene **102** (2.17 g, 5.9 mmol) was next added followed immediately with HMPA (1 mL, 5.9 mmol). The reaction was stirred overnight in the dark and the clear orange reaction was quenched with 1.5 M HCl and extracted with 3 x 100 mL ether, dried with $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The mixture was then placed on flash silica and eluted with 400 mL hexanes (which contained Bu_4Sn) followed by 10 % EtOAc/hexanes to afford 1.6 g (73 %) product. $GC1_{T1}$ = 8.8 min; IR neat, cm^{-1} (intensity) 2960 (s), 2880 (s), 1475 (m), 1395 (m), 1270 (s), 1210 (m), 1110 (s), 1040 (s), 850 (s), 790 (m); MS/CI, isobutane, m/z, (%) 397 (trace), 163 (100); ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.92 (9H, s), 1.4 - 1.6 (14H, m), 1.65 (3H, s), 1.59 (3H, s), 1.95 (1H, dt, J = 14 Hz, 4 Hz), 2.21 (1H, q, J = 8 Hz), 3.57 (1H, m), 3.89 (1H, m), 4.01 (1H, m), 4.22 (1H, m), 4.61 (1H, t, J = 4 Hz), 5.10 (1H, dt, J = 8 Hz, 1 Hz), 5.34 (1H, dt, J = 8 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ -5.3, 16.0, 16.3, 19.6, 25.5, 25.9, 30.7, 31.8, 39.2, 39.3, 62.2, 63.1, 63.6, 76.6, 97.7, 120.4, 120.6; Anal calcd for $C_{23}H_{44}O_3Si$: C = 69.64, H = 11.18, O = 12.10, Si = 7.08; Found: C = 69.43, H = 10.97.

Preparation of 3(*E*),8(*E*)10-(*O*-Tetrahydropyranyl)-4,8-dimethyl-decadien-1-ol (96).

To silyl protected alcohol **100** (0.54 g, 8.9 mmol) was added *n*-Bu_4NF in THF (10 mL, 10 mmol). The reaction immediately turned dark brown. Stirring was continued for 30 min and quenched with 1.5 M HCl. The aqueous phase was extracted with 3 x 100 mL ether, and the ether phase was washed with 3 x 50 mL 1.5 M HCl. The ether was dried with $MgSO_4$, filtered through Celite, concentrated

in vacuo, and purified by flash chromatography (30 % EtOAc/hexanes) to yield 0.4 g (73 %) **96**. $GC1_{T1}$ = 7.4 min; IR neat, cm^{-1} (intensity) 3650 - 3200 (br, s), 2960 (s), 2890 (s), 1450 (m), 1390 (s), 1210 (m), 1130 (s), 1030 (s), 920 (m), 880 (m), 820 (m); ^1H NMR ($CDCl_3$) δ 1.45 - 1.56 (12H, m), 1.60 - 1.66 (4H, m), 1.97 (3H, t, J = 8 Hz), 2.26 (3H, q, J = 4 Hz), 3.50 (1H, m), 3.60 (1H, t, J = 6 Hz), 3.88 (1H, m), 4.00 (1H, m), 4.21 (1H, m), 4.61 (1H, t, J = 7 Hz), 5.12 (1H, td, J = tq, J = 6.2 Hz, 1 Hz), 5.33 (1H, tq, J = 6.3 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 16.09, 16.28, 19.59, 25.50, 25.92, 30.72, 31.52, 39.15, 39.34, 62.26, 62.49, 63.68, 97.84, 120.01, 120.82, 138.50, 140.04; MS/CI, isobutane, m/z, (%) 282 (trace), 181 (100), 163 (62), 137 (35), 125 (5), 103 (15); Anal calcd for $C_{17}H_{30}O_3$: C = 72.30, H = 10.71, O = 16.99; Found: C = 71.96, H = 10.92.

Preparation of (3*E*)-Ethyl 7-Iodo-4-methyl-heptenoate (86).

To 2.92 g (10 mmol) $ZrCp_2Cl_2$ in 1,2-dichloroethane (25 mL) was added Me_3Al (10 m, 20 mmol, 2.0 M, 2 eq) and the reaction was stirred for 15 min to provide a lemon yellow solution. To this was added iodoalkyne **70** (1.2 mL, 10 mmol) and the reaction stirred for 24 hr in the dark. The mixture was placed under vacuum for 4 hr to remove the solvent and excess Me_3Al, transferred *via* canula with 3 x 25 mL pentane into a new flask ($ZrCp_2Cl_2$ remained) and cooled to -30 °C. Then, *n*-BuLi (4 mL, 10 mmol) and HMPA (1.76 mL, 10 mmol) were added to produce a yellow precipate. To this was added ethyl bromoacetate (1.34 mL, 12 mmol). The reaction was stirred in the dark overnight and placed under vacuum for 6 hr.

