AN EFFICIENT SYNTHESIS OF SUSPENSOLIDE

by

Ginna Hidalgo Del Vecchio
B.Sc. Universidad de Costa Rica 1991

THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE
in the Department
of
Chemistry

SIMON FRASER UNIVERSITY
NOVEMBER 1993

APPROVAL

Name: Ginna Hidalgo Del Vecchio

Degree: Master of Science (Chemistry)

Title: AN EFFICIENT SYNTHESIS OF SUSPENSOLIDE

Examining Committee:

Chairman: S. Wolfe

A.C. Oehlschlager, Professor
Senior Supervisor

K.N. Slessor, Professor

R. H. Hill, Assistant Professor

A. Bennet, Assistant Professor
Internal Examiner

Date Approved: November 10, 1993.

PARTIAL COPYRIGHT LICENSE

I hereby grant to Simon Fraser University the right to lend my thesis, project or extended essay (the title of which is shown below) to users of the Simon Fraser University Library, and to make partial or single copies only for such users or in response to a request from the library of any other university, or other educational institution, on its own behalf or for one of its users. I further agree that permission for multiple copying of this work for scholarly purposes may be granted by me or the Dean of Graduate Studies. It is understood that copying or publication of this work for financial gain shall not be allowed without my written permission.

Title of Thesis/Project/Extended Essay:

An Efficient Synthesis of Sospensolide

Author: _____

(signature)

Ginna Hidalgo DelVecchio

(name)

December 15 1993

(date)

ABSTRACT

The total synthesis of a major component of the pheromone blend of the Caribbean and Mexican fruit flies, (E,E)-4,8-dimethyl-3,8-decadien-10-olide, suspensolide, is described. The synthesis was based on a double methyl alumination of 1,6-heptadiyne. The dialane produced from this stereospecific cis addition of trimethylaluminum was converted to the dialuminate by reaction with n-butyllithium. The latter was coupled with paraformaldehyde to give the symmetrical diol (E,E)-3,7-dimethyl-2,7-nonen-1,9-diol. Selective protection of one allylic hydroxyl of the symmetrical diol allowed conversion of the remaining free hydroxyl to a chloride by Corey's method (NCS/DMS). Addition of one carbon to the chloride containing chain was effected by displacement of the allylic chloride by cyanide or the lithium salt of an orthothioester. Hydrolysis of the masked carbonyls thus produced and deprotection of the ω-hydroxyl gave (E,E)-4,8-dimethyl-3,8-decadien-10-ol oic acid. This diunsaturated hydroxyacid was cyclized to suspensolide in 30% yield using the Mitsunobu procedure. The overall yield of suspensolide in this eight step synthesis was 10%.

A mis padres, Danilo y Janina,

que siempre me enseñaron con el ejemplo.

A Jorge por todo lo demás.

TABLE OF CONTENTS

	Page
APPROVAL	ii
ABSTRACT	iii
DEDICATION	iv
LIST OF SCHEMES	vi
LIST OF FIGURES	viii
LIST OF ABREVIATIONS	ix
INTRODUCTION	1
RESULTS AND DISCUSSION	11
A) Approach 1	11
B) Approach 2	31
C) Approach 3	37
CONCLUSIONS	44
EXPERIMENTAL	46
REFERENCES	82

LIST OF SCHEMES

Page

Scheme I. Volatile substances from male *Anastrepha suspensa* and *Anastrepha ludens*. 4

Scheme II. Previous synthesis of suspensolide. 6

Scheme III. Unpublished synthesis of suspensolide. 8

Scheme IV. Retrosynthetic analysis of the present synthesis of suspensolide (Approach #1). 11

Scheme V. Approach #1 to the synthesis of suspensolide. 13

Scheme VI. Methyl cupration of acetylenes. 14

Scheme VII. Carboalumination of 1,6-heptadiyne. 14

Scheme VIII. Attempted synthesis of **16**. 16

Scheme IX. Monoprotection of symmetrical diols with NaH/TBDMSCl. 18

Scheme X. Monoprotection of symmetrical diols with n-BuLi/TBDMSCl. 19

Scheme XI. Monoprotection of symmetrical diols with TMS. 19

Scheme XII. Alternative routes for the halogenation of **36**. 21

Scheme XIII. Halogenation of **27**. 23

Scheme XIV. Corey's double activation lactonization method. 26

Scheme XV. Masamune's lactonization method. 27

Scheme XVI. Mixed Anhydride lactonization method. 28

Scheme XVII. Mitsunobu's lactonization method. 29

Scheme XVIII. Expansion of the carbon chain *via* coupling with an orthothioester (Approach #1). 30

Scheme XIX. Retrosynthetic analysis of the synthesis of suspensolide (Approach #2). 31

Scheme XX. Approach #2 to the synthesis of suspensolide. 33

Scheme XXI. Monocarboalumination of 1,6-heptadiyne (concentration of diyne = 2M). 35

Scheme XXII. Monocarboalumination of 1,6-heptadiyne (concentration of diyne = 1M). 36

Scheme XXIII. Approach #3 to the synthesis of suspensolide. 38

Scheme XXIV. Attempted synthesis of **47**. 41

Scheme XXV. Model synthesis for the transformation **59** to **15a**. 43

LIST OF FIGURES

	Page
Figure 1. Distribution of the Caribbean and Mexican fruit flies.	2
Figure 2. Tosylation of geraniol in the presence of geraniol-TMS.	20
Figure 3. Protection of geraniol with ethyl vinyl ether in the presence of geraniol-TMS.	22
Figure 4. Acetylation of geraniol in the presence of geraniol-TMS.	22
Figure 5. Carboalumination of 1,6-heptadiyne ($AlMe_3$:Cp_2ZrCl_2:diyne = 2:0.2:1).	35
Figure 6. Carboalumination of 1,6-heptadiyne ($AlMe_3$:Cp_2ZrCl_2:diyne = 2.5:1:1).	35
Figure 7. Carboalumination of 1,6-heptadiyne ($AlMe_3$:Cp_2ZrCl_2:diyne = 2:1:1).	35
Figure 8. Carboalumination of 1,6-heptadiyne ($AlMe_3$:Cp_2ZrCl_2:diyne = 2:0.2:1).	36
Figure 9. Carboalumination of 1,6-heptadiyne ($AlMe_3$:Cp_2ZrCl_2:diyne = 2:2:1).	36
Figure 10. Carboalumination of 1,6-heptadiyne ($AlMe_3$:Cp_2ZrCl_2:diyne = 1:1:1).	36

Abbreviations

Ac	Acetate
Anal Calc	Analytical calculated
aq	Aqueous
bp	Boiling point
Bu	Butyl
ca	Approximately
Cp	Cyclopentadienyl
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DMAP	4-N,N-dimethylaminopyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
EE	Ethoxyethyl
Et	Ethyl
GC	Gas chromatography
h	Hour (s)
HMPA	Hexamethylphosphoric triamide
HOAc	Acetic acid
KAPA	Potassium 3-aminopropylamide
LDA	Lithuim diisopropylamide
M	Molar
Me	Methyl
min	Minutes
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NMR	Nuclear magnetic resonance

[ox]	Oxidating agent
P	Protecting group
PDC	Pyridinium dichromate
Ph	Phenyl
PPTS	Pyridinium *para*-toluensulfonate
Py	Pyridine
TBDMS	*tert*-butyldimethylsilyl
tbutyl	*ter*-butyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMS	Trimethylsilyl
TosOH	*para*-toluensulfonic acid
TosCl	*para*-toluensulfonyl chloride
rt	Room temperature

With respect to NMR spectra

b	Broad
d	Doublet
δ	Chemical shift, ppm from tetramethylsilane
J	Coupling constant
m	Multiplet
ppm	Parts per million
q	Quartet
s	Singlet
t	Triplet

INTRODUCTION

Pheromones are chemicals released by one individual that affect the physiology or behaviour of another member of the same species. They are widely used by insects to communicate life sustaining activities. Because of the low toxicity,[1] minute amounts required, species specificity and relative simplicity of their structures, pheromones are finding increased use in management of insect pest populations. Pheromone-based monitoring, mass trapping and mating disruption currently represent a $32 million industry in North America that is growing at the rate of 30% per year.[2] Most of the projected increases in the use of pheromones revolve around government mandated reductions in the levels and types of insecticides allowed to be used on food crops. The challenge for the organic chemist in this arena is to devise efficient syntheses for pheromones that are likely to find use in management of the populations of economically important insect pests.

The Caribbean fruit fly, *Anastrepha suspensa* (Loew) and the Mexican fruit fly, *Anastrepha ludens* (Loew) are major pests of many fruits in Central and neotropical North America[3] (Figure 1). In Florida 84 fruit crops are at risk as known hosts of *A. suspensa*.[4] The major concern is the potential of this fruit fly as a pest of citrus.[5] *A.ludens* destroys 10% of the citrus in Mexico.[6]

Fumigation with ethylene dibromide, to prevent the spread of fruit flies has been curtailed due to health hazards. The substitute, methyl bromide,[7] is an important fumigant used world-wide to disinfect fresh fruit. Unfortunately, ingested methyl bromide is carcinogenic to rats[8] and its use is

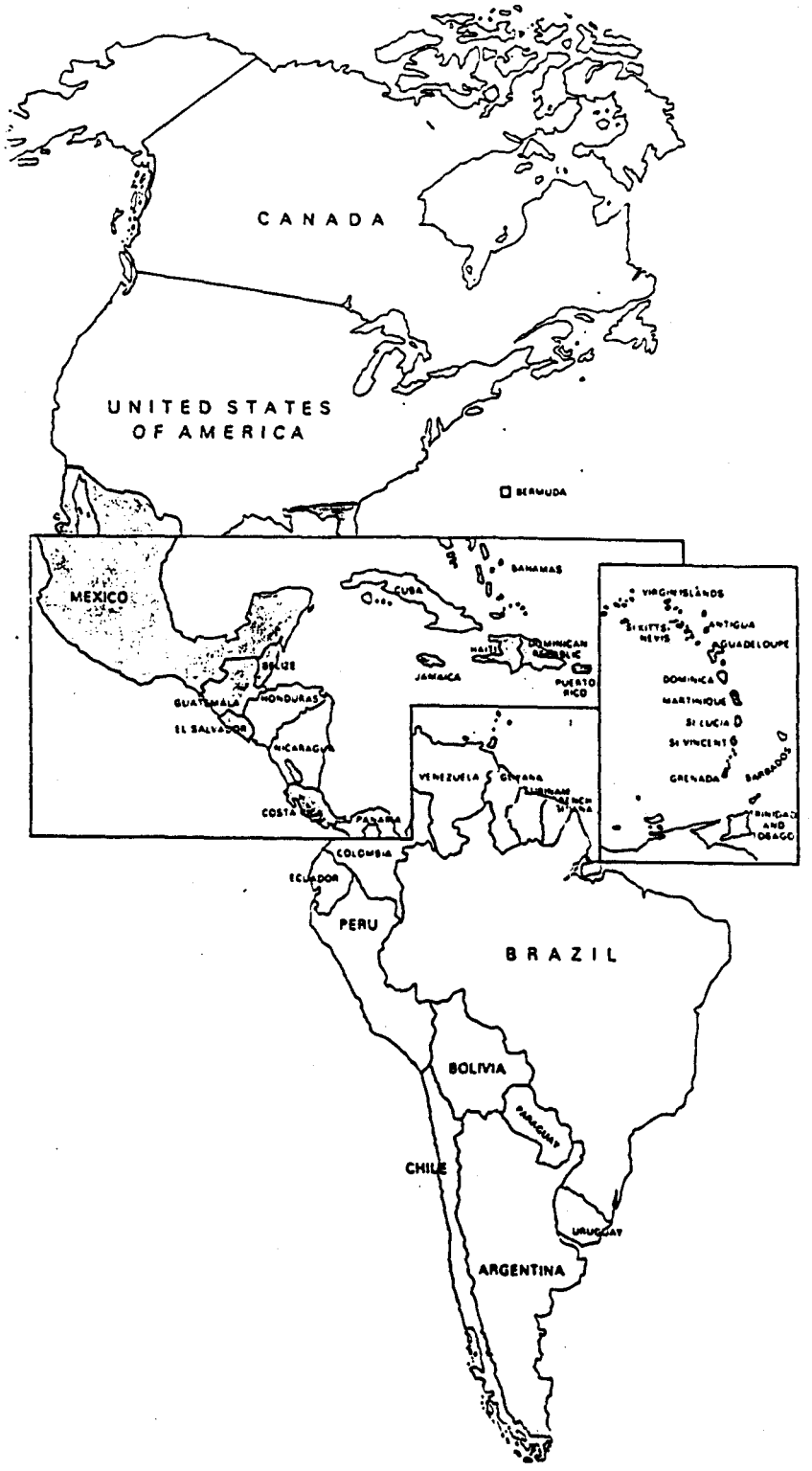


Figure 1. Distribution of the Caribbean and Mexican fruit flies.[3]

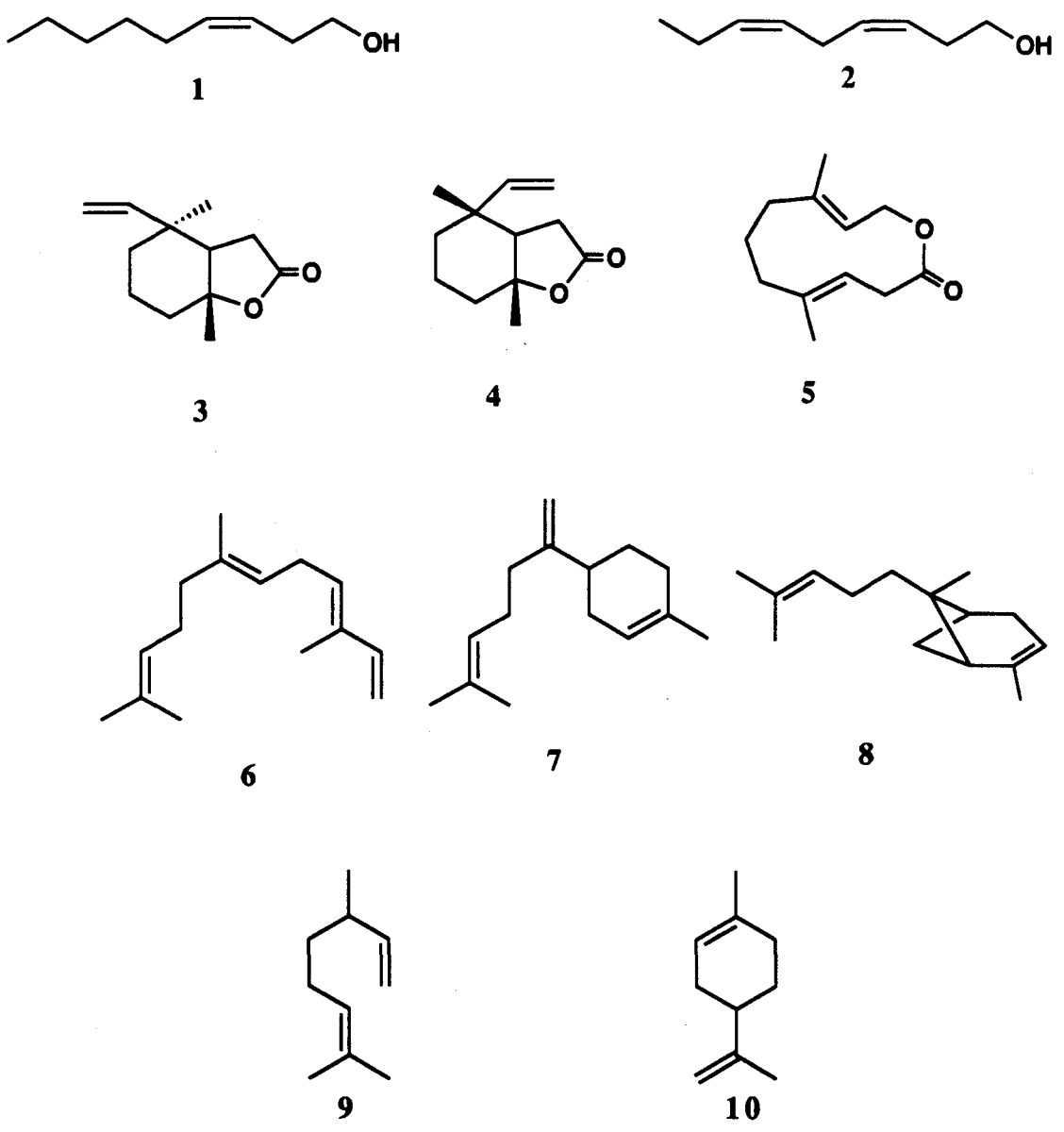
also likely to be curtailed. To lower residual methyl bromide levels in fruit commodities, fumigation parameters[9] and residue photohydrolysis[10] have been studied.

Propargylic alcohols and ethers have been tested as alternative pesticides against the Caribbean fruit fly, however these experiments were only moderately successful.[11]

Caribbean fruit fly quarantine is presently practised on fruits from Florida shipped to citrus-growing states such as Texas and California. Quarantine treatments include hot air,[12] hot water,[13] vapor heat[14] and shrink-wrapping of the fruit.[15] These procedures were successful in some cases, in others the fruit suffered physical damage.

The use of pheromones in the management of fruit fly populations was first proposed in 1976.[16] The suggestion was based on the observation that males of the genus *Anastrepha* attracted females in a process that eventually led to mating. It was not until the late 1980's that all compounds released by the males and that were suspected to be responsible for the attraction and mating of Caribbean and Mexican fruit flies were identified. The biological activity of individual male specific compounds in each species has not yet been fully elucidated due to the difficulty in preparation of some of the components. Male *A. suspensa* specifically produce (*Z*)-non-3-en-1-ol, **1**,[17] (*Z,Z*)-3,6-nonadien-1-ol, **2**,[17] anastrephin **3**,[18] and epianastrephin **4**,[18] a macrolide, (*E,E*)-4,8-dimethyl-3,8-decadien-10-olide, **5**, called suspensolide,[19] α-farnesene, **6**,[20] β-bisabolene, **7**,[20] α-trans-bergamotene,

8[20] and ocimene, **10**.[20] *A. ludens* males produce (*Z*)-non-3-en-1-ol, **1**,[21] (*Z,Z*)-3,6-nonadien-1-ol, **2**,[21] anastrephin, **3**,[18] and epianastrephin, **4**,[18] suspensolide, **5**,[20] α-farnesene, **6**,[20] β-bisabolene, **7**,[20] α-trans-bergamotene, **8**,[20] and limonene, **9**[20] (Scheme I).

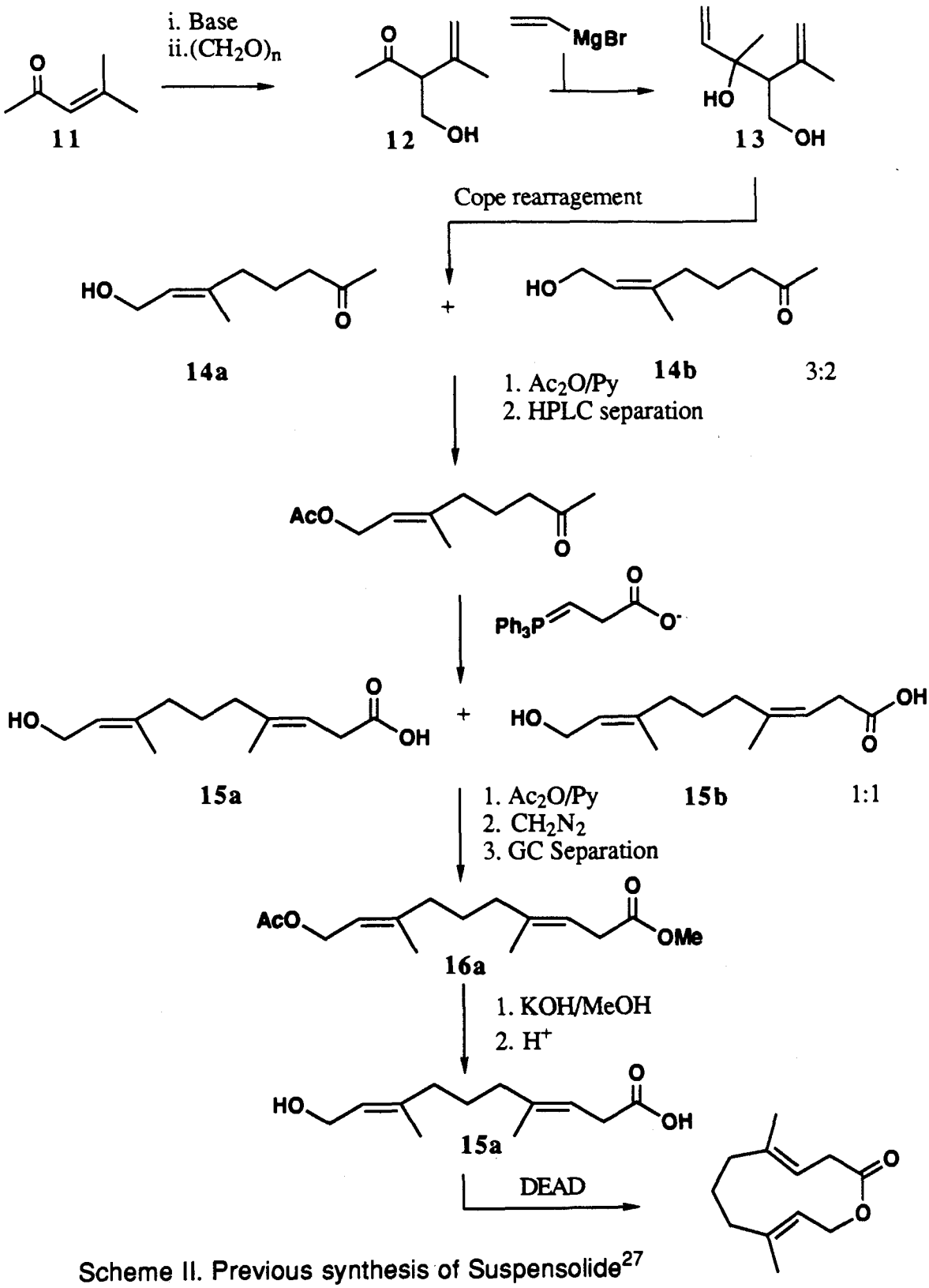


Scheme I. Volatile substances from Anastrepha suspensa and Anastrepha ludens males.

Compounds **1-4** elicit responses in the antennae of both species using the electroantennogram technique.[22] These chemicals have also been shown to induce behavioural responses of female Mexican fruit flies, measured in a wind tunnel bioassay.[22] The corresponding biological data for compounds **5-10** is unavailable since the identity of these male specific compounds was only recently reported.[20]

The reported syntheses of **1** and **2** *via* coupling of acetylenes with alkyl halides followed by catalytic reduction of the triple bonds is straightforward.[23] Sesquiterpenes **6-8** and monoterpenes **9-10** were either commercially available or have been previously synthesized by more demanding multistep procedures.[24] The syntheses of the two isoprenoid 12-carbon lactones: anastrephin **3** and epianastrephin **4** were first achieved by cyclization of the hydroxyacid precursor of **5** in the presence of a Lewis acid.[25] More recently, **3** and **4** have been prepared by isomerization of **5** under the same conditions.[26]

Development of an efficient synthesis of suspensolide **5** was the goal of the present work. The Battiste group in Florida reported the first synthesis of suspensolide (**5**) in 1988.[27] Their synthesis (Scheme II), commenced with base catalysed condensation of mesityl oxide **11** with paraformaldehyde to give **12**. To this was added vinylmagnesium bromide to yield **13**. This 1-5 diene was heated to induce a Cope rearrangement to a 3:2 mixture of *E* and *Z* isomers of 8-hydroxy-6-methyloct-6-en-2-one **14a** and **14b**. After acetylation the *E*-isomer was separated by HPLC and subjected to a Wittig reaction with 2-carboxyethyl triphenylphosphonium chloride. This afforded hydroxyacid **15** as a mixture of 3*E*, 8*E* and 3*Z*, 8*E* isomers, which were separated on a small scale

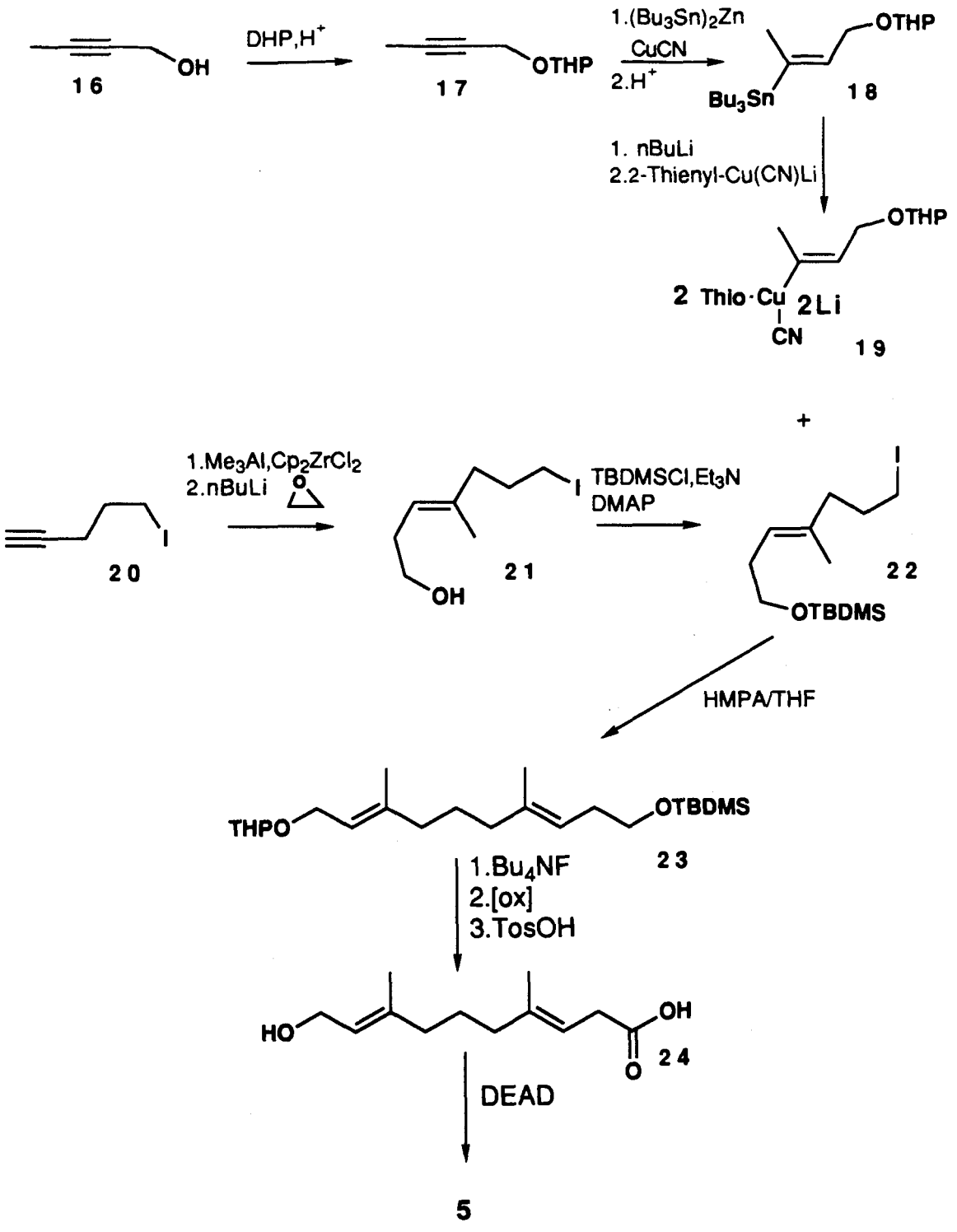


Scheme II. Previous synthesis of Suspensolide[27]

by preparative GC, after derivatization of the alcohol and acid moietys. Finally, after deprotection, the (*E,E*)-4,8-dimethyl-3,8-decadien-10-ol-oic acid (**15a**) was lactonized by the Mitsunobu procedure[28] to give **5** in low yield.

The disadvantage of the published synthesis of **5** is that it involves two separations of geometrical isomers of intermediates. The separation techniques used render impractical preparation of operationally useful quantities of the pheromone.

Another synthesis[29] of **5** used the strategy of coupling the fragments **19** and **22** in the presence of HMPA to give **23** (Scheme III). Removal of the silyl protecting group followed by oxidation of the resulting homoallylic acid and cleavage of the THP group, gave the ω-hydroxyacid **15a**. Cyclization of **15a** gave low yields of suspensolide (**5**) contaminated with isomers. Compound **19** was made by the stannylzincation of the triple bond of **17** followed by transmetallation of the tributyltin group of **18** by a higher order cuprate. Fragment **22** was prepared by the carboalumination of 5-iodo-1-pentyne followed by transmetallation of the alane with n-butyllithium and coupling with ethylene oxide to give the allylic alcohol **21**, which was then protected by silylation. The major drawback of this synthetic procedure was the oxidation of the homoallylic alcohol to the carboxylic acid, which gave low yields of impure products with unknown double bond geometry. Another problem in this synthesis was the carboalumination of 5-iodo-1-pentyne, followed by reaction with n-butyllithium. The latter could react either with the alane or the iodide.



Scheme III. Previous synthesis of suspensolide

Both previous syntheses of **5** involved preparation of the hydroxy acid precursor and its cyclization to **5**. Lactonization of long chain hydroxyacids is a common and successful strategy for the preparation of macrolides . I viewed the shortcomings of the previous syntheses of **5** not to be in the strategy of lactonization but in the methods used in the preparation of the hydroxyacid.

The present synthesis of suspensolide was approached by three different strategies. Only one of the three synthetic plans was completely successful. The lessons learned from the routes that posed unsurmounted difficulties will be discussed.

The key structural features of suspensolide that were considered in the design of the synthesis of this pheromone were as follows:

a) Suspensolide contains an eleven membered ring lactone that is highly strained[30] due to the presence of two *E*-double bonds. These unsaturations would render lactonization or acyclic precursors more difficult than in saturated analogs.

b) The geometry of the two *E*-trisubstituted double bonds is an important structural feature. The method of introduction of these unsaturations constituted the weakness of the Battiste synthesis.[24]

c) The immediate precursor of suspensolide, the acyclic hydroxyacid, contains a highly reactive allylic alcohol. This must be protected with a group that can

prevent displacements[31] and oxidations[32] and be capable of removal under conditions that do not isomerize the unsaturations.

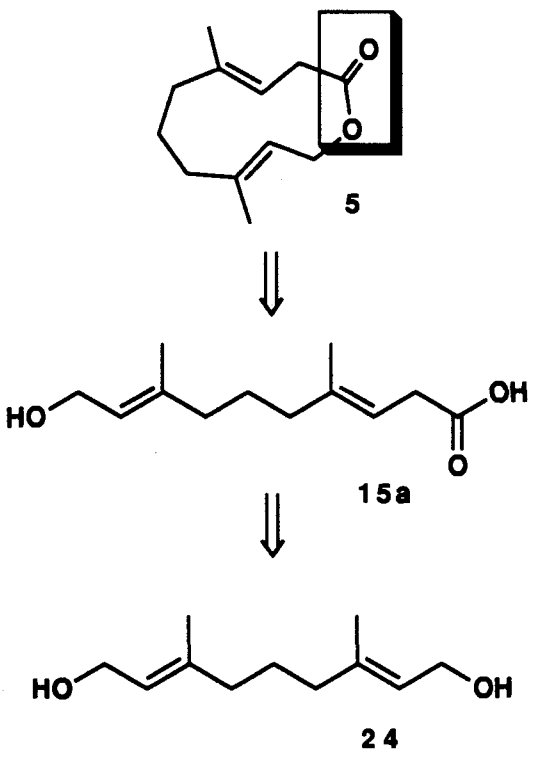
d) The hydroxyacid contains a β,γ-unsaturated carboxylic acid that is prone to isomerization to the α,β-unsaturated analog under both acidic and basic conditions.[33]

RESULTS AND DISCUSSION.

APPROACH 1

RETROSYNTHETIC ANALYSIS

One synthetic strategy was based on the observation that suspensolide is symmetrical except for the presence of the carboxyl group (Scheme IV). It was envisioned that one could first build a symmetrical skeleton (**24**) then extend the chain at one end by a carbon to make hydroxyacid (**15a**). Cyclization of **15a** would give **5**.



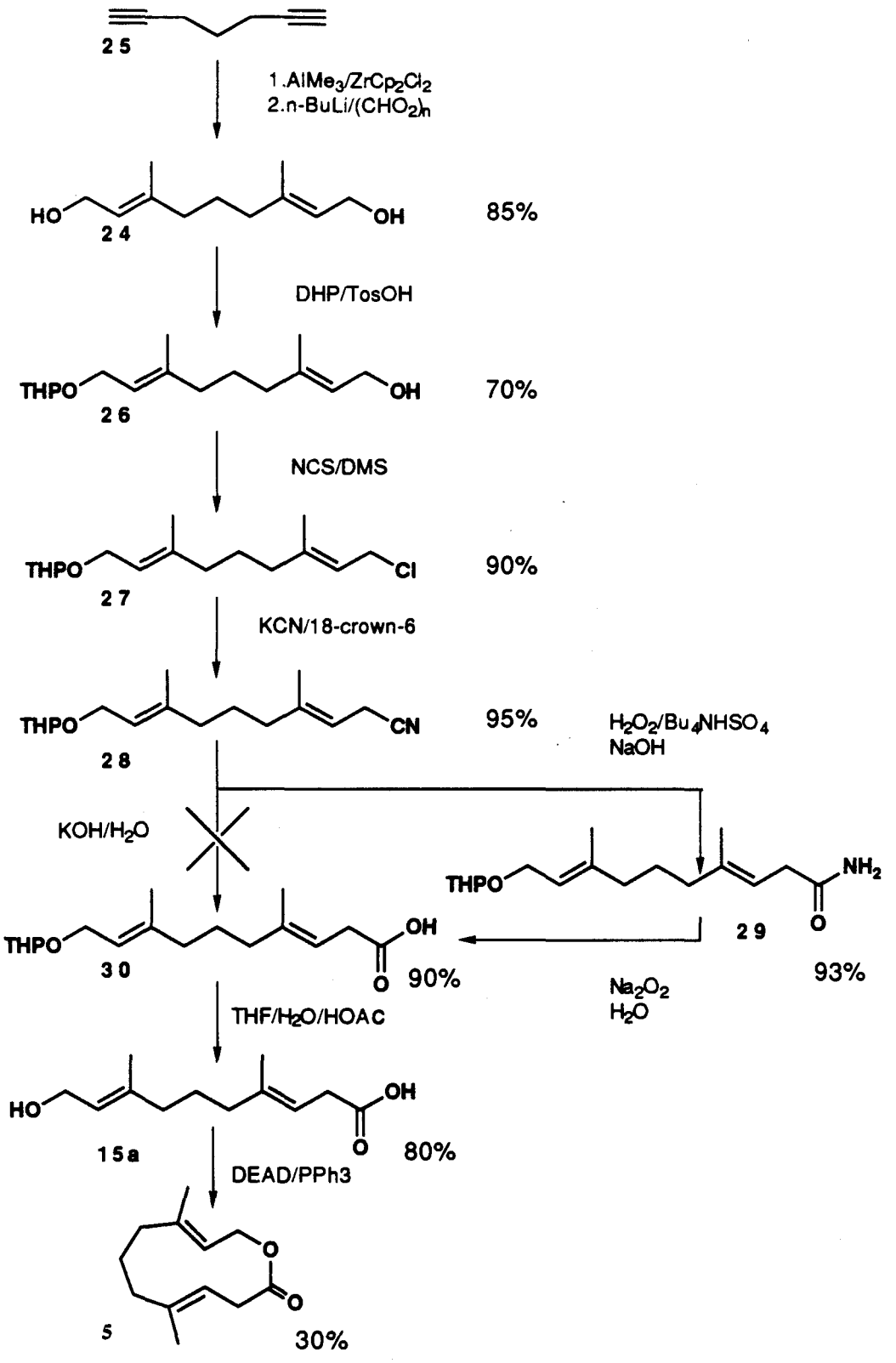
Scheme IV. Retrosynthetic analysis of the synthesis of suspensolide. (Approach #1.)

SYNTHETIC APPROACH.

The first approach employing this strategy (Scheme V) involved initial formation of the trisubstituted double bonds. Because olefins of this substitution occur widely in nature[34] many methods for their synthesis have been developed.[35] Among the most stereo- and regioselectve are those based on the addition of organometallics to acetylenes.[36] Within this category are zirconium-catalyzed carboalumination[37] and uncatalyzed carbocupration.[38] Both of these organometallic systems result in the cis addition of a methyl and metal to the alkyne. The regioselectivity of both carboalumination[39] and carbocupration[40] is >98%. Both methods have been employed to synthesize natural products. Functionalities are introduced easily by reaction of the vinyl-metal intermediates with electrophiles such as carbon dioxide,[41] iodine,[42] epoxides,[43] aldehydes,[44] and enones.[45]

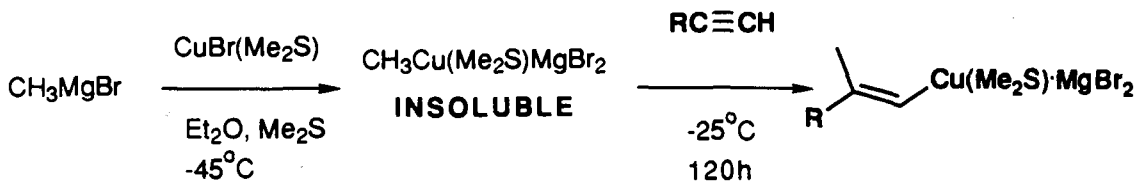
Carbocupration is often attended by formation of diene due to the Cu^{+2} catalyzed dimerization of vinyl copper intermediates. Since total absence of Cu^{+2} is very difficult to achieve this dimerization often becomes the major reaction. Even if Cu^{+2} is excluded and dimerization suppressed methylcupration is a tediously slow process[46] due to the insolubility of the methyl copper reagents. Even dimethyl sulphide-methyl copper complex suffers from this drawback (Scheme VI).

The catalyzed methylalumination provides high yields of the required methylated vinyl aluminum adducts in only 1 hour.[47] The vinyl aluminum intermediates are easily converted to aluminates by reaction with alkyl lithiums.



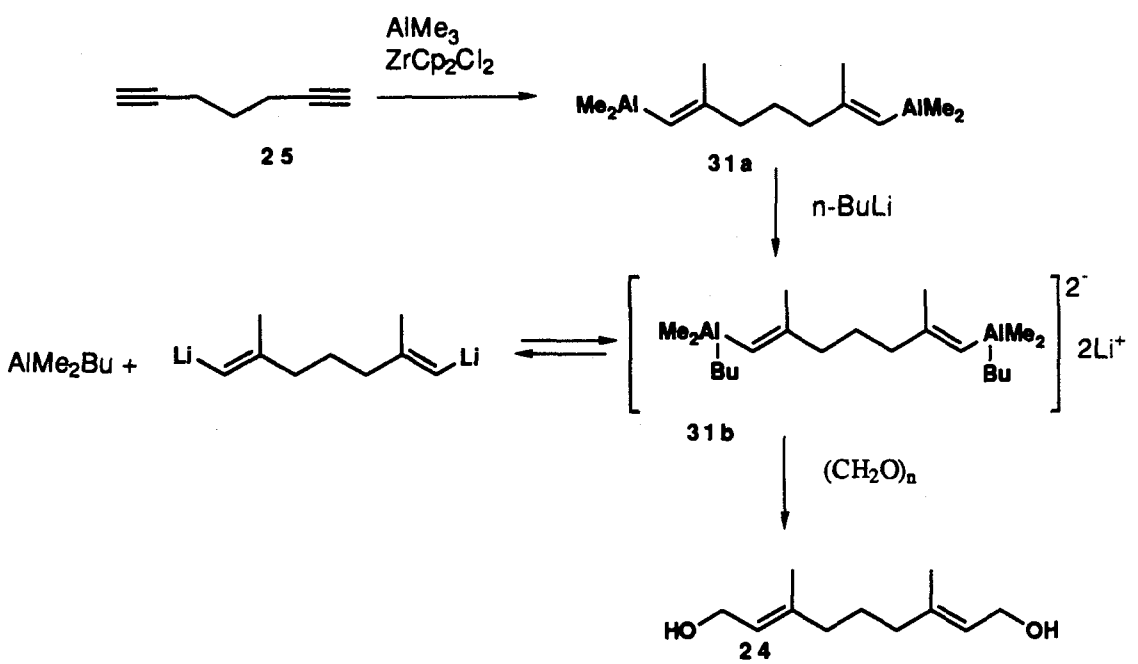
Scheme V. Approach #1 to the synthesis of suspensolide.

The aluminates react with a wide variety of electrophiles allowing introduction of functional groups such as alcohols and carboxylic acids.



Scheme VI. Methylcupration of acetylenes.