The product was purified by flash chromatography (in the dark, 10 % EtOAc/hexanes) to afford 2.27 g (75 %) **86**. $GC2_{T2}$ = 8.8 min; IR neat, cm^{-1} (intensity) 3000 (s), 2950 (s), 1740 (s), 1620 (s), 1540 (s), 1450 (m), 1375 (m), 1300 (s), 1180 (m), 1040 (m), 810 (w); MS/EI, m/z, (%) 296 (trace), 223 (30), 181 (15), 169 (100), 155 (40), 123 (60), 95 (70), 81 (20), 67 (15), 55 (10); ^1H NMR ($CDCl_3$) δ 1.3 (5H, m), 1.6 (3H, t, J = 13 Hz), 2.0 (4H, m), 3.1 (2H, q, J = 8 Hz), 4.2 (2H, q, J = 12 Hz), 5.3 (1H, m); Anal calcd for $C_{10}H_{17}IO_2$: C = 40.55, H = 5.80, I = 42.85, O = 10.80; Found: C = 40.12, H = 5.56.

Preparation of 4(*E*),6(*E*)-1,10-Dichloro-4,7-dimethyl-decadiene (92).

This product resulted from the attempt to couple bromo ortho ester **89** with the alane resulting from **93** using palladium catalysis (Figure 20).

To $ZrCp_2Cl_2$ (4.38 g, 15 mmol) in 1,2-dichloroethane (30 mL) at rt was slowly added Me_3Al in hexanes (15 mL, 30 mmol, 2 M) with stirring for 15 min. Then, 5-chloropentyne (1.6 mL, 15 mmol) was added and the reaction was stirred over night. Then, a mixture of $Pd(PPh_3)_4$ (0.87 g, 0.75 mmol), and bromo ortho ester **89** (3.10 g, 15 mmol, $GC2_{T5}$ = 6.4 min) in THF (40 mL) were added at once to produce an orange solution. The reaction was stirred overnight and carefully quenched with 1 M HCl and extracted with 3 x 100 mL ether. The ether was dried with $MgSO_4$, filtered through Celite, and concentrated. Flash chromatography (10 % EtOAc/hexanes) afforded 2.6 g (74 %) **92** $GC1_{T1}$ = 5.5 min; IR neat, cm^{-1} (intensity) 2950 (s), 2870 (s), 1450 (s), 1390 (m), 1320 (s), 1300 (s), 1270 (m), 980 (m), 900 (m), 820 (m), 730 (m), 670 (s); MS/CI, isobutane, m/z, (%) 235 (100), 237 (65), 207 (55), 209 (45), 171 (20), 173 (5), 145 (30), 147 (9), 131 (trace); ^1H NMR ($CDCl_3$) δ 1.75 (6H, s), 1.90 (4H, p, J = 6 Hz), 2.20 (4H, t, J = 6 Hz), 3.51 (4H, t, J = 6 Hz), 6.03 (2H, s); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 16.32, 30.90, 37.24, 44.52, 45.43, 121.81, 134.89; Anal calcd for $C_{12}H_{20}Cl_2$: C = 61.27, H = 8.59, Cl = 30.14; Found: C = 60.96, H = 8.48.

Preparation of 3(*E*)-7-Chloro-4-methyl-hepten-1-ol (104).

Preparation and purification were identical as the corresponding iodo compound **101**, except **104** was not handled in the dark, to yield 4.10 g (76 %) **104**. $GC1_{T1}$ = 2.9 min; $GC2_{T2}$ = 6.7 min; IR neat, cm^{-1} (intensity); 3650 - 3120 (s, br), 2950 (s), 1455 (m), 1280 (m), 1060 (s), 890 (m), 750 (m); ^1H NMR ($CDCl_3$) δ 1.60 (3H, br, s), 1.83 (2H, m), 2.00 (1H, br), 2.11 (2H, p, J = 7 Hz), 2.28 (2H, q, J = 7 Hz), 3.48 (2H, m), 3.57 (2H, m), 5.14 (1H, tq, J = 7 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 16.0, 30.7, 31.5, 36.7, 44.4, 62.3, 121.2, 136.5; MS/EI, m/z, (%) 162 (trace), 144 (2), 133 (8), 131 (25), 95 (65), 83 (9), 81 (19), 69 (32), 67 (60), 57 (10), 55 (100), 43 (9), 41 (45); MS/CI, isobutane, m/z (%) 165 (32), 163 (100), 147 (20), 145 (65), 126 (20), 109 (23); Anal calcd for $C_8H_{15}ClO$: C = 59.07, H = 9.30, Cl = 21.80, O = 9.84; Found: C =58.88, H =9.01.