Negishi's zirconium catalyzed procedure was chosen because of the rapid addition of trimethylaluminum to alkynes and the ease of functionalization of the vinyl aluminum intermediates.[37]



Scheme VII. Carboalumination of 1,6-heptadiyne.

Commercially available 1,6-heptadiyne (**25**) was subjected to a double carboalumination (Scheme V) followed by evaporation of the solvent (1,2-dichloroethane). This left a yellow precipitate that contained alanate, **31a**, mixed with the catalyst ($ZrCp_2Cl_2$) (Scheme VII). To remove catalyst the aluminum complex was extracted with hexane then filtered under argon. Aluminate, **31b**, was formed by addition of n-butyllithium and this was coupled with parafomaldehyde to give symmetrical diol, **24**.

Because this is the first instance of a double carboalumination the reaction was studied in some detail using different concentrations of reagents and conditions to maximize the yield of diol. The highest yields were obtained using 3.5 times more trimethylaluminium than 1,6 heptadiyene at an alane concentration of 0.7 M. The highest isolated yield of (*E,E*)-3,7-dimethyl-2,7-nonadien-1,9-diol was 85% (Table 1).

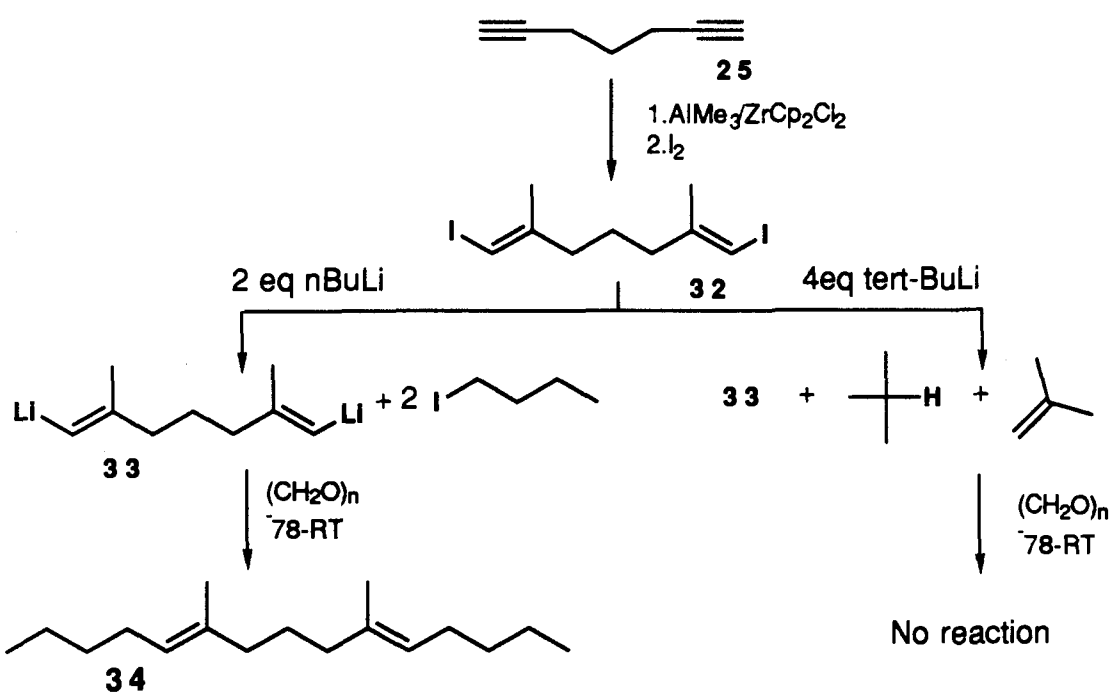
Table 1. Molar concentration of reagents in the synthesis of **24**.

Entry	$AlMe_3$	$ZrCp_2Cl_2$	Alkyne	% Yield[3]
1	0.4	0.2	0.2[1]	20
2	0.4	Catalytic	0.2[1]	15
3	0.5	0.3	0.2[1]	54
4	0.7 or 0.8	0.3	0.2[1]	85
5[2]	0.4[2]	0.2[2]	0.2[2]	87[2]

1. 1,6-heptadiyne
2. Control reaction: As reported by Negishi[41] for the carboalumination of 6-methyl-5-hepten-1-yne with coupling to paraformaldehyde.
3. Isolated yield.

The (*E*) geometry was assigned to diol **24** and the other olefins synthesized based on the ^{13}C chemical shifts of the vinyl methyl carbons. Numerous reports[48,19] reveal that ^{13}C chemical shifts of (*E*)-methyl carbons associated with trisubstituted double bonds are near 17 ppm while (*Z*)-methyl carbons give signals near 24 ppm.

Although the (*E,E*)-3,7-dimethyl-2,7-nonadien-1,9-diol **24** was prepared in one pot, it was a complicated procedure. An easier preparation of the diol involved carboalumination of **25** followed by quenching with iodine to give 1,7-diiodo-2,6-dimethyl-1,6-heptadiene **32** (Scheme VIII). This was converted to the divinyldilithio derivative by metal-halogen exchange then coupled with paraformaldehyde.



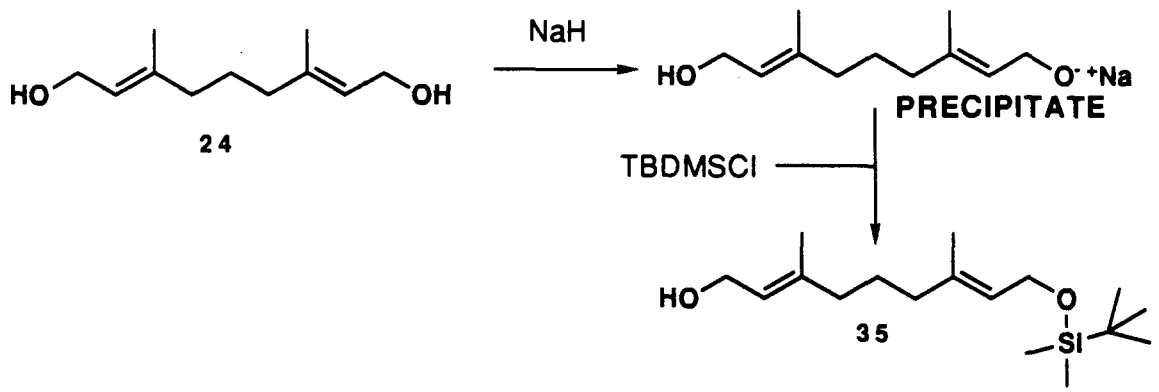
Scheme VIII. Attempted synthesis of **24**

The second reaction sequence was not without problems. Use of two equivalents of n-butyllithium led to formation of a voluminous white precipitate, presumably due to the dianion **33**. No reaction occurred with the electrophile at low temperatures (-78 to -40 °C) or room temperature. Only hydrocarbon **34** was obtained. This was the result of coupling of butyl iodide formed in the metal-halogen exchange and dianion **33**. This side reaction was avoided by use of four equivalents of *tert*-butyllithium.[49] The first two equivalents participate in the metal-halogen exchange and the remaining two rapidly react with the *tert*-butyl iodide formed to give isobutane and 2-methylpropene. I was unable to find conditions under which the insoluble lithium dianion could be reacted with paraformaldehyde. Addition of HMPA as a co-solvent, use of a crown ether or THF instead of diethyl ether as a solvent failed to promote reaction. In the final analysis the insolubility of **33** curtailed nucleophilic attack on paraformaldehyde and the most efficient synthesis of diol **24** was *via* the first procedure involving direct reaction of the divinyl dialane with paraformaldehyde.

Extension of the symmetrical diol at one end of the chain required monoprotection of the diol (Scheme V). Monoprotection of 1,n diols is not straightforward.[50] A common procedure is to use a stoichiometric amount of the diol and protecting reagent. This would be expected to yield a statistical mixture of unprotected, monoprotected and diprotected products. Utilization of a large excess of the starting diol[51] is applicable only when the diol is inexpensive or can be recycled.

A superior approach is that of Mc Dougal and his group[52] which consists of treatment of a diol with one equivalent of NaH, causing precipitation of the

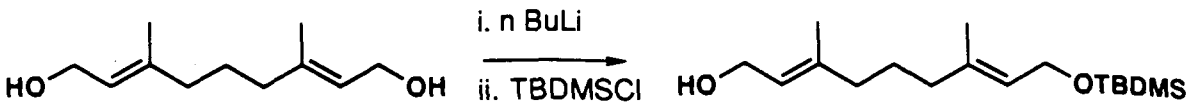
mono alkoxylate and preventing dialkoxylate formation. When this is followed by addition of a silylating agent high yields of the monoprotected product were obtained .



Scheme IX. Monoprotection of symmetrical diols with TBDMS.

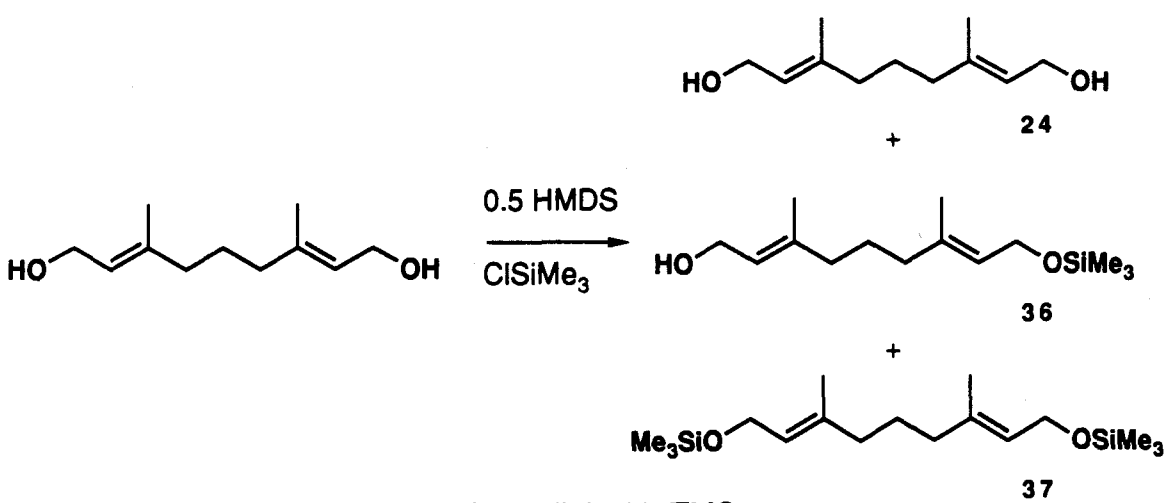
Application of this procedure to the symmetrical diol in question gave only low yields of **35** (10-20%) and 80% recovery of starting material. It was observed by Mc Dougal, that as the length of the carbon chain increased the temperature required for successful reaction increased and the reaction time increased. He suggested this was due to obstruction of further reaction because of inclusion of the diol in the precipitated and aggregated monosodium salt (Scheme IX).

Another route to the differentially protected diol consisted of abstraction of one hydroxylic proton with n-butyllithium[53] followed by addition of a silylating agent (Scheme X). This approach was less successful than the previous one. Very little reaction was observed, even when the formation of the lithium salt was conducted at room temperature.



Scheme X. Monoprotection of 1,n-diols.

A different approach consisted of treatment of diol **24** with 0.5 equivalents of HMDS in THF catalyzed by trimethylchlorosilane,[54,55] to give diol, **24**: monosilylated diol, **36**: disilylated diol, **37** in a ratio of 1:2:2 (Scheme XI). Although the yield of the desired product was low, the methodology provided sufficient material to continue to the next step.



Scheme XI. Monoprotection of 1,n-diol with TMS.

Halogenation of the allylic alcohol was attempted by reaction of **36** with NBS in dimethyl sulphide.[56] Several products were detected by GC analysis of the reaction mixture, and the loss of the trimethylsilyl protecting group was confirmed by the ^{1}H NMR analysis of crude product.

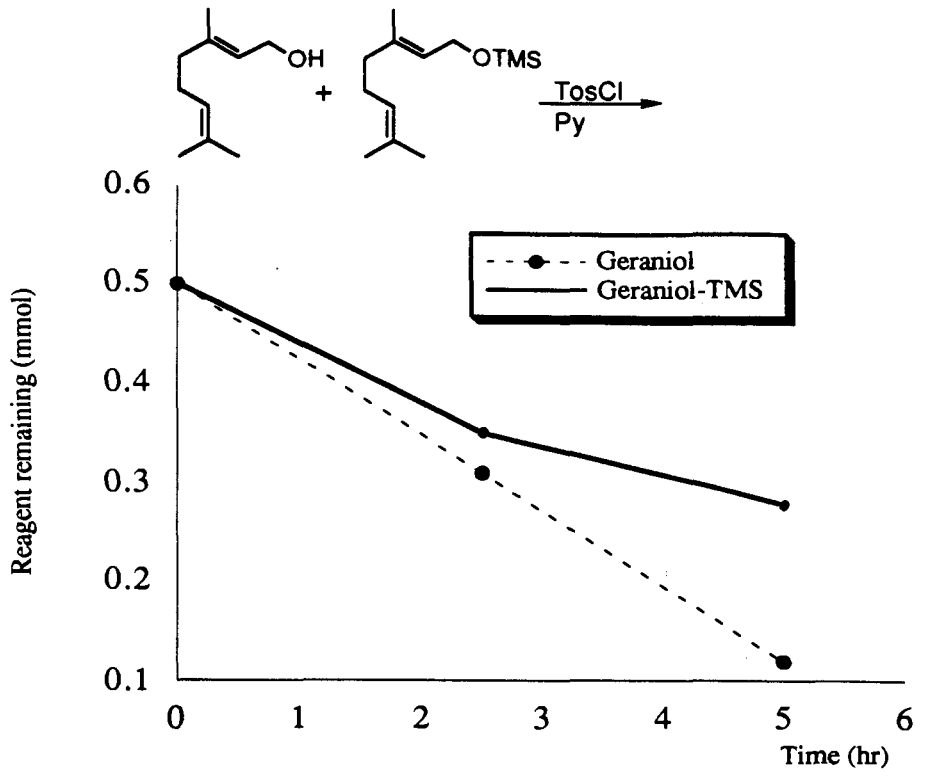
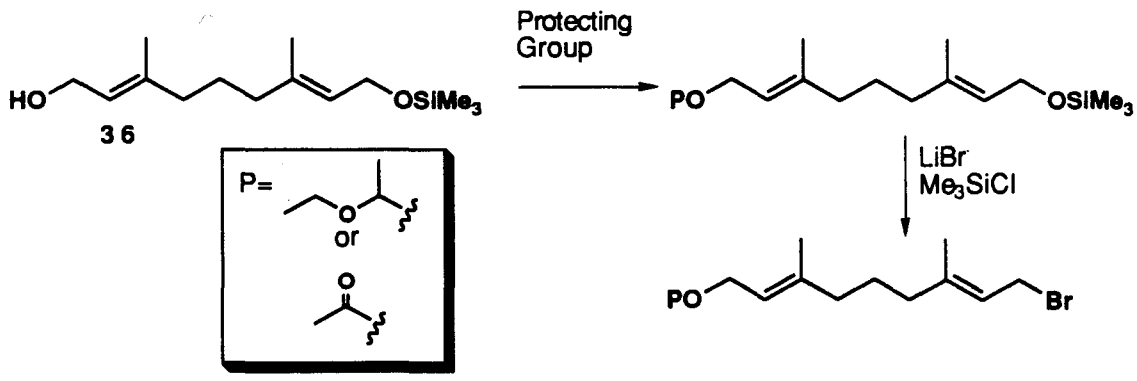


Figure 2.Tosylation of geraniol in the presence of geraniol-TMS

Another approach consisted of tosylation of the allylic alcohol, followed by displacement of the p-toluensulfonyl group by halide anion. Because the monosilyl diol, **36** was so difficult to obtain, a model experiment was conducted consisting of reaction of a 1:1 mixture of geraniol and geraniol-TMS with one equivalent of TosCl and pyridine. Progress of the reaction was followed by GC, using dodecane as an internal standard. The desired result was consumption of geraniol and no consumption of geraniol-TMS. Unfortunately, consumption of geraniol-TMS occurred concomitant with formation of geranyl-tosylate (Figure 2). Therefore, tosylation of the allylic alcohol did not appear to be an attractive option.

The high reactivity of the silyl protecting group in **36** encouraged

consideration of the use of this group for the halogenation reaction.[57] If the allylic alcohol could be initially protected with a less labile protecting group, displacement of the silyl group by a halide could subsequently proceed (Scheme XII).



Scheme XII. Alternative route for the halogenation of **36**

Two additional model experiments were conducted to achieve hydroxyl protection. I examined ethyl vinyl ether (Figure 3) and acetate (Figure 4) protection. In both cases appearance of the protected geraniol-derivative occurred at expense of the consumption of geraniol and geraniol-TMS. Neither of these two protecting groups facilitated the desired transformation.

In the above I considered hydrolysis of the trimethylsilyl ether,[58] **36**, was problematic and sought a more stable protecting group for diol **24**.

Monoprotection of diol **24** to a statistical distribution of products was successful when it was reacted with one equivalent of DHP using TosOH as a catalyst under high dilution conditions[59] (Scheme V). Purification of the crude reaction mixture by column chromatography gave the monoprotected tetrahydropyranyl-derivative **26** in 70% when the diol was recycled once.

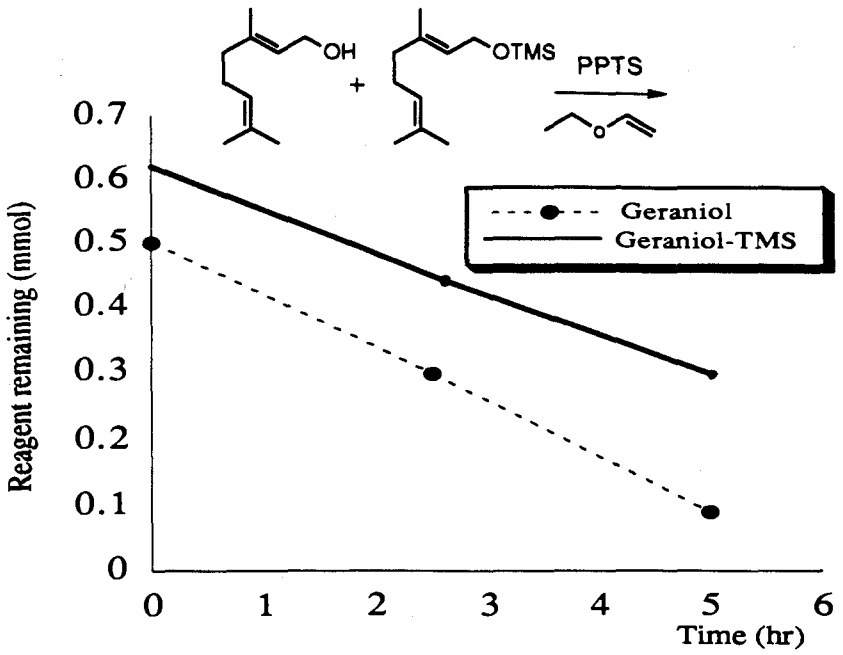


Figure 3. Protection of geraniol with ethyl vinyl ether in the presence of geraniol-TMS

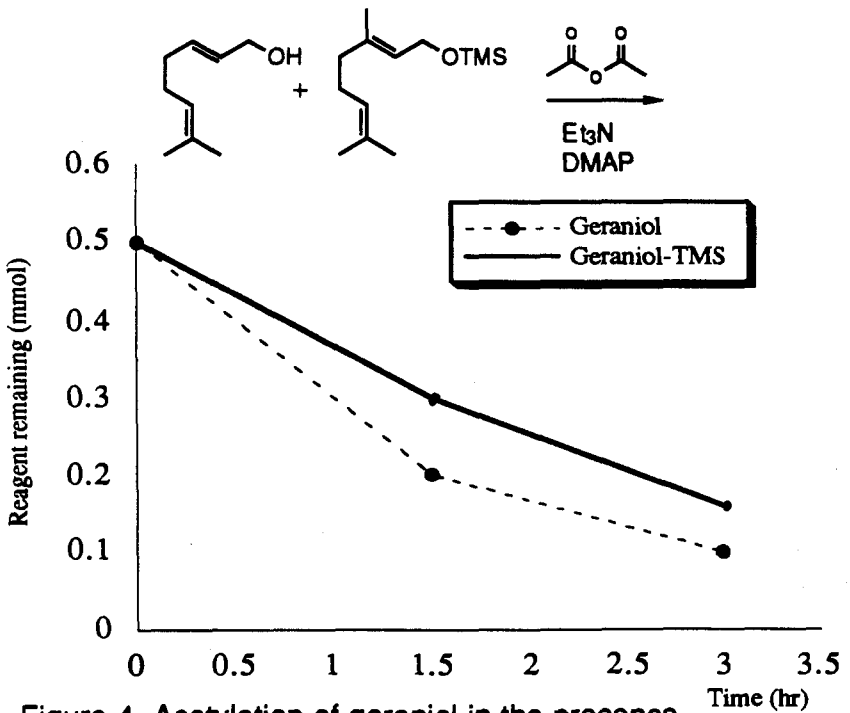
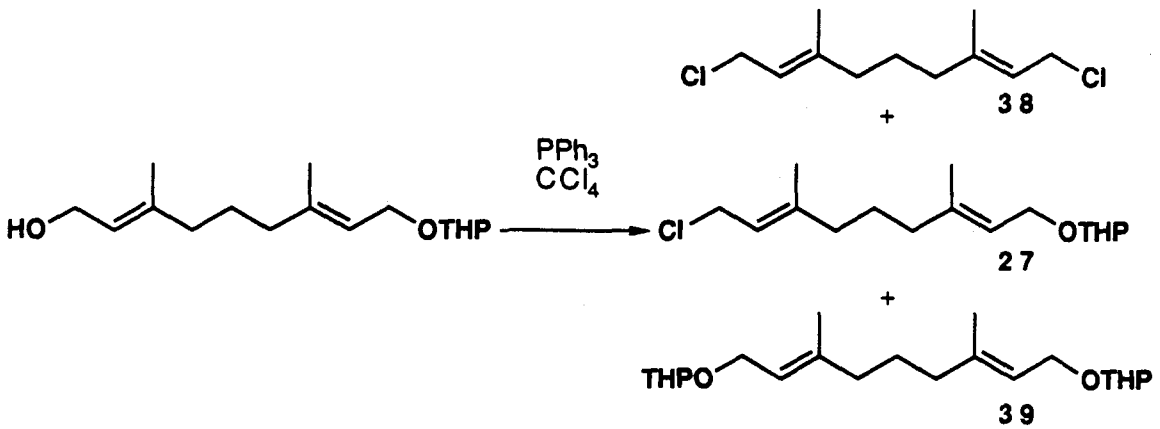


Figure 4. Acetylation of geraniol in the presence of geraniol-TMS.

Halogenation of **26** was first attempted with triphenylphosphine in carbon tetrachloride,[60] but an unexpected mixture of the products **27**, **38** and **39**, in a ratio of 3:1:1, was obtained (Scheme XIII). Formation of **38** probably involves reaction of triphenylphosphine dichloride with the THP. This reagent is known to convert epoxides to dichlorides.[61]



Scheme XIII. Halogenation of **26**.

Finally, chlorination by reaction of equivalent amounts of methyl sulphide, N-chlorosuccinimide and **26** in methylene chloride at -25°C,[51] gave 9-chloro-3,7-dimethyl-1-tetrahydropyranyl-2,7-nonadien-1-ol (**27**) in 90% yield (Scheme V).

Extension of the chain of **27** was conducted by two different methods. The first involved nucleophilic attack by cyanide anion on the allylic halide. Until the introduction of phase transfer agents this type of displacement was conducted under refluxing conditions in ethanol or water.[62] Agents such as 18-crown-6 allow smooth reaction in acetonitrile or benzene through solubilization of nucleophiles such as (potassium) cyanide.[63] In the present case these conditions were used to convert allylic chloride **27** to nitrile **28** in 95% yield.

Hydration of nitriles to carboxylic acids[64] is commonly conducted under highly basic[65] or acidic[66] conditions, which are not compatible with β,γ-unsaturated nitrile **28**. Hydrolysis of homoallylic nitriles without isomerization, reported by Hoye and Kurth[67], failed in our hands. We isolated 2:1 *E:Z* mixtures of isomers of the corresponding carboxylic acid which were identified by the ^{13}C NMR chemical shifts of the methyl carbons. Similar mixtures were obtained when **28** was refluxed with catalytic amounts of arenesulfonic acids,[68] as well as with ethylene glycol-KOH[69] or sodium hydroxide in water.[70] When the reaction was conducted at room temperature starting materials were recovered.

Because hydrolysis of **28** to carboxylic acid **30** was difficult to conduct in one step without isomerization, an alternative route was undertaken. The nitrile was first hydrolyzed to the amide. This transformation has been described under several basic and acidic conditions.[71] Among the most mild procedures is the use of basic hydrogen peroxide under phase transfer conditions.[72] When nitrile **28** was subjected to these conditions amide, **29**, was formed in 92% yield.

Primary amides are hydrolyzed to carboxylic acids under either acid or basic catalysis. Water alone is usually not effective in this reaction because NH_2 is a poor leaving group. Drastic acid[73] or basic conditions[74] and prolonged heating is often required. The hydrolysis can be performed under very mild conditions using an aqueous solution of sodium peroxide[75] or potassium *tert*-butoxide in a ether-water mixture at room temperature.[76] The former method was employed to obtain the *E,E*-carboxylic acid **30** in 90% yield.

Deprotection of the allylic alcohol of **30** was initially executed with PPTS in ethanol, but the process was accompanied by esterification of the carboxylic acid. Since the esterification of acids is reversible, the excess of ethanol drove the equilibrium to the quantitative formation of the carboxylic ester. The THP group was successfully removed with dilute aqueous acetic acid and THF (to make the substrate soluble in the medium).[77] After 6 hours of reaction at room temperature, the *E,E*-hydroxyacid, **15a**, was isolated in 80% yield. This corresponds to an overall yield over 7 steps of 34%.

In recent years many methods for intramolecular lactonization have been developed and applied to the generation of naturally occurring macrolides.[78] While the efficiency of these is certainly a function of reagent, ring size is also a primary determinant of yield.[79] ω-Hydroxyacids containing long carbon chains place the two reactive centres in a lactonization far from each other. Hence, the rate of cyclization is largely controlled by entropic factors. The cyclization of **15a** to suspensolide **5** is expected to be poor because of such effects.

Many different macrolactonization reagents and procedures have been reported in the last two decades.[80] Four of the more general and higher yielding were considered for the lactonization of **15a**:

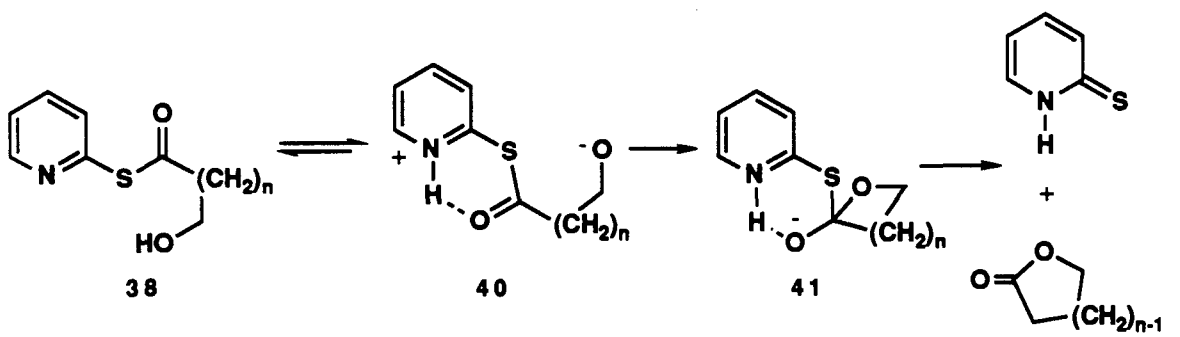
Method 1. Corey's double activation method.[81]

Method 2. The activation of a thiolester towards the nucleophilic displacement of the alcohol by the use of a thiophilic metal ion.[82]

Method 3. The formation of the mixed anhydride of a hydroxycarboxylic acid and 2,4,6-trichlorobenzoic acid, followed by the nucleophilic attack of the hydroxyl group.[83]

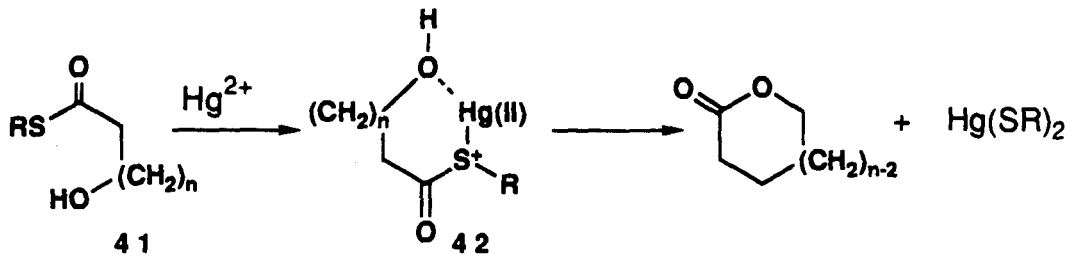
Method 4. Cyclization of the hydroxyacid using a combination of diethyl azodicarboxylate and triphenylphosphine, commonly called Mitsunobu's method.[84]

Corey's double activation method (Method 1) involves the formation of derivatives of pyridyl or imidazoyl thiolesters[85] wherein the heterocyclic nitrogen functions as a base, deprotonating the alcohol (Scheme XIV). The protonated nitrogen then is presumed to protonate the carbonyl as in intermediate **40** activating it toward nucleophilic attack by the deprotonated hydroxyl.[86]. If the hydroxy(2-pyridinethiol)ester is heavily substituted near the reaction centers (i.e., near the hydroxyl and acyl groups) steric interactions slow the reaction leading to **41**.[87] This retardation constitutes the major drawback to the application of this method. Although the substitution of **15a** did not mitigate against this method it was not employed because: 1) the reaction is carried out by prolonged heating of a solution of hydroxyacid and the 2-pyridinethiol; 2) the addition of reagents it is conducted over several hours and 3) Battiste et al reported that the use of this reagent was unsuccessful.[19]



Scheme XIV. Corey's double activation lactonization method.

Method 2 offers the advantage that the reaction of a metal ion such as Hg(II) with the thiol ester, creates a highly reactive trivalent sulphur intermediate, **42**, and lactone formation proceeds very rapidly at room temperature (Scheme XV). The major disadvantage of the method and the reason it was not employed is that Hg(II) can react with alkenes to give alcohols.[88]



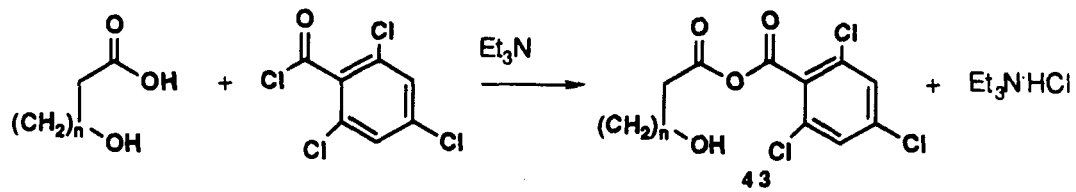
Scheme XV. Masamune's lactonization method.

The mixed anhydride method (Scheme XVI) has been successfully used in the synthesis of several macrolides.[89] It was not applied for cyclization of **15a** because it is conducted in two steps the second of which involves the addition of the mixed anhydride **43** to a solution of DMAP over 8 hours. It was suspected that prolonged heating could isomerize the β,γ- unsaturation of **15a** or **5**.

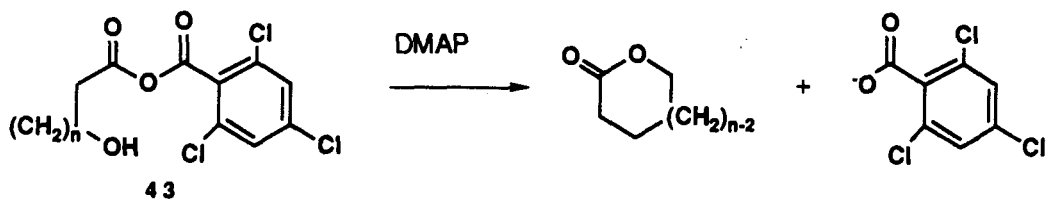
The use of diethylazodicarboxylate and triphenylphosphine to cyclize ω-hydroxyacids (Scheme XVII), involves the displacement of triphenylphosphine oxide in an S_N2 reaction by the carboxylate anion.[90] Mitsunobu's method was chosen for ring closure reaction of **15a**, because it is a single step process, conducted under mild neutral conditions that do not involve long periods of addition of the reagents or prolonged heating.

Numerous macrolactonizations were attempted on **15a** in a published work,[19] with less than satisfactory results. In the present work it was found that **15a** lactonized in the presence of triphenylphosphine and diethyl azodicarboxylate to give **5** in 30% yield. Accompanying **5** in the reaction mixture were the two anastrephins **3** and **4** in a combined yield of 40%. The anastrephins were presumably formed by cyclization of suspensolide catalyzed by small amounts of acetic acid present in the hydroxyacid **15a**.[26]

Step 1



Step 2

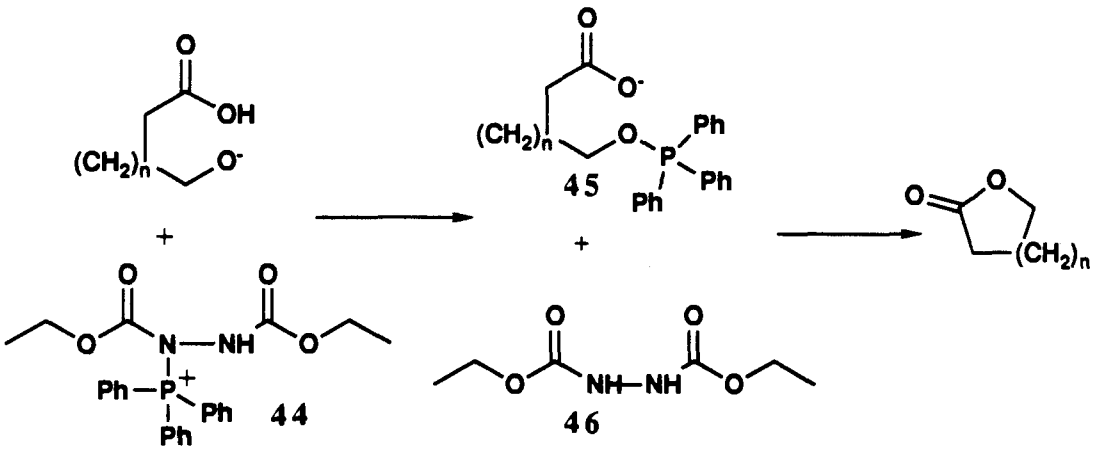


Scheme XVI. Mixed Anhydride lactonization method.

The ^{1}H and ^{13}C NMR spectra of **5** is in agreement with previously published data.[91] The ^{1}H NMR spectrum contains a broad band at 4.6 ppm corresponding to the C10-hydrogens consistent with conformational interconversion that is slow on the NMR time scale.[26]

The total synthesis of suspensolide was realized in 8 steps with 10% overall yield. The only low yield reaction was the cyclization step. To improve

this step cleavage the THP group should be conducted with PPTS in water rather than acetic acid. The former is easier to remove from **15a**. Acid free **15a** would probably not yield the anastrephins when lactonized.

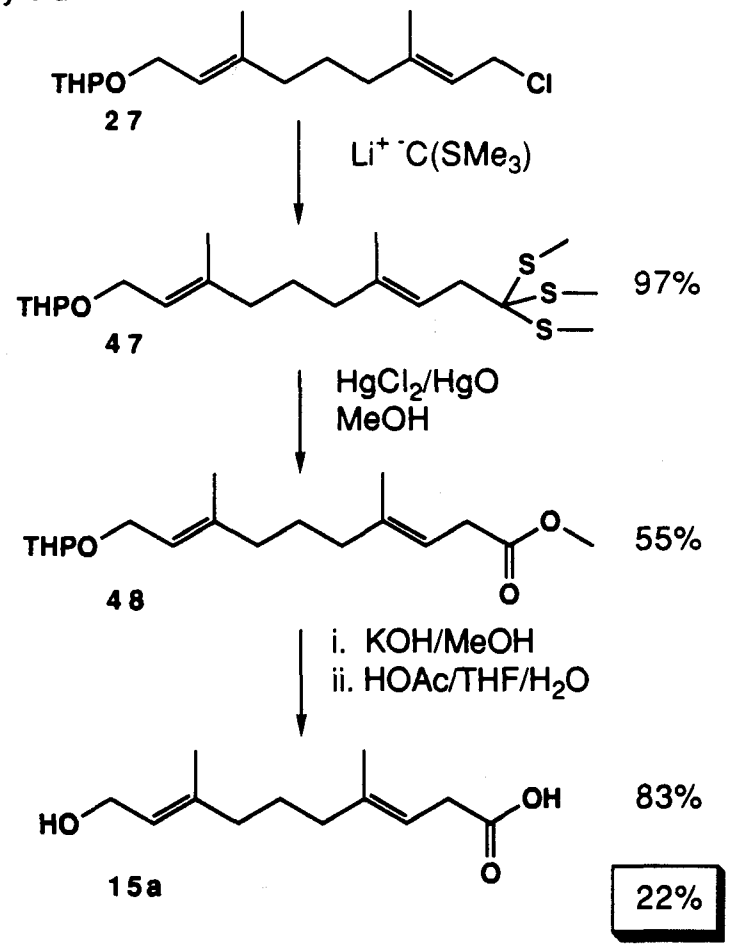


Scheme XVII. Mitsunobu's lactonization method.

Chain extension of allylic chloride **27** was conducted by two methods. The second one, outlined in the Scheme XVIII, takes advantage of the fact that carboxy anion equivalents such as lithio orthothioformates are known to undergo alkylation with a variety of electrophiles.[92,93] Thus, nucleophilic attack of the allylic chloride was effected by the treatment with [tris(methylthio)-methyl]lithium at low temperature (-70 to -60°C) to give the alkylated orthothio ester **47** in excellent yield (96%).

Orthothiocarboxylates are usually unmasked with NBS[94] or $HgCl_2/HgO$.[95] Hydrolysis of unsaturated substrates cannot be performed with NBS because olefins are readily converted to bromohydrins with aqueous NBS,[96] therefore, mercury (II) in methanol was employed at room temperature for 4 hours and one equivalent of a base such as HgO, or $CdCO_3$ was added to

neutralize the liberated HCl and avoid isomerization. The methyl ester (**48**) was isolated in 55% yield.



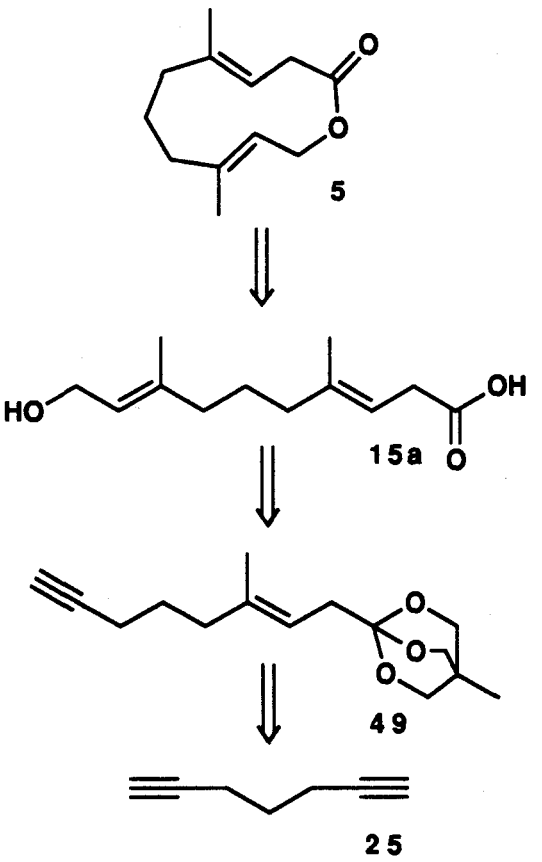
Scheme XVIII. Expansion of the carbon chain *via* coupling orthothioester (Approach # 1).

Saponification of **48** was conducted in 10% KOH/MeOH at room temperature for 2 hours without loss of olefin geometry. Cleavage of the THP group was achieved with a mixture HOAc/THF/H_2O, to give **15a** in 83% yield in 7 steps and an overall yield of 22%.