Preparation of 3(*E*)-1-(*O*-Tertiarybutyldimethylsilyl)-7-chloro-4-methyl-heptene (105).

Product was converted to the silyl protected derivative and purified identically as for the iodo **102** analogue, except it was not handled in the dark, to afford 4.8 g (93 %). $GC1_{T1}$ = 4.7 min; IR, neat, cm^{-1} (intensity) 2990 (s), 2970 (s), 2880 (s), 1485 (m), 1475 (m), 1400 (w), 1270 (s), 1110 (s), 955 (m), 855 (s), 835 (m), 790 (s), 675 (w); ^1H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.88 (9H, s), 1.61 (3H, br, s), 1.86 (2H, m), 2.12 (2H, p, J = 7 Hz), 2.22 (2H, q, J = 7 Hz), 3.50 (2H, m), 3.58 (2H, m), 5.17 (1H, tq, J = 7 Hz, 1 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ -5.28, 0.98, 16.0, 25.94, 30.79, 31.84, 36.70, 44.49, 62.96, 121.83, 135.15; MS/CI, isobutane, (%) 279 (10), 277 (25), 221 (8), 219 (20), 147 (30), 145 (100), 109 (32); Anal calcd for $C_{14}H_{29}ClOSi$: C = 60.72, H = 10.56, Cl = 12.8, O = 5.78, Si = 10.14; Found: C = 60.55, H = 10.11.

Preparation of 2(*E*)-1-(*O*-Tetrahydropyranyl)-butene (81).

This product was isolated both from de-stannation of **77** and from the reaction involving the D_2O quenching experiment (Figure 18). The attempted coupling was performed exactly as for **82.** $GC1_{T1}$ = 1.6 min; $GC2_{T2}$ = 5.2 min; MS/EI, m/z, (%) 101 (10), 85 (65), 67 (20), 55 (100), 41 (40); The volatility of the compound did not allow for satisfactory elemental analysis.

Preparation of 2-Butynoic acid (74).

To ethyl 2-butynoate **79** (2.0 g, 17.8 mmol) in CH_3OH (20 mL) was added 1 M KOH (20 mL) and the reaction stirred overnight. The reaction was acidified with 1 M HCl to a pH of 1, and extracted with 3 x 50 mL ether. The ether was dried with $MgSO_4$, filtered through Celite and concentrated *in vacuo*. The solid was placed under vacuum for 2 hr to afford 1.36 g (91 %) white powder **74.** mp = 78 °C; $GC2_{T2}$ = 3.8 min; IR, nujol, cm^{-1} (intensity) 3400 - 2600 (br, w), 1710 (m), 1470 (m), 1390 (w); ^1H NMR ($CDCl_3$) δ 2.00 (3H, s), 8.7 - 8.9 (1H, br);$^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 3.84, 71.89, 88.49, 158.12; MS/EI, m/z, (%) 84 (100), 67 (95), 56 (18), 44 (25); Anal calcd for $C_4H_4O_2$: C = 57.14, H = 4.80, O = 38.06; Found: C = 56.90, H = 4.66.

Preparation of 2-(2'-butynyl)-4,4-dimethyl-2-oxazoline (68).[42]

To 2-amino-2-methyl-1-propanol (0.91 g, 10.2 mmol) in benzene (50 mL) and activated 4 Å molecular sieves (5 g) were added acid **74** (1 g, 10.2 mmol) and refluxed 18 hr to afford a whitish precipate. The flask was cooled to 0 °C, the suspension filtered and placed under vacuum 2 hr to afford 0.95 g (62 %) white solid **68**. mp = 130 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (6H, s), 1.80 (3H, s), 3.12 (2H, s), 3.54 (2H, s); Anal calcd for $C_9H_{13}NO$: C = 71.48, H = 8.68; N = 9.26, O = 10.58; Found: C = 71.19, H = 8.21, N = 9.11.

Preparation of 3(*E*),8(*E*)-Ethyl 4,8-dimethyl-10-hydroxy-decadienoate (78).