APPROACH 2

RETROSYNTHETIC ANALYSIS

This synthetic plan arose from the same observation on which Approach 1 was based. That is, if the carboxyl group is excluded, suspensolide is symmetrical. In the second approach structural asymmetry is introduced in the initial steps rather than late in the sequence.(Scheme XIX). Thus, starting with 1,6-heptadiyne **25**, we sought to carboaluminate only one triple bond, then extend the chain in two steps, to give a synthon equivalent to the masked



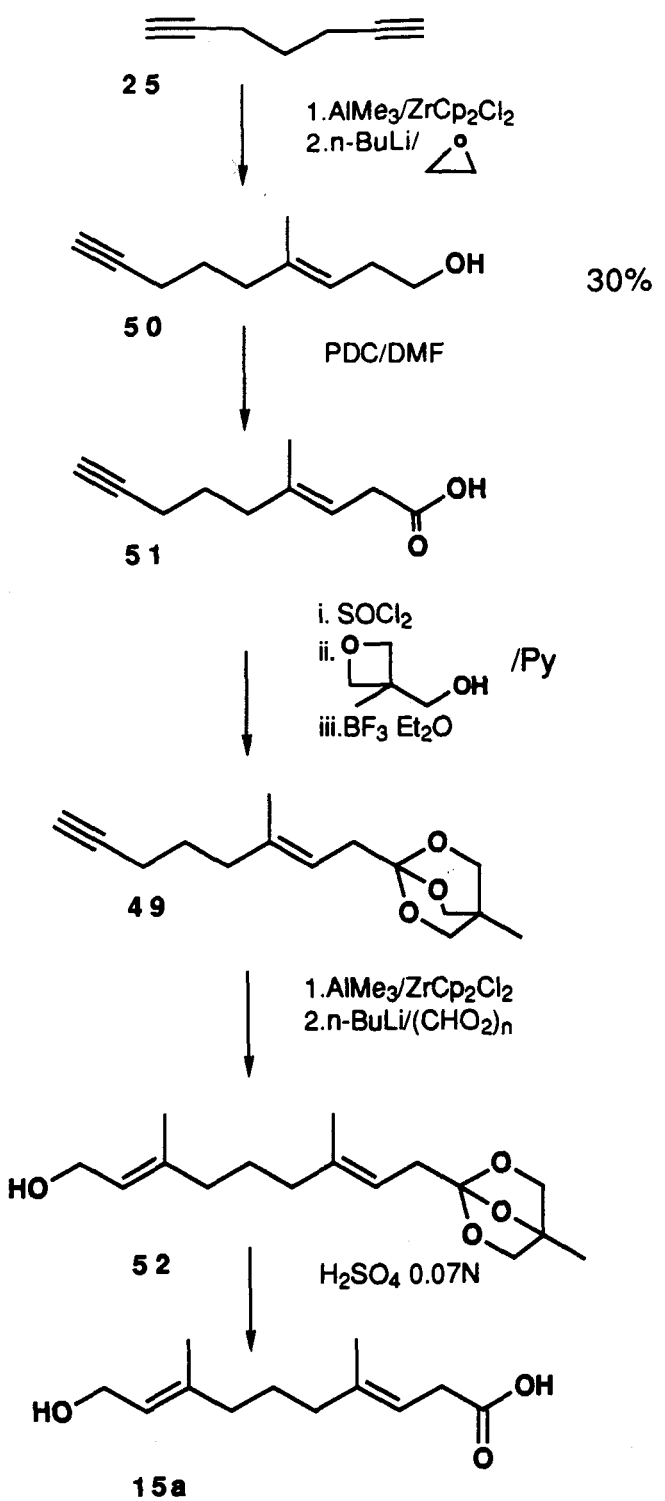
Scheme XIX. Retrosynthetic analysis of the synthesis of suspensolide (Approach #2)

homoallylic carboxylic acid, **49**. We would then carboaluminate the remaining triple bond, extend the chain in one carbon and hydrolyze the ortho ester leading to give **15a**.

SYNTHETIC APPROACH.

The second synthetic approach was envisioned to commence with the monocarboalumination of **25** followed by coupling with ethylene oxide, to give the homoallylic alcohol, **50** (Scheme XX). Oxidation of the hydroxyl group was projected to be achieved under mild conditions employing non-aqueous PDC. This would give the homoallylic carboxylic acid **51** the carboxyl group of which could be protected as an orthoester derivative.[97] Conversion of **51** to the bridged orthoester was envisioned *via* the acid chloride and the alcohol, 2,2-bishydroxymethyl-1-propanol, to give the corresponding ester. Treatment of the latter with boron trifluoride-etherate should yield the bridged ortho ester **49**. Carboalumination would then be performed, followed by coupling with paraformaldehyde to give **52**. The last step would involve regeneration of the carboxylic acid under mild acidic conditions to give **15a**.

It was important to determine if monocarboalumination of 1,6-heptadiyne (**25**), which is the crucial step of this synthesis, was possible. Carboaluminations were conducted in which the concentration of **25** was 0.2 M (Scheme XXI) and the variants were the use of catalytic amounts of Cp_2ZrCl_2 (Figure 5) and the use of an excess of trimethylaluminum (Figure 6). A control reaction employed the reagents in the commonly used ratio (Figure 7).[98] In a second set of experiments (Scheme XXII) the concentration of **25** was 0.1 M



Scheme XX. Approach #2 to the synthesis of suspensolide.

and the variants were the presence of catalytic quantities of $ZrCp_2Cl_2$ (Figure 8), a control reaction (Figure 9) and a deficiency of trimethylaluminium (Figure 10).

It was observed that when the concentration of 1,6-heptadiyne is 0.1 M monocarboalumination was the major process in the first 45 min of reaction. In the best of the cases, the maximum yield of monocarboaluminated product was 57% (without isolation) (Figure 9). It was also observed that the dicarboaluminated product was formed in higher yields when the concentration of 1,6-heptadiyne was 0.2 M and the trimethylaluminium was in excess. Finally, it was also observed that only 30% of the starting material was consumed when the trimethylaluminium was present in deficient amounts.

Control of the ratio of mono and dicarboaluminated products was more problematic when the carboalumination of **25** was conducted using conditions that promote formation of the monocarboaluminated product (Figure 9) and the vinyl aluminum intermediate was activated and coupled with ethylene oxide. Thus, the carboalumination was conducted for 45 minutes to optimize the formation of monocarboalumination product. Then the solvent was evaporated and the catalyst was removed from the product as previously described. During the solvent removal the carboalumination continued leading to **50** in only 30% isolated yield. Even with the low yield of this reaction, the next step was attempted.

Oxidation of an homoallylic alcohol to the corresponding carboxylic acid without concomitant isomerization is a very difficult transformation. In the

Figure 5. $AlMe_3$: Cp_2ZrCl_2 : 25 = 2:0.2:1

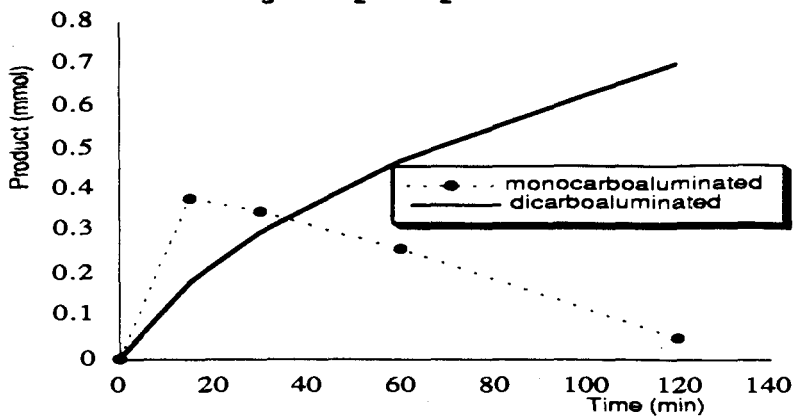


Figure 6. $AlMe_3$: Cp_2ZrCl_2 : 25 = 2.5:1:1

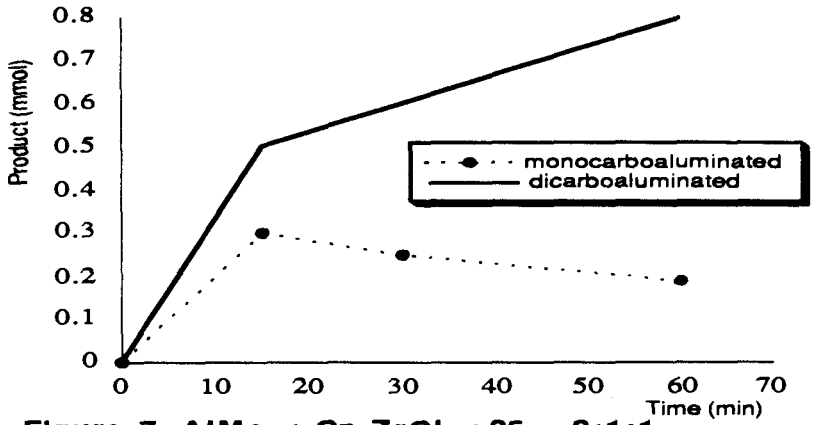
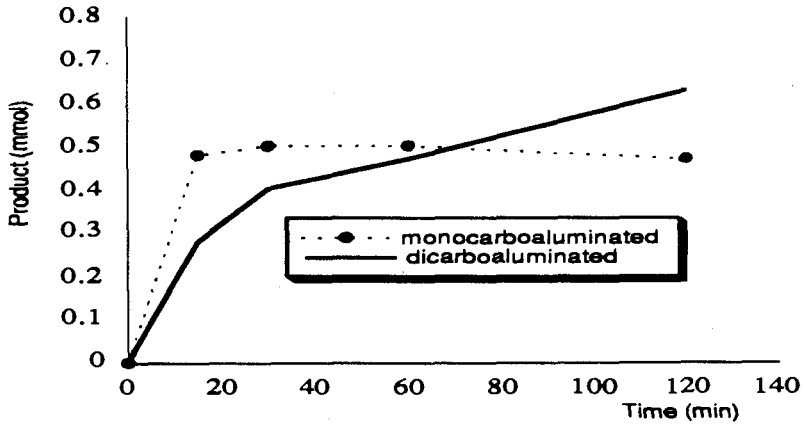
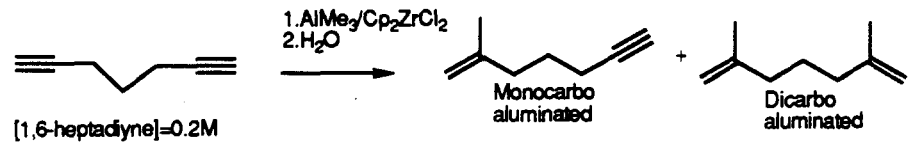


Figure 7. $AlMe_3$: Cp_2ZrCl_2 : 25 = 2:1:1



Scheme XXI.



[1,6-heptadiyne]=0.2M

Figure 8.$AlMe_3$: Cp_2ZrCl_2 : 25 = 2:0.2:1

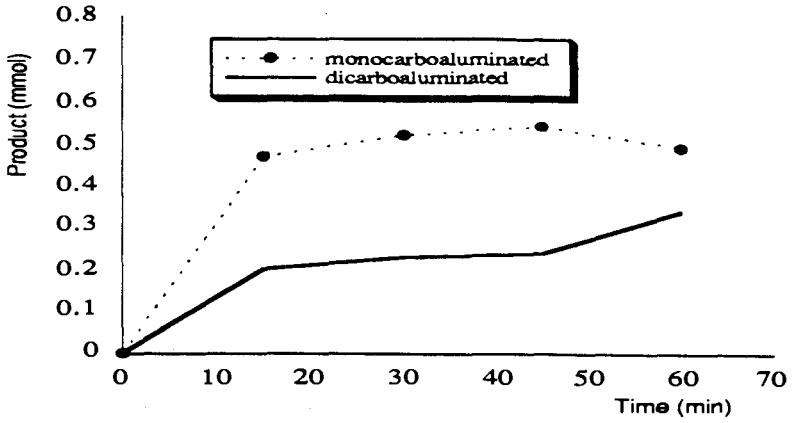


Figure 9.$AlMe_3$: Cp_2ZrCl_2: 25 = 2:1:1

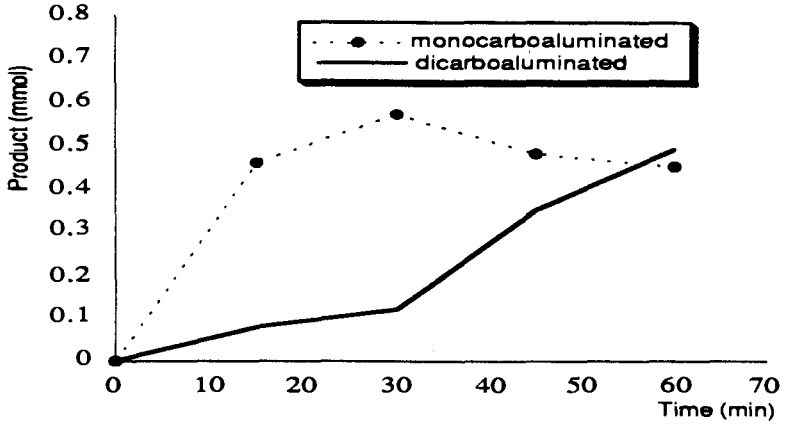
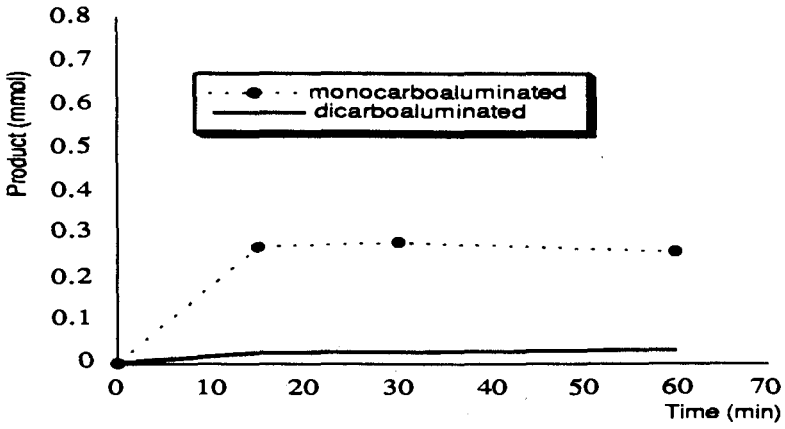
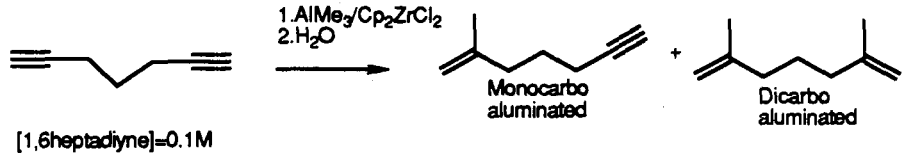


Figure 10. $AlMe_3$: Cp_2ZrCl_2 : 25 = 1:1:1



Scheme XXI.



[1,6heptadiyne]=0.1M

several methods employed for this transformation isomerization of the double bond configuration (from *E* to *Z*) or position (from β–γ to α–β) was observed. Isomerization was significant in the oxidation of (*E*)-4-methyl-3-undecenol with Jones' reagent in acetone at 0 °C.[99] The neutral oxidation system, pyridinium dichromate in DMF,[100] gave at two or three apparently isomeric products by gas chromatography. In all the cases the ^{1}H NMR spectra of the crude reaction products revealed two broad triplets around 5.50 ppm indicating the presence of the (*E*) and (*Z*) isomers of the β–γ unsaturated carboxylic acid. Signals at 6.30 and 5.70 ppm, attributed to the α–β unsaturated carboxylic acids were also evident in these spectra.

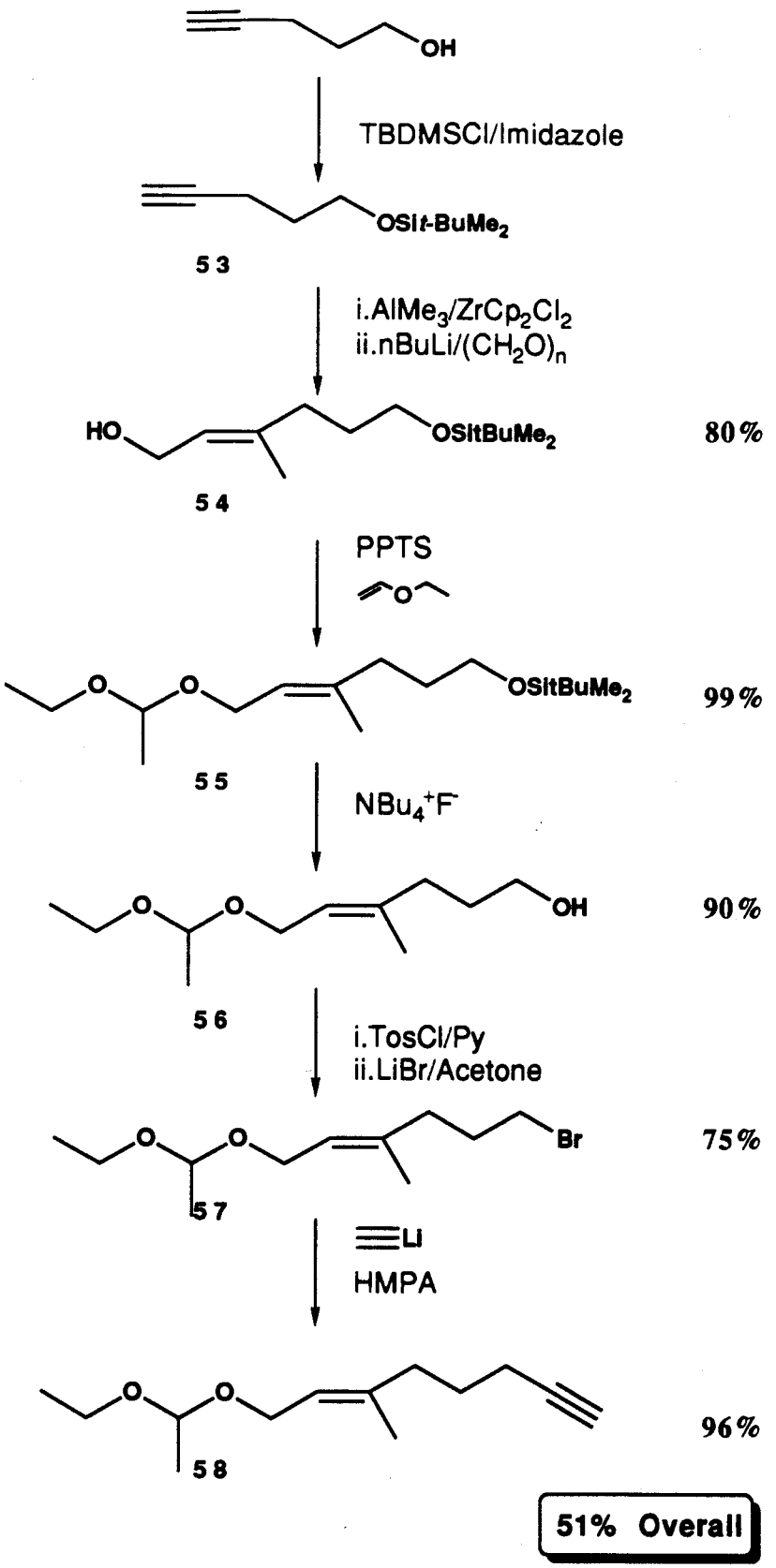
Addition of chromic oxide-pyridine complex to the alcohol in methylene dichloride at RT for 15 minutes gave the corresponding aldehyde in 70% yield without isomerization. Oxidation to the carboxylic acid with AgO[101] or Ag_2O[102] was attended by isomerizations as described above.

Work on this approach was halted at this point.

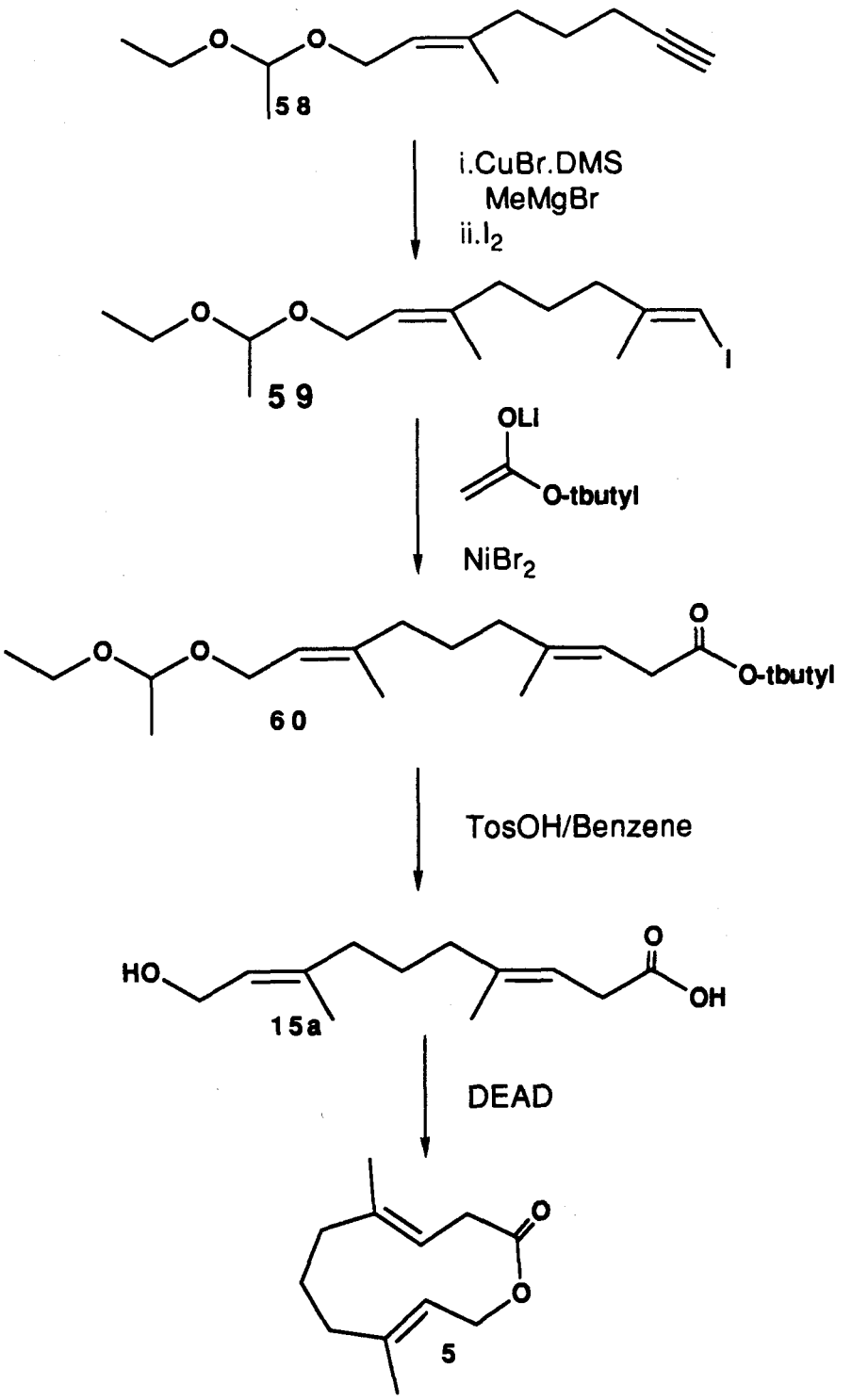
APPROACH 3

SYNTHETIC APPROACH.

The third approach to the synthesis of suspensolide involved creation of one trisubstituted double bond first, the addition of an acetylenic moiety and the methyl-metalation of the latter.



Scheme XXIII. Approach #3 to the synthesis of suspensolide. (Continue)



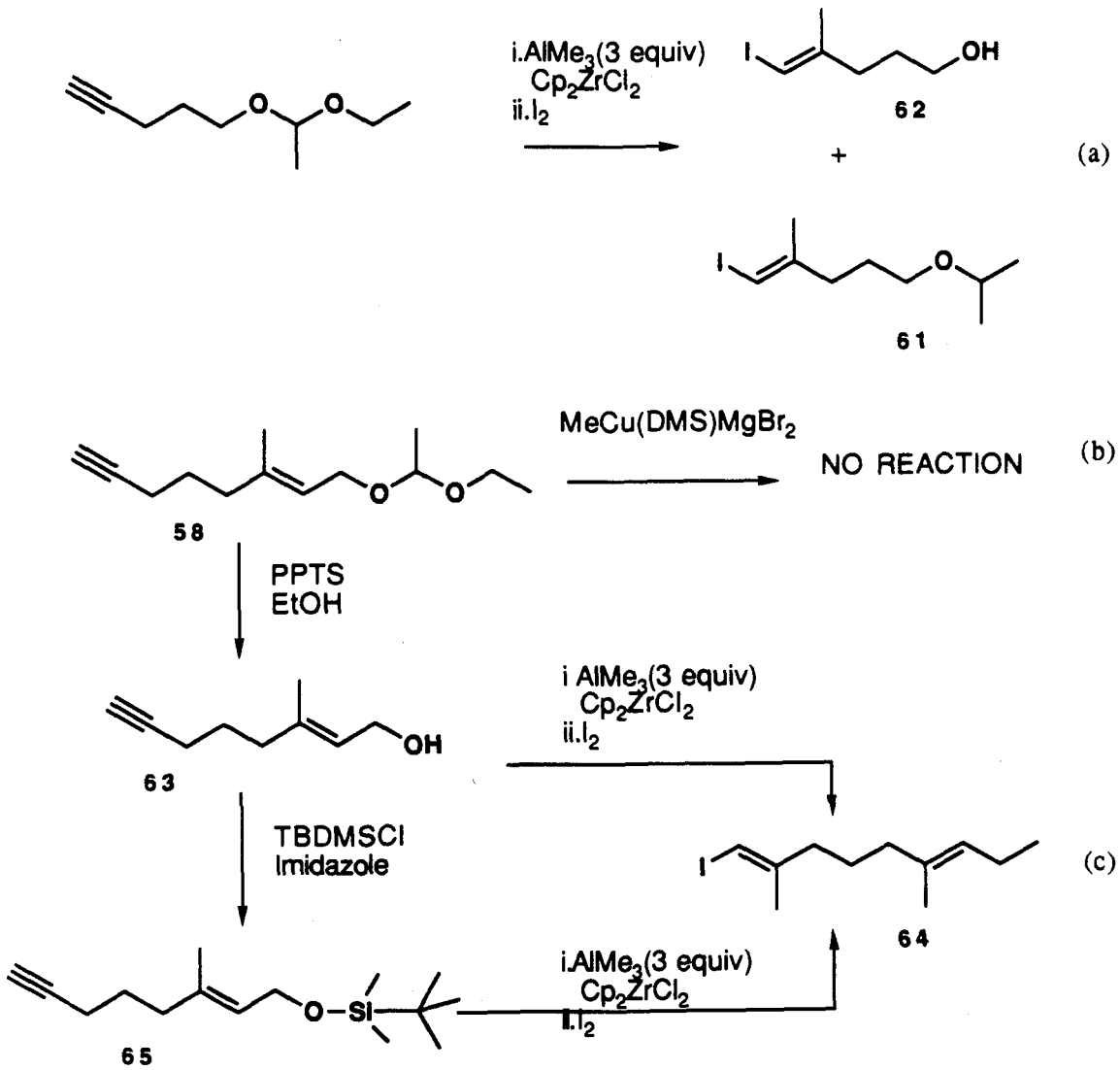
SchemeXXIII. Approach #3 to the synthesis of suspensolide.

This approach commenced by protection of 4-pentynol as the *tert*-butylsilyldimethyl ether **53** using imidazole as a catalyst and dimethylformamide as solvent [103](Scheme XXIII). Carboalumination[104] of the triple bond with $AlMe_3/Cp_2ZrCl_2$ followed by coupling with paraformaldehyde, gave allylic alcohol **54** in 80% overall yield. Reaction of the allylic hydroxyl group with ethyl vinyl ether at -22°C using pyridinium *p*-toluenesulfonate[105] as a catalyst quantitatively gave **55**. Selective cleavage of the *tert*-butyldimethylsilyl ethers in the presence of 1-ethoxyethyl or tetrahydropyranyl ethers has been reported to be successful with a variety of reagents[106] however, tetrabutylammonium fluoride in THF is the most commonly used. Addition of the fluoride salt solution to a THF solution of **55** gave **56** in 90% yield in one hour.

Tosylation was executed by reaction of alcohol **56** with TosCl and pyridine in methylene chloride. Purification of the tosylate by distillation or column chromatography with silica gel pre-treated with triethylamine resulted in decomposition. The tosylate was used in the next step in its crude isolated form.

(*E*)-6-Bromo-3-methyl-2-hexenyl-1-ethoxyethyl ether, **57**, was prepared from the corresponding tosylate by treatment with lithium bromide in dry acetone,[107] to give the product in 75% overall yield from the alcohol **56**. Alkylation of lithium acetylide with the alkyl bromide **57** in THF was unsuccessful (total recovery of **57**) unless HMPA was present as a co-solvent.[108] Under the latter conditions reaction proceeded to give the alkyne **58** in 96%, which corresponds to a 51% overall yield.

To examine the reactivity of the ethoxy ethyl protecting group in **58** during the carboalumination, a model reaction was conducted with 4-pentyn-1'-ethoxyethyl ether (Scheme XXIV, equation a). Methyl alumination of this alkyne gave a mixture 2:3 of 5-iodo-4-methyl-4-pentenyl-1'-



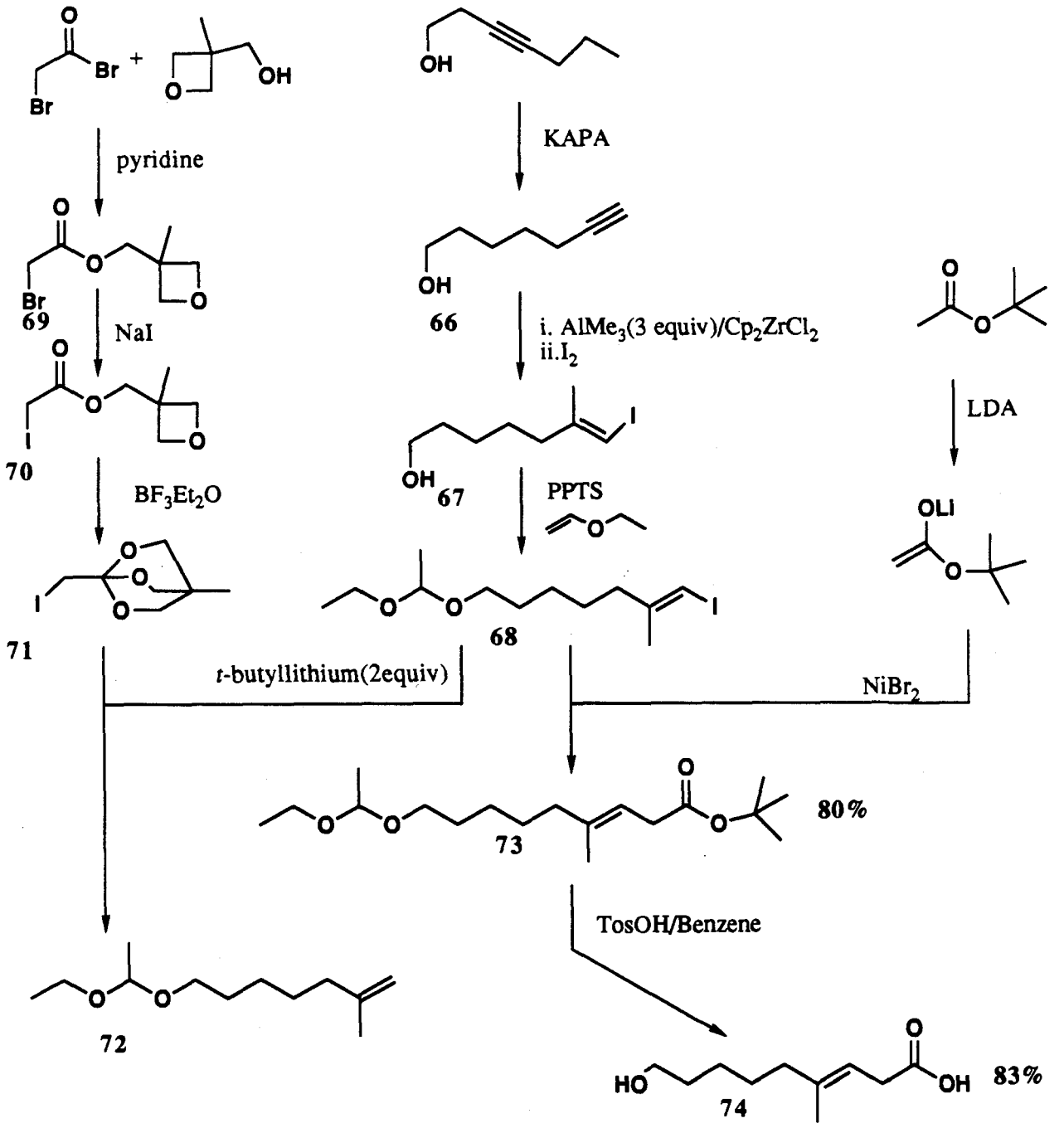
Scheme XXIV Attempted synthesis of **47**.

isopropyl ether, **61**, and 5-iodo-4-methyl-4-pentenyl-1-ol, **62**. Because, the hydroxyl protecting group was the origin of unwanted side reaction, **58** was deprotected in an ethanolic solution with PPTS to give allylic alcohol **63** (Scheme XXIV). Carboalumination of **63** yielded 1-iodo-2,6-dimethyl-1,6-(*E,E*)-nonadiene, **64** as the sole product (equation c). Apparently, the allylic alcohol was sufficiently reactive to undergo displacement with trimethylaluminium to quantitatively give the alkenyl halide. Due to the high reactivity of the allylic alcohol, a bulky *tert*-butyl dimethyl silyl group was substituted as a protecting group **65**. Carboalumination of **65** gave vinyl halide, **64**.

Carboalumination was not an effective procedure for the transformation of **58** to **59**. Methylcupration of **58** was also unsuccessful in several attempts (equation b). Starting material was isolated from reactions which were conducted for as long as 150 hours at -18 °C. Ethylcupration of **58** under equivalent conditions yielded the ethylated product in 80% yield, indicating that introduction of a methyl group by this method, is not straightfoward.

At this point, two steps from the synthetic target, hydroxyacid **15a**, this route reached a dead end. The remaining steps were, however, executed on model compounds. A molecule similar to (*E,E*)-8-Iodo-3,6-dimethyl-2,7-octadienyl-1'-ethoxyethyl ether, **59**, is (*E*)-7-Iodo-6-methyl-6-heptenyl-1'-ethoxyethyl ether. The latter was prepared, as shown in Scheme XXV from 3-heptyn-1-ol which was transformed to **66** by a zipper reaction.[109] Carboalumination of the terminal triple bond followed by quenching with iodine gave alcohol, **67**, which was protected with ethyl vinyl ether to give **68**. Halogen-metal exchange with *tert*-butyl lithium followed by coupling with iodo

ortho ester, **71**, did not give coupled product, instead **72**, the product of hydrolysis of the vinyl lithium reagent was isolated.



Scheme XXV. Model synthesis for the transformation **59** → **15a**

The coupling reaction was successfully executed using $NiBr_2$/n-butyllithium catalysis to vinylate the enolate of *tert*-butyl acetate, **73**.[110] This gave the carboxylic ester **74** in 80% yield. Deprotection of both the hydroxyl and carboxyl of **74** was achieved with TosOH in benzene at 40 °C for 4 hours,[111] to give the ω-hydroxyacid, **75**, in 83% yield.

CONCLUSIONS

The total synthesis of suspensolide was performed in 8 steps with 10% overall yield. This result improved the previous syntheses because the yield was considerable higher, stereochemical purity achieved without microseparation of geometrical isomers and the possibility of scaling up the reactions.

The best conditions for the synthesis of **24** were found to be the use of an excess of trimethylaluminiun with respect to the dialkyne in a highly concentrated reaction.

Selective monoprotection of symmetrical diols was found to be difficult, especially when dealing with substrates with long hydrocarbon chains. In the present case the best option was to obtain a statistical distribution of products using high dilution conditions, then purify and recycle the diol.

TMS was not a reliable protecting group for allylic alcohols, because it was removed by a wide variety of reagents used in this study.

Hydrolysis of the (*E*)-homoallylic nitrile of interest to the corresponding carboxylic acid could not be performed by simple base or acid treatment without isomerization of the double bond, use of phase transfer reagents circumvented isomerization and allowed clean conduct of this transformation.

Monocarboalumination of symmetrical dialkynes was difficult to achieve as was oxidation of (*E*)-homoallylic alcohols without isomerization of the olefin.

Allylic alcohols were found to undergo methylation of the hydroxyl group under Negishi's carboalumination conditions.

EXPERIMENTAL

A) GENERAL METHODS

Glassware, stirbars and syringes were dried (8 hr at 125°C), assembled hot, and cooled under argon. Air and water sensitive reagents were handled in a nitrogen atmosphere bag.

Thin layer chromatography (TLC) was conducted on commercial Merck 5554 aluminum plates. The plates were developed with iodine, short-wave UV, a 1% $KMnO_4$ solution, or a mixture of ceric sulphate (1%), molybdic acid (1.4%) in 10% H_2SO_4, followed by heating. Flash chromatography was performed according to the procedure of Still[112] on Merck Art. 9385 230-400 Mesh. ^1H and ^{13}C NMR were obtained on Bruker AMX 400 or Bruker SW 100 spectrometers, ambiguous assignments were resolved on the basis of 2D H-H and C-H correlations. IR spectra were recorded on a Perkin-Elmer 1600 Series FT spectrometer.

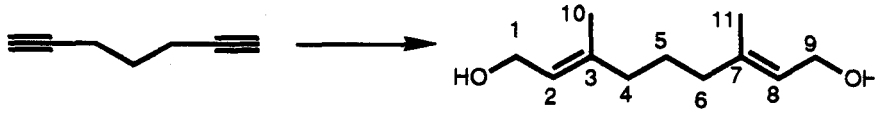
THF and diethyl ether were freshly distilled from potassium benzophenone ketyl under argon before use. Molecular sieves (4Å) were activated by heating for 12 h at 150 °C under vacuum. 1,2- Dichloroethane and dichloromethane were freshly distilled from P_2O_5. DMF was stored over activated molecular sieves. Ethyl vinyl ether and DHP were distilled from sodium. Acetone was distilled over $KMnO_4$, HMPA was distilled from CaH_2 and stored in the dark over molecular sieves. Diisopropylamine was freshly distilled from KOH, 1,3-diaminopropane was distilled from BaO and stored over molecular sieves. KCN was ground and then dried at 100°C for 24 h under

vacuum. NCS and NBS were dried for 10 hr at 70°C under vacuum. Paraformaldehyde was dried at 40°C for 24 h under vacuum.

The titration of organometallic reagents was performed by the method of Watson and Eastman.[113] All other commercial chemicals were analytical grade, and unless otherwise mentioned, were used without purification.

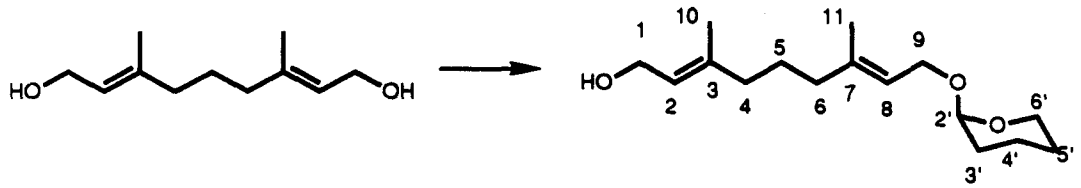
B) EXPERIMENTAL METHODS

Note: The numeration employed for the NMR assignments does not necessary correspond with IUPAC rules.



Preparation of (*E,E*)-3,7-dimethyl-2,7-nonadien-1,9-diol (24): To a solution of Cp_2ZrCl_2 (4.38 g, 15 mmol) in 40 mL of 1,2-dichloroethane was added trimethylaluminum (2.52 g, 3.35 mL, 35 mmol) at 0°C. To the yellow solution thus obtained was added dropwise 1,6-heptadiyne (0.92 g, 1.13 mL, 10 mmol) in 10 mL of 1,2-dichloroethane at room temperature. After the mixture was stirred for 3 hr, volatile compounds were evaporated at reduced pressure. The residue was extracted with n-hexane which allowed the removal of the soluble product by filtration under inert atmosphere. To the extract at -78°C, was added n-butyllithium in hexane (8 mL, 2.5 M, 20 mmol). THF was added to dissolve the precipitate which formed and paraformaldehyde (1.8 g, 60 mmol) was then added. The reaction mixture was stirred overnight, quenched with ice-cold water and extracted with ether (3 x 50 mL). The extract was dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The crude product was purified on a silica gel column using ether as the eluant, to give 1.56 g of **24** in 85%.