To a suspension of $ZrCp_2Cl_2$ (0.47 g, 1.61 mmol) in 1,2-dichloroethane (15 mL) was added Me_3Al (2.42 mL, 4.83 mmol, 2 M in hexanes) and stirred for 15 min. This was followed by the addition of deprotected alcohol **83** (0.222 g, 1.61 mmol). Reaction was stirred overnight, and the solvent and excess Me_3Al were removed under vacuum for 3 hr. The yellow slurry was extracted with 3 x 15 mL pentane *via* canula into a second rbf, cooled to -78 °C, and *n*-BuLi (0.67 mL, 1.61 mmol) added to produce a slurry. Then, HMPA (0.30 mL, 1.61 mmol) and ethyl bromoacetate (0.54 mL, 4.83 mmol) were added in succession and warmed to rt. Reaction was mixed with excess 1 M HCl, and extracted with 3 x 100 mL ether. The residue was saponified *in situ* with KOH (3 eq) in methanol (20 mL) to produce 76 mg (18 %) acid **85**.

Alternate preparation of 3(*E*),8(*E*)-Ethyl 4,8-dimethyl-10-hydroxy-decadienoate (78).[43,44]

Alcohol **83** (1.23 g, 8.9 mmol) was carboaluminated as above and placed under vacuum for 6 hr. The residue was transferred *via* canula with 3 x 20 mL pentane into a new flask. The pentane was removed under vacuum and the residue re-dissolved in THF (30 mL). This was added to an ice-cold solution of 9-*B*-methoxy-9-borabicyclo[3.3.1]nonane **52** (1.44 mL, 9 mmol) and stirred for 30 min. This was added to a solution of potassium *t*-butoxide (1.01 g, 9 mmol) and 2,6 di-*t*-butylphenol (1.86 g, 9 mmol) in THF (20 mL). To the resulting solution was added *t*-butyl alcohol (18 mmol) and drop-wise ethyl bromoacetate (2.2 mL, 20 mmol) and allowed to stir at rt for 2 hr. The reaction was quenched with 3 eq NaOAc/H_2O_2 (1:1) for 2 hr and extracted with 3 x 100 mL ether. The residue was

saponified *in situ* with KOH (3 eq) in methanol (20 mL) to produce 30 mg (17 %) acid **85**.

Preparation of Pyridinium dichromate (95).[45]

To CrO_3 (20 g, 0.2 mmol) in H_2O (20 mL) at 0 °C was slowly added pyridine (16.2 mL, 0.2 mmol). The solution produced a precipate that required swirling to achieve mixing. After *ca* 9 mL pyridine was added, the reaction started to become homogeneous. The reaction was diluted with acetone (80 mL) and cooled at -25 °C for 1.5 hr. The crystals were vacuum collected, washed with acetone and dried under vacuum to afford 29.03 g (37 %) bright orange crystals. mp = 139 - 141 °C; IR, nujol, cm^{-1} (intensity) 1470 (m), 1390 (m), 950 (w), 735 (w).

Preparation of 2(*E*),7(*E*)-3,7-Dimethyl-1,10-decadienedicarboxylic acid (106).

To alcohol **96** (100 mg, 0.36 mmol) in acetone (10 mL) was added drop-wise Jones reagent **99** (*ca* 3 drops) to produce an immediate green solution and precipate. The reaction was mixed with isopropyl alcohol (10 mL) and extracted with 3 x 25 mL ether. The ether was dried with $MgSO_4$, filtered through Celite, and concentrated *in vacuo* to afford 62 mg (76 %) yellow oil which showed two IR acid carbonyl stretches at 1708 cm^{-1} and 1692 cm^{-1} (conjugated). The product was assumed to be (*E,E*).

Preparation of 3(*E*),8(*E*)-10-(*O*-Tetrahydropyranyl)-4,8-dimethyl-decadien-1-al (98).[46]

To oxalyl chloride (3.34 mL, 38.23 mmol) in CH_2Cl_2 (20 mL) at -78 °C was slowly added DMSO (3.61 mL, 50.84 mmol) and stirred for 10 min. The alcohol **96** in 10 mL CH_2Cl_2 was then added and the reaction was stirred for an additional 10 min. This was followed by the addition of Et_3N (10.56 mL, 76.44 mmol). The reaction was allowed to warm to rt, when H_2O (10 mL) was added and extracted with 3 x 50 mL ether. The ether was then washed with 3 x 20 mL 1 M HCl, dried over $MgSO_4$, filtered through Celite and concentrated *in vacuo*. The residue was purifyed by flash chromatography (30 % EtOAc/hexanes) but even two attempts did not produce a sample more than 75 % pure. Based on this, 2.75 g (77 %) were afforded which was assumed to be (*E,E*). A crude IR showed an aldehyde carbonyl at 1710 cm^{-1}.

Preparation of 3(*E*),8(*E*)-4,8-Dimethyl-10-(*O*-tetrahydropyranyl)-decadienoic acid (97).