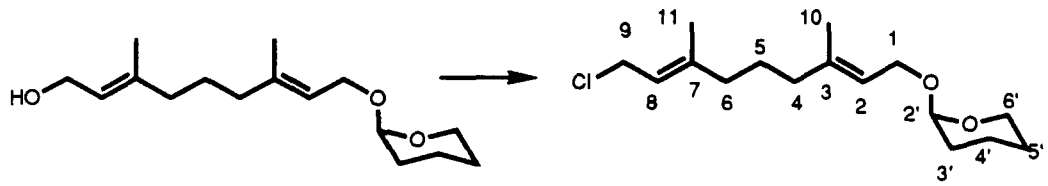
IR (film) 3354, 2932, 1660, 1458, 1175, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.41 (H2, H8: ttq, *J* = 7.0, 1.5, 1.5 Hz; 2H), δ 4.15 (H1, H9: d, *J* = 7.0 Hz; 4H), δ 2.10 (H4, H6: t, *J* = 7.5 Hz; 4H), δ 1.67 (H10, H11: s; 6H), δ 1.56 (H5: tt, *J* = 7.5, 7.5 Hz, 2H), δ 1.46 (-OH: s; 1H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 139.57 (C3, C7), δ 123.57 (C2, C8), δ 59.38 (C1, C9), δ39.07 (C4, C6), δ16.5 (C5), δ16.1 (C10, C11) ppm. Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.70%; H, 10.94%. Found: C, 71.58%; H, 11.02%.



Preparation of (*E,E*)-3,7-dimethyl-2,7-nonadien-(9-tetrahydropyran-2'-yloxy)-1-ol (26): To a solution of **24** (2.5 g, 14 mmol) in ether (320 mL)was added 1.27 mL (1.17 g , 14 mmol) of DHP and 4.7 mg of TosOH. The solution was stirred at room temperature. Aliquots were periodically withdrawn from the reaction mixture quenched, extracted and analyzed by gas chromatography. When 50% of **26** was produced water (3 mL) was added and the organic phase was washed with 2% $NaHCO_3$ (25 mL) and brine (15 mL), dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography using ether: hexane, 4:1 as the eluant. The diol isolated was recycled to give 2.62 g of **26** in two steps (70%). IR (film) 3415, 2940, 1667, 1440, 1382, 1353, 1321, 1261, 1199, 1183, 1117, 1076, 1024, 906, 867, 813, 733.cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.39 (H2: ttq, *J* = 6.5, 1.1, 1.1 Hz; 1H), δ 5.34 (H8: ttq, *J* = 7.0, 1.1, 1.1 Hz; 1H), δ 4.60 (H2': bt, *J* = 3.2 Hz; 1H), δ 4.22 and 4.01 (H9: dd, *J* = 6.4, 11.92 Hz; 2H), δ 4.13 (H1: bd, *J* = 6.5 Hz; 2H), δ 3.87 and 3.49 (H6': m; 2H), δ 2.00 (H4: bt, *J* = 6.7 Hz; 2H), δ 1.98 (H6: t, *J* = 6.7 Hz; 2H), δ 1.65 (H10: s; 3H), δ 1.61 (H11: s; 3H), δ 1.54 (H3', H4',

H5': m; 6H), δ 1.47 (H5: tt, J = 6.7, 6.7 Hz; 3H), δ 1.40 (OH: s; 1H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 139.80 (C3), δ 139.06 (C7), δ 123.63 (C2), δ 120.77 (C8), δ 97.68 (C2'), δ 63.52 (C9), δ 62.11 (C6'), δ 59.10 (C1), δ 39.04 (C4)*, δ 38,99 (C6)*, δ 30.58(C5')•, δ 25.51 (C5), δ25.38 (C3')•, δ 19.45 (C4')•, δ 16.16 (C10), δ 16.02 (C11) ppm. Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.59%; H, 10.52%. Found: C, 71.18%; H, 10.58%.

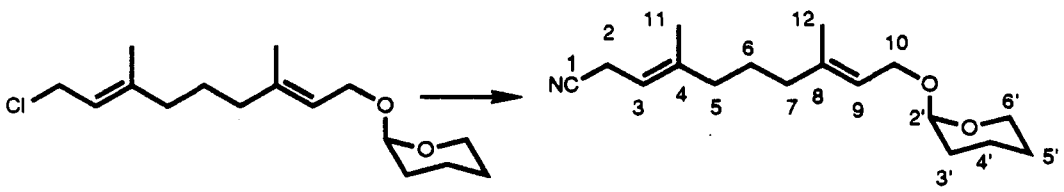
*,•: Assignments not definitive.



Preparation of (*E,E*)-9-chloro-3,7-dimethyl-1-(tetrahydropyran-2'-yloxy)-2,7-nonadienol (27): To a magnetically stirred solution of 1.41 g (10.56 mmol) of N-chlorosuccinimide in 10 mL of anhydrous methylene chloride, under argon, was added dropwise at 0°C 0.90 mL (11.52 mmol) of dimethyl sulfide. The reaction was cooled to -20°C and 2.41 g (9 mmol) of (*E,E*)-3,7-dimethyl-2,7-nonen-9-(2-tetrahydrofuranoxy)-1-ol (**26**) in 5 mL of methylene chloride was added gradually over 5 min. The resulting solution was warmed to 0°C, stirred for 1 hr. and poured in 40 mL of ice-cold brine. The aqueous phase was extracted with two 20-mL portions of ether. The combined organic phase was washed with two 20-mL portions of cold brine and dried over anhyd. $MgSO_4$. Filtration and concentration *in vacuo* gave 2.32 g of chloride **27** (90%). IR (film) 2939, 2869,1663, 1440, 1384, 1353, 1254, 1199, 1182, 1132, 1117, 1077, 1024, 976, 906, 869, 814, 667.cm^{-1}. ^1H NMR (C_6D_6, 400 MHz) δ 5.58 (H8: ttq; J = 6.5, 1.0, 1.0 Hz; 1H), δ 5.54 (H2: ttq, J = 8.0, 1.1, 1.1 Hz; 1H), δ 4.77 (H2': bt, J = 3.3 Hz; 1H), δ 4.46 and 4.15 (H1:ddd, J = 6.5, 12.3 ; 0.6 Hz; 2H), δ 3.92 (H6', axial: ddd, J = 11.0; 9.6, 3.0 Hz; 1H), δ 3.81 (H9: d, J =

8.0 Hz; 2H), δ 3.48 (H6', eq: dddd, J = 11.03; 4.5, 4.5, 1.2 Hz; 1H), δ 1.79 (H4*: bt, J = 7.2 Hz; 2H), δ 1.88 (H6*: bt, J = 7.6 Hz; 2H), δ 1.80-1.5 (H3', H4', H5': m; 6H), δ 1.58 (H11: s; 3H), δ 1.47 (H5: m; 2H), δ 1.37 (H10: s; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 142.25 (C7), δ 138.84 (C3), δ 122.27 (C8), δ 120.98 (C2), δ 97.58 (C2'), δ 63.65 (C1), δ 61.57 (C6'), δ 40.82 (C9), δ 39,17 (C6)*, δ 39.00 (C4)*, δ 31.07 (C5')*, δ 25.98 (C5), δ 25.67 (C3')*, δ 19.61 (C4')*, δ 16.23 (C11), δ 15.69 (C10) ppm. Anal. Calcd. for $C_{16}H_{27}O_2Cl$: C, 67.09%; H, 9.51%. Found: C, 67.20%; H, 9.61%.

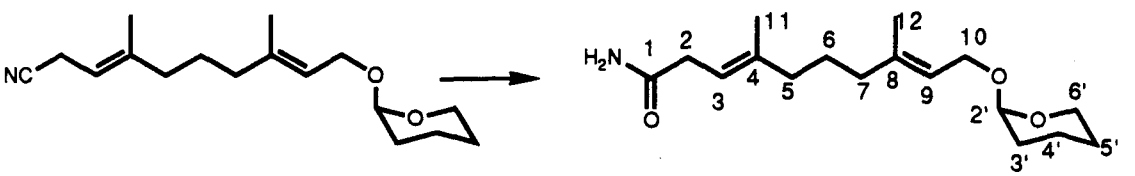
,: Assignments not definitive.



Preparation of (*E*,*E*)-3,7-dimethyl-2,7-nonadien-9-(tetrahydropyra-2'-yloxy)-1-cyanide (28): Into a 5 mL round bottom flask equiped with a magnetic stirring bar and under argon atmosphere, were placed 0.84 g (12 mmol) of dry KCN and 2.5 mL of an acetonitrile solution containing 1.71 g of (*E*,*E*)-9-chloro-3,7-dimethyl-2,7-nonadien-1-tetrahydropyra-2'-yloxy (**27**) (6 mmol) and 12 mg (0.045 mmol) of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6). The two phase system was stirred 12 h at room temperature. Solvent removal left a residue which was tritured with 3:1 hexane/EtOAc and filtered to separate the 18-crown-6. Solvent removal left **28** as a colorless oil (3.19 g, 11.52 mmol, 96%) of sufficient purity for the subsequent step. The nitrile could be purified by silica gel column chromatography using ether:hexane, 1:1, as the eluant.

IR (film) 2934, 2214, 1738, 1668, 1454, 1383, 1353, 1241, 1116, 1023, 905, 869 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.92 (H9: ttq; *J* = 6.5, 1.0, 1.0 Hz; 1H), δ 4.79 (H3: ttq; *J* = 8.0, 1.1, 1.1 Hz; 1H), δ 4.76 (H2': bt; *J* = 3.3 Hz; 1H), δ 4.46 and 4.15 (H10: ddd; *J* = 6.5; 12.3 ; 0.6 Hz; 2H), δ 3.93 (H6', axial: ddd; *J* = 11.0; 9.6, 3.0 Hz; 1H), δ 3.47 (H6', eq: dddd, *J* = 11.03; 4.5,4.5,1.2 Hz; 1H), δ 2.23 (H2: d; *J* = 8.0 Hz; 2H), δ 1.85 (H5*: bt; *J* = 7.2 Hz; 2H), δ 1.75 (H7*: *J* = 7.6 Hz; 2H), δ 1.58 (H12: s; 3H), δ 1.35 (H6: m; 2H), δ 1.2 (H11: s; 3H), δ 1.80-1.30 (H3', H4',H5': m; 6H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 141.51 (C8), δ 138.74 (C4), δ 122.38 (C9), δ 118.02 (C1), δ 112.58 (C3), δ 97.74 (C2'), δ 63.73 (C10), δ 61.67 (C6'), δ 39.18 (C5)*, δ 38,76 (C7)*, δ 31.11 (C3')•, δ 25.98 (C5')•, δ 25.65 (C6), δ 19.45 (C4')•, δ 16.26 (C2), δ 15.75 (C12), δ 15.71 (C11) ppm. Anal. Calcd. for $C_{17}H_{27}O_2N$: C,73.61, %; H,9.81; N,5.05%. Found: C,71.34 %; H,9.31; N, 5.19 %.

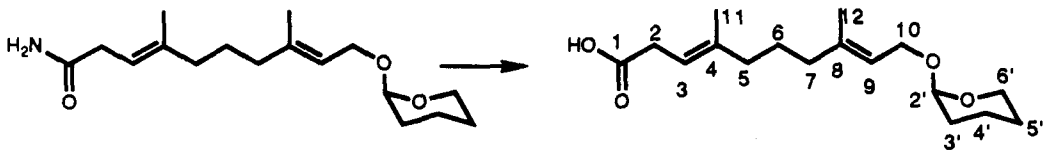
*,•: Assignments are not definitive.



Preparation of (*E,E*)-4,8-dimethyl-3,8-decadien-10-(tetrahydropyra-2'-yloxy) amide (29): To a magnetically stirred methylene dichloride solution (2 mL) of (*E,E*)-3,7-dimethyl-2,7-nonadien-9-tetrahydropyra-2'-yloxy-1-cyanide (**28**; 1.29 g, 4.6 mmol) cooled in an ice bath, was added 30% hydrogen peroxide (2.2 mL), tetrabutylammonium hydrogen sulphate (0.35 g, 1.0 mmol), and a 20% aqueous solution of sodium hydroxide (2 mL). The reaction mixture is allowed to warm to room temperature and maintained with stirring. After 8 hr. dichloromethane was added, the organic layer was separated, washed with saturated sodium chloride solution, and dried over anhyd. sodium sulphate.

The solvent was removed under reduced pressure to give an oil, purified by chromatography on silica gel using ether:hexane, 4:1 as the initial eluant. When the impurities were eluted the eluant was changed to ether to give 1.24 g 93% (4.27 mmol) of **29**. IR (film) 3340, 3196, 2936, 1681, 1441, 1384, 1322, 1263, 1200, 1182, 1158, 1117, 1023, 905, 869, 813 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 6.82 (NH: bs, 2H), δ 5.60 (H9: bt, *J* = 7.0 Hz; 1H), δ 5.28 (H3: bt, *J* = 7.3; 1H), δ 4.75 (H2': bt, *J* = 3.4 Hz; 1H), δ 4.45 and 4.15 (H10: dd, *J* = 11.9; 7.1 Hz; 2H), δ 3.91 and 3.50 (H6': m, 2H), δ 2.80 (H2: d, *J* = 7.3 Hz; 2H), δ 1.95 (H7*: t, *J* = 7.6 Hz; 2H), δ 1.88 (H5*: t, *J* = 7.4 Hz; 2H), δ 1.62 (H12: bs; 3H), δ 1.67-1.10 (H3', H4', H5': m; 6H), δ 1.46 (H6: m; 2H), δ 1.42 (H11: bs; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 173.85 (C1), δ 139.48 (C8), δ 139.15 (C4), δ 122.12 (C9), δ 117.79 (C3), δ 97.70 (C2'), δ 63.74 (C10), δ 61.68 (C6'), δ 39.34 (C7)*, δ 38,27 (C5)*, δ35.64 (C2), δ 31.07 (C5')•, δ 26.02 (C3')•, δ25,94 (C6), δ 19.54 (C4')•, δ16.27 (C12), δ 15.99 (C11) ppm. Anal. Calcd. for $C_{17}H_{29}O_3N$: C, 69.12%; H, 9.89%, N,4.74%. Found: C, 68.93%; H, 10.04%; N, 4.58%.

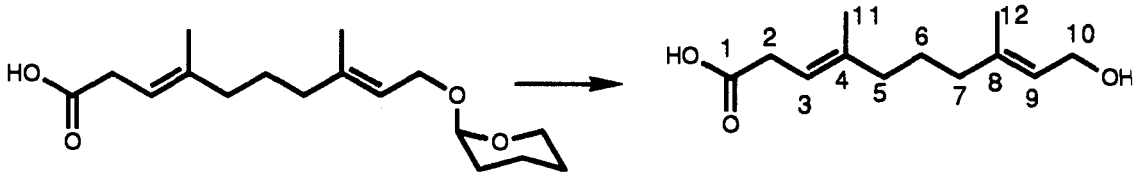
*,•: Assignments are not definitive.



Preparation of (*E*,*E*)-4,8-dimethyl-3,8-decadien-10-tetrahydropyra-2'-yloxy carboxylic acid (30): (*E*,*E*)-4,8-Dimethyl-3,8-decadien-10-tetrahydropyra-2'-yloxy amide **29** (0.5 g, 1.60 mmol) was suspended in 5 mL of water. Sodium peroxide (0.129 g, 1.29 mmol) was then added portionwise with care [the reaction can be exothermic when conducted on a large scale]. After heating at 80°C for 8 hours, the resulting solution was cooled to 0°C and

carefully acidified by dropwise addition of cold HCl 2M to pH 5. The solution was extracted with methylene dichloride (3 X 3 mL) and the extracts dried over anhyd. $MgSO_4$. Evaporation of the solvent gave 0.42 g (1.44 mmol, 90%) of **30**. IR (film) 3530, 2938, 1741, 1668, 1436, 1384, 1318, 1261, 1200, 1023, 906, 869, 814 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 9.0-8.0 (OH: bs, 1H), δ 5.60 (H9: ttq, *J* = 7.0, 1.1, 1.1 Hz; 1H), δ 5.40 (H3: ttq, *J* = 7.3, 1.1, 1.1; 1H), δ 4.78 (H2': bt, *J* = 3.3 Hz; 1H), δ 4.45 and 4.17 (H10: dd, *J* = 12.0, 6.3 Hz; 2H), δ 3.92 (H6', axial: ddd, *J* = 11.0, 9.6, 3.0 Hz; 1H), δ 3.47 (H6'eq: dddd, *J* = 11.03, 4.5,4.5,1.2 Hz; 1H), δ 2.93 (H2: d, *J* = 7.0 Hz; 2H), δ 1.93 (H7*: t, *J* = 7.5 Hz; 2H), δ 1.89 (H5*: t, *J* = 7.5 Hz; 2H), δ 1.60 (H12: bs; 3H), δ 1.68-1.10 (H3', H4', H5': m; 6H), δ 1.47 (H6: m; 2H), δ 1.41 (H11: bs; 3H) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz) δ 170.95 (C1), δ 139.20 (C8), δ 138.88 (C4), δ 122.05 (C9), δ 115.96 (C3), δ 97.57 (C13), δ 63.72 (C10), δ 61.57 (C6'), δ 39.28 (C7)*, δ 39,22 (C5)*, δ33.58 (C2), δ 31.04 (C4')•, δ 25.94 (C3')•, δ 25.94 (C6), δ 19.56 (C5')•, δ16.25 (C12), δ 16.07 (C11) ppm. Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89%; H, 9.52%. Found: C, 66.88%; H, 9.44%.

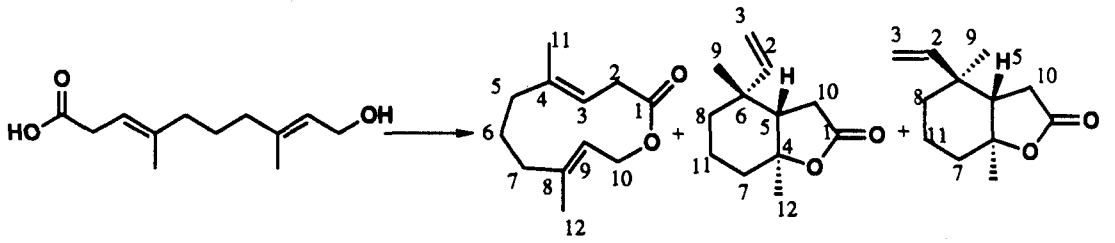
*,•: Assignments are not definitive.



Preparation of (*E,E*)-10-hydroxy-4,8-dimethyl-3,8-decadien-10-olic acid (15a): (*E,E*)-4,8-Dimethyl-3,8-decadien-10-tetrahydropyra-2'-yloxy carboxylic acid **30** (0.30 g, 1.01 mmol) was dissolved in 10 mL of 4:2:1 acetic acid-tetrahydrofuran-water. The resulting solution was heated at 45°C for 4 hr. The mixture was extracted with three-5 mL portions of ether, the organic phase

was washed with water and brine and dried over anhyd. $MgSO_4$, to give 0.17 g (0.8 mmol, 80 %) of pure hydroxyacid **15a**. IR (film) 3500, 2933, 1714, 1385, 1285, 998 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 9.0-8.0 (OH: bs, 1H), δ 5.54 (H9: ttq; J = 7.1, 1.2, 1.1 Hz; 1H), δ 5.48 (H3: ttq J = 7.0, 1.1, 1.1; 1H), δ 4.01 (H10: bd; J = 6.6 Hz; 2H), δ 3.00 (H2: d; J = 7.0 Hz; 2H), δ 1.94 (H7*: t; J = 7.5 Hz; 2H), δ 1.91 (H5*: t; J = 7.5 Hz; 2H), δ 1.49 (H11,H12: bs; 6H), δ 1.47 (H6, OH: m; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 171.69 (C1), δ 138.46 (C8), δ 137.94 (C4), δ 125.09 (C9), δ 116.95 (C3), δ 59.31 (C10), δ39.20 (C7)*, δ 39.13 (C5)*, δ 33,95 (C2), δ 25.87 (C6), δ16.10 (C12), δ 15.98 (C11) ppm.

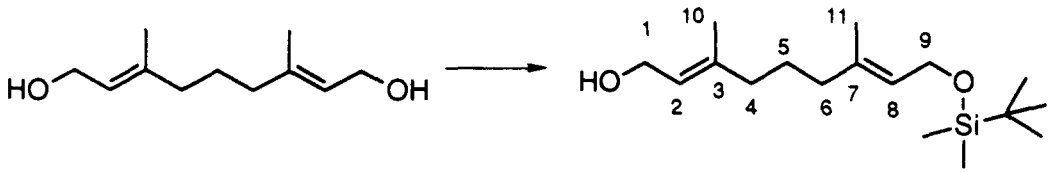
,: Assignments are not definitive.