To PDC **95** (6.5 g, 17.14 mmol) in DMF (20 mL) was added aldehyde **98** (2.4 g, 8.57 mmol) and the reaction was allowed to stir for 2 days. The mixture was added to 150 mL H_2O and the pH taken to *ca* 1 by 1.5 M HCl. The gum was extracted with 4 x 150 mL ether. The combined etheral extracts were washed with 3 x 100 mL H_2O. The ether was dried with $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The residue was purified by flash chromatography (30 % EtOAc, hexanes, 1 % HOAc) resulting in cleavage of the OTHP group affording 1.61 g (87 %) hydroxy acid **85**.

Preparation of 3(*E*),8(*E*)-4,8-Dimethyl-10-hydroxy-decadienoic acid (85).

This product resulted fortuitously from the column purification of **97** (see above preparation of **97**). IR, neat, cm^{-1} (intensity) 3705 - 3075 (br, s), 2920 - 3000 (s), 1745 (m), 1720 (m), 1455 (w), 1395 (w), 1245 (m), 1170 (m). A ^1H NMR was not resolved enough to absolutely establish the alkene geometry. The former two literature syntheses of this molecule also did not report NMR data.[11,12]

Preparation of 4(*E*),8(*E*)-4,8-Dimethyl-decadienolide.[47]

To PPh_3 (2.10 g, 8 mmol) in THF (300 mL) was slowly added DEAD (1.23 mL, 8 mmol) and the resulting orange solution stirred at rt for 30 min. To addition funnel A (Figure 21) was placed 4(*E*),8(*E*)-4,8-Dimethyl-10-hydroxy-decadienoic acid (0.85 g, 4 mmol) and the contents added to the refluxing THF over 25 hr. The solvent was removed *in vacuo*, and the residue purified by flash chromatography (10 % ether/hexanes) to afford 0.32 g (21 %) lactone, which was co-injected with the genuine lactone. $GC1_{T1}$ = 3.7 min.

Preparation of 3(*E*),8(*E*)-4,8-Dimethyl-decadienolide (Suspensolide) (9).[47]

To PPh_3 (0.346 g, 1.32 mmol) in THF (200 mL) was added diethyl azo dicarboxylate (0.21 mL, 1.32 mmol) and the reaction was stirred for 30 min. The acid-alcohol **85** (140 mg, 0.66 mmol) was placed in the addition funnel A (Figure 21) in THF (40 mL). The THF was refluxed gently and the contents of the funnel were added overnight. The THF was removed *in vacuo* and product purified by 2

flash chromatography columns (10 % ether/hexanes) to afford 7 mg (6%) **9**. A co-injection with an authentic sample resulted in the same retention time. $GC1_{T1}$ = 4.3 min; IR neat, cm^{-1} (intensity) 2960 (m), 2880 (w), 1741 (s), 1452 (m), 1260 (m), 1245 (m), 1210 (m), 1120 (w), 945 (w); ^1H NMR ($CDCl_3$) δ 1.32 (2H, m), 1.45 (3H, s), 1.48 (3H, s) 1.92 (4H, m), 2.71 (2H, m), 4.79 (1H, t, J = 8 Hz), 5.02 (1H, t, J = 8 Hz), 4.51 (2H, m); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 15.38, 25.97, 36.05, 41.88, 61.35, 116.64, 120.75, 144.09, 142.15, 169.55; MS/CI, isobutane, m/z, (%) 195 (100), 135 (10), 125 (8), 113 (38); MS/EI, m/z, (%) 194 (trace), 179 (18), 166 (19), 151 (10), 135 (22), 123 (15), 108 (45), 93 (58), 81 (100), 67 (38), 53 (20); Anal calcd for $C_{12}H_{18}O_2$: C = 74.18, H = 9.36, O = 16.47; Found: C = 73.94, H = 9.11.

Alternate preparation of 3(*E*),8(*E*)-4,8-Dimethyl-decadienolide (Suspensolide) (9).[47]

To PPh_3 (2.47 g, 9.42 mmol) in THF (200 mL) was added diethyl azo dicarboxylate (1.5 mL, 9.42 mmol) and the reaction was stirred for 30 min. The acid-alcohol **85** (1.01 g, 4.75 mmol) was placed in the addition funnel A (Figure 21) in THF (40 mL). The THF was refluxed gently and the contents of the funnel were added over 48 hr. The THF was removed *in vacuo* and product purified by flash chromatography (10 % ether/hexanes) to afford 100 mg (10 %) suspensolide **9** in 90 % purity. A second column rearranged suspensolide into a 1:1:1 ratio of suspensolide **9**, anastraphin **4** and epianastraphin **5** verified by co-injection with authentic samples.

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