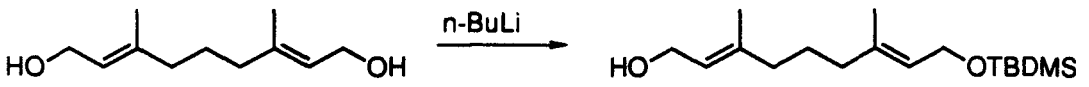
Preparation of (*E*,*E*)-4,8-dimethyl-3,8-decadien-10-olide (5): A solution of (*E*,*E*)-10-hydroxy-4,8-dimethyl-3,8-decadienoic acid, **15a** (260 mg, 1.2 mmol), DEAD (0.30 mL, 1.8 mmol) and triphenylphosphine (0.47 g, 1.8 mmol) in 102 mL of anhydrous benzene was stirred at 23°C for 12 h. Concentration of the mixture *in vacuo*, followed by chromatography on silica gel with ether:hexane (3:7) as the eluant gave, in order of elution, a mixture of anastrephin, **3**, and epianastrephin, **4**, (93 mg, 0.48 mmol, 40%) and suspensolide, **5** (70 mg, 0.36 mmol, 30%). Suspensolide: IR (film) 2932, 1772, 1633, 1454, 1370, 1268, 1104, 1043, 1006, 914, 770 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.11 (H9: t; J = 8.0Hz; 1H), δ 4.85 (H3: t J = 8.1 Hz; 1H), δ 4.62 (H10: bs; 2H), δ 3.00 (H2: bs; 2H), δ 2.21 (H5, H7: m; 4H), δ 1.87 (H6: m; 2H), δ 1.67 (H12: bs; 3H), δ 1.60 (H11, bs; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ

170.4 (C1), δ 144.7 (C8), δ 142.7 (C4), δ 120.0 (C9), δ 115.9 (C3), δ 61.1 (C10), δ 41.5 (C7,C5), δ 35.7 (C2), δ 25.6 (C6), δ15.1 (C12), δ 14.0 (C11) ppm. Anastrephin: ^{1}H NMR (C_6D_6, 400 MHz) δ 5.27 (H2: dd; J = 10.7, 17.4 Hz; 1H), δ 4.80 (H3: dd; J = 10.7, 0.9 Hz; 1H), δ 4.71 (H3: dd; J = 17.4, 0.9 Hz; 1H), δ 3.00 (H10: m; 2H), δ 1.95 (H12: s; 3H), δ 1.47 (H9: s; 3H), δ 2.10-1.55 (H7, H8, H11, m; 6H) ppm. Epianastrephin: ^{1}H NMR (C_6D_6, 400 MHz) δ 5.68 (H2: dd; J = 10.6, 17.4 Hz; 1H), δ 5.01 (H3: dd; J = 10.6, 2.0 Hz; 1H), δ 4.87 (H3: dd; J = 17.4, 2.0 Hz; 1H), δ 3.00 (H10: m; 2H), δ 1.95 (H12: s; 3H), δ 1.47 (H9: s; 3H), δ 2.10-1.55 (H7, H8, H11, m; 6H) ppm. **NOTE:** The stereochemistry of anastrephin and epianastrephin was not assigned in this work.

Preparation of (*E*,*E*)-1,7-diiodo-2,6-dimethyl-1,6-heptadiene (32): To a solution of Cp_2ZrCl_2 (1.46 g, 5 mmol) in 50 mL of 1,2-dichloroethane was added trimethylaluminum (5.76 g, 7.66 mL, 80 mmol) at 0°C. To the yellow solution thus obtained was added dropwise 1,6-heptadiyne (1.91 g, 2.35 mL, 20 mmol) in 10 mL of 1,2-dichloroethane at room temperature. After the mixture was stirred for 12 hours it was treated with iodine (12.19 g, 48 mmol) in 26 mL of THF at -30 °C, warmed to 0 °C, stirred for 2 hr, then hydrolyzed with 10 mL of saturated aqueous K_2CO_3. The heterogeneous mixture was extracted with hexane (4 X 20 mL) and ether (2 X 50 mL), and the combined extracts were dried over anhyd. $MgSO_4$. After concentration *in vacuo* 8.87 g of **32** were isolated and purified by column chromatography on silica gel using ether:hexane (1:4) as the eluant, to give 5.34 g (70%) of pure **32**. ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.89 (H1,H7: bs; 1H), δ 2.20 (H3,H5:t; J = 7.0 Hz; 2H), δ 1.70 (H8,H9:s; 3H), δ 1.55 (H4:m; 1H).

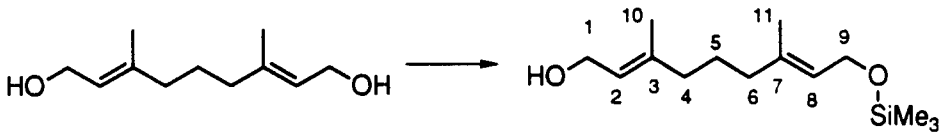


Preparation of (*E*,*E*)-3,7-dimethyl-2,7-nonadien-9-(*tert*-butyldimethylsiloxyl)-1-ol (35): Sodium hydride (0.013 g, 0.54 mmol) was washed with hexane then suspended in dry THF (2 mL). Diol (0.1 g, 0.54 mmol) was added to this mixture at room temperature, and the suspension heated at 55 °C for 18 hr. *tert*-Butyldimethylsilyl chloride was added and stirring was continued at room temperature for 24 hr. The mixture was poured into ether (18 mL), washed with 10 % aqueous K_2CO_3 (5 mL) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography using ether:hexane (1:4) as the eluant, to give 30 mg (18 %) of **35**. ^{1}H NMR ($CDCl_3$, 400 MHz) 5.44 (H2: bt, J = 6.7 Hz; 1H), 5.35(H8: bt, J = 6.6 Hz; 1H), 4.17 (H1, H9: d, J = 6.7 Hz; 4H), 2.10 (H4,H6: t, J = 7.0 Hz; 4H), 1.70 (H10: s; 3H), 1.67 (H11: s; 3H), 1.53 (H5: m; 2H), 0.92 (Si-C-C$\underline{H}_3$: s; 9H), 0.11 (Si-C$\underline{H}_3$: s; 6H) ppm.

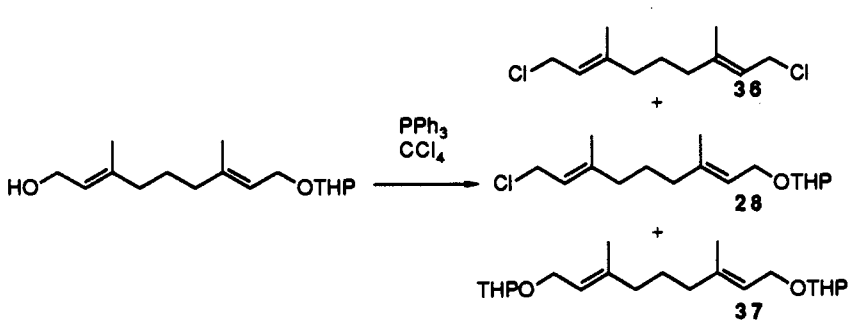


Preparation of (*E*,*E*)-3,7-dimethyl-2,7-nonadien-9-(*tert*-butyldimethylsiloxyl)-1-ol (35): To a magnetically stirred solution of diol (0.23 g, 1.25 mmol) in 20 mL of hexane and 4 mL of dry THF cooled at -35°C under argon, was added dropwise 0.51 mL of a solution 2.45 M of n-butyllithium in hexane (1.25 mmol). The mixture was either warmed to 0°C and stirred for 1

h or stirred for 1 h at -35°C. Then TBDMSiCl (1.88 g, 1.25 mmol) was added diluted in 5 mL of dry THF. After stirring for 1 h the reaction was hydrolyzed with water (5 mL), extracted with ether (3 X 10 mL), washed with brine and dried over anhyd. $MgSO_4$ to give total recovery of the starting material.

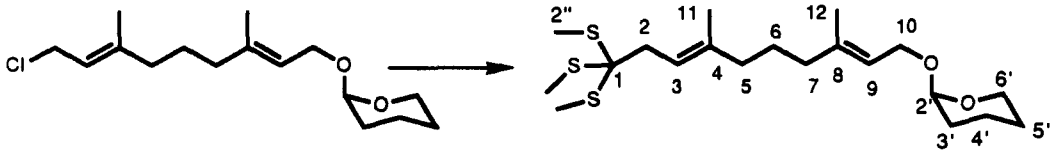


Preparation of (*E*,*E*)-3,7-dimethyl-2,7-nonadien-9-(trimethylsiloxyl)-1-ol (36): Hexamethyldisilazane (1.73 g, 10.78 mmol) and the diol (3.97 g, 21.57 mmol) in THF (224 mL) with TMS (0.22 g, 2.1 mmol) were heated under reflux for 4 hr. The solvent was removed *in vacuo* and the product purified by chromatography on silica gel using ether:hexane (9:1) as the eluant to give 2.23 g (41 %) of monoprotected alcohol. ^1H NMR ($CDCl_3$, 400 MHz) 5.41 (H2: bt, J = 6.8 Hz; 1H), 5.33 (H8: bt, J = 6.6 Hz; 1H), 4.21 (H1, H9: d, J = 6.8 Hz; 4H), 2.12 (H4,H6: t, J = 7.0 Hz; 4H), 1.69 (H10: s; 3H), 1.67 (H11: s; 3H), 1.53 (H5: m; 2H), 0.11 (Si-C<u>H</u>3: s; 6H) ppm.



Reaction of 26 with triphenylphosphine and carbon tetrachloride: To a solution of (*E*,*E*)-3,7-dimethyl-2,7-nonen-9-tetrahydrofuranoxy-1-ol **26** (0.54 g, 2 mmol) in carbon tetrachloride (1.82 mL) was added 0.66 g of

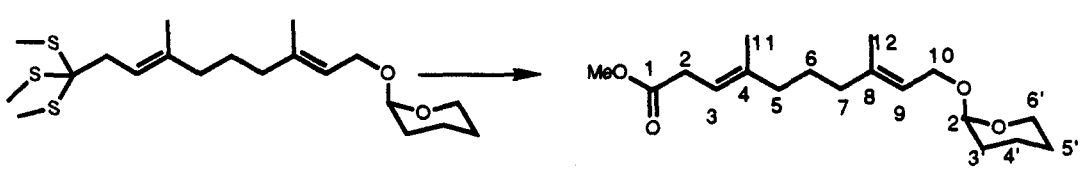
triphenylphophine (2.5 mmol). The reaction was mixture stirred and heated to reflux for 1 h. The mixture was allowed to cool to room temperature; dry pentane was added (2 mL) and the triphenylphosphine oxide which precipitated was filtered and washed with 1 mL of pentane. Evaporation of the solvent gave 0.54 g of an oil. Purification by chromatography on silica gel using ether:hexane (1:9) as the eluant gave 60 mg of **36** (18%), 200 mg of **28** (63%) and 40 mg of **37** (18%). ^{1}H NMR (C_6D_6, 400 MHz) of **36**: δ 5.44 (H2, H8: bt, J = 7.9 Hz; 2H), δ 4.10 (H1, H9: d, J = 7.9 Hz 4H), δ 2.01 (H4,H6: t, J = 7.0 Hz; 4H), δ 1.67 (H10, H11: s; 6H), δ 1.60 (H5: m; 2H) ppm. ^{1}H NMR (C_6D_6, 100 MHz) of **38** was as reported. ^{1}H NMR (C_6D_6, 400 MHz) of **37**: δ 5.34 (H2, H8: ttq, J = 6.5 Hz, 1.0, 1.0 Hz; 2H), δ 4.65 (H2', H2": bt J = 3.4 Hz; 2H), δ 4.43 and 4.19 (H1, H9: dd, J = 6.5, 12.3 Hz; 4H), δ 3.90 and 3.47 (H6', H6": m; 4H), δ 2.00 (H4, H6: t, J = 6.7 Hz; 4H), δ 1.65 (H10, H11: s; 6H), δ 1.56 (H3', H4', H5', H3", H4", H5": m; 12H), δ 1.47 (H5: t. J = 6.7 Hz; 2H) ppm.



Preparation of (*E*,*E*)-trimethyl orthothio-4,8-dimethyl-3,8-decadien-10-tetrahydropyra-2'-yloxy-ate (47): n-Butyllithium (1.7 mmol, 0.68 mL of a solution 2.5 M) was added to a solution of tris(methylthio)methane (0.5 mL, 3.84 mmol) in 7 mL of THF. The mixture was stirred at -70°C for 30 min, then a solution of **27** (0.43 g, 1.5 mmol) in 6 mL of THF was added. The mixture was stirred for 4 hr. while the temperature increased from -70°C to -20°C. The reaction was quenched with 15 mL of saturated ammonium chloride solution at -60°C. After warming to room temperature, the layers were separated and the

aqueous layer was extracted with ether (2 X 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhyd. $MgSO_4$. Removal of the solvent *in vacuo* gave a yellow oil which was purified by chromatography on silica gel using ether:hexane (1:9) as the eluant to give 0.58 g (1.45 mmol, 97%) of pure **47.** IR (film) 2918, 1666, 1434, 1383, 1261, 1199, 1183, 1132, 116, 1023, 906,3, 869, 814 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.80 (H3: bt, J = 6.4 Hz; 1H), δ 5.66 (H9: bt, J = 6.3; 1H), δ 4.77 (H2': t, J = 3.3 Hz; 1H), δ 4.45 and 4.17 (H10: dd, J = 12.0, 6.3 Hz; 2H), δ 3.91 (H6', axial: ddd, J = 11.0; 11.3, 3.0 Hz; 1H), δ 3.48 (H6', eq: dddd, J = 11.3, 4.4, 3.0, 1.0 Hz; 1H), δ 2.73 (H2: bd, J = 6.4 Hz; 2H), δ 2.05 (H5, H7: m; 4H), δ 1.99 (HS2": s, 9H), δ 1.60 (H6: m; 2H), δ 1.86-1.30 (H3', H4', H5': m; 6H), δ 1.63 (H11: bs; 3H), δ 1.57 (H12: bs; 3H), ppm. ^{13}C NMR (C_6D_6, 100.6 MHz) δ 139.32 (C4), δ 137.42 (C8), δ 122.16 (C3), δ 119.65 (C9), δ 97.54 (C2'), 83.5 (C1), δ 67.71 (C10), δ 61.55 (C6'), δ 39.59 (C7)*, δ 39,29 (C5)*, δ37.47 (C2), δ 31.11 (C5')•, δ 26.19 (C3')•, δ 26.02 (C6), δ 19.62 (C4')•, δ16.45 (C12), δ 16.31 (C11), δ 13.05 (C2") ppm. Anal. Calcd. for $C_{20}H_{36}O_3S_3$: C, 59.36%; H, 8.97%. Found: C, 59.20%; H, 9.09%.

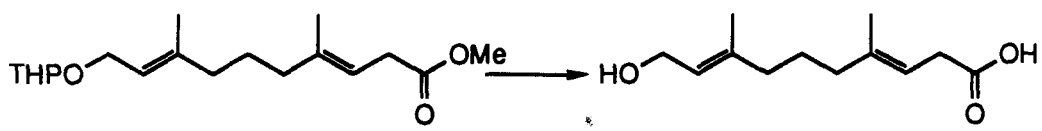
*,•: Assignments are not definitive.



Peparation of (*E,E*)-methyl-4,8-dimethyl-3,8-decadien-10-tetrahydropyra-2'-yloxy-ate (48): A mixture of 200 mg (0.5 mmol) of **48**, 0.54 g (2 mmol) of mercuric chloride and 0.108 g (0.5 mmol) of mercuric oxide

in 13 mL of 12:1 methanol:water was stirred at room temperature for 4 hr. The mixture was filtered and the solid residue was washed with dichloromethane (2 X 6 mL) and saturated ammonium chloride solution (2 X 6 mL) and dried over anhyd. $MgSO_4$. Removal of the solvent *in vacuo* gave 80 mg of **48** (0.27 mmol, 55%). IR (film) 2918, 1666, 1434, 1383, 1261, 1199, 1183, 1132, 116, 1023, 906,3, 869, 814 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.80 (H3: bt, J = 6.4 Hz; 1H), δ 5.66 (H9: bt, J = 6.3; 1H), δ 4.77 (H2': t, J = 3.3 Hz; 1H), δ 4.45 and 4.17 (H10: dd, J = 12.0, 6.3 Hz; 2H), δ 3.91 (H6', axial: ddd, J = 11.0; 11.3, 3.0 Hz; 1H), δ 3.48 (H6', eq: dddd, J = 11.3, 4.4, 3.0, 1.0 Hz; 1H), δ 4.77 (H2: d, J = 6.4 Hz; 2H), δ 2.05 (H5, H7: m; 4H), δ 1.99 (Me: s; 3H), δ 1.60 (H6: m; 2H), δ 1.86-1.42 (H3', H4', H5': m; 6H), δ 1.63 (H12: bs; 3H), δ 1.57 (H11: m; 3H), ppm. ^{13}C NMR (C_6D_6, 100.6 MHz) δ 172.91 (C1), δ 139.35 (C8), δ 138.90 (C4), δ 122.05 (C9), δ 115.50 (C3), δ 97.56 (C2'), δ 63.73 (C10), δ 61.60 (C6'), δ 51.70 (Me), δ 39.01 (C7)*, δ 38.95 (C5)*, δ33.45 (C2), δ 31.10 (C5')•, δ 25.93 (C3')•, δ 25.95 (C6), δ 19.50 (C4')•, δ16.23 (C12), δ 16.31 (C11) ppm.

*,•: Assignments are not definitive.



Preparation of (*E*,*E*)-4,8-dimethyl-3,8-decadien-10-olic acid (15a): (*E*,*E*)-Methyl-4,8-dimethyl-3,8-decadien-10-tetrahydropyra-2'-yloxy-ate **48** (80 mg, 0.26 mmol) was dissolved in 2.7 mL of a solution 10% of KOH/MeOH. The mixture was stirred 2 hr. at room temperature. Acidification of the reaction mixture and extraction with ether (2 X 5 mL) followed by evaporation of the solvent gave an oil that was dissolved in 3 mL of 4:2:1 acetic acid-tetrahydrofuran-water. The resulting solution was heated at 45°C for 4 hr and the mixture was extracted with three-5 mL portions of ether. The organic phase

was washed with water and brine and dried over anhyd. $MgSO_4$. Removal of the solvent *in vacuo* gave 47 mg (0.22 mmol, 83%) of pure hydroxyacid **15a**.

Tosylation of geraniol in the presence of geraniol-TMS: A solution of geraniol (0.07 g, 0.5 mmol), geraniol-TMS (0.11 g, 0.5 mmol), 40 μL of dodecane, pyridine (2.5 g, 2.5 mL, 31 mmol) in 6 mL of 1,2-dichloromethane was stirred for one minute at 0 °C. An aliquot was removed, quenched with water, extracted with dilute acid, the organic phase separated, dried over anhyd. $MgSO_4$ and analyzed by gas chromatography as "time 0". Tosyl chloride (0.25 g, 1.31 mmol) was added at 0°C and then the reaction was stirred 5 h at the same temperature. Aliquots were removed, worked up and analyzed after 2.5 and 5 h. The results were plotted on Figure 2.

Protection of geraniol with ethyl vinyl ether in the presence of geraniol-TMS: A solution of geraniol (0.07 g, 0.5 mmol), geraniol-TMS (0.11 g, 0.5 mmol), 40 μL of dodecane, PPTS (16 mg) in 4 mL of dichloromethane was stirred for one minute. An aliquot was removed, worked up as above and analyzed by GC as "time 0". Ethyl vinyl ether (0.07 mL, 0,7 mmol) was added and the reaction was stirred for 4 h. Aliquots were removed, worked up and analyzed by GC after 2.5 and 5 h. The results were plotted on Figure 3.

Acetylation of geraniol in the presence of geraniol-TMS: A solution of geraniol (0.07 g, 0.5 mmol), geraniol-TMS (0.11 g, 0.5 mmol), 40 μL of dodecane and triethylamine (76 mg, 0.1 mL, 0.75 mmol) was stirred for one minute at 0 °C. An aliquot was removed, worked up as above and analyzed by

gas chromatography as "time 0". Acetic anhydride (76 mg, 0.1 mL, 0,75 mmol) was added at 0 °C and the reaction was then stirred for 3 h at RT. Aliquots were removed, worked up and analyzed by gas chromatography after 1.5 and 3 h. The results were plotted on Figure 4.

Monocarboalumination of 1,6-heptadiyne.

a. Experiment using 1,6-heptadiyne at 0.2 M and $ZrCp_2Cl_2$ as a catalyst: To a solution of $ZrCp_2Cl_2$ (0.12 g, 0.4 mmol) in 8 mL of 1,2-dichloroethane was added trimethylaluminium (27 mg, 0.38 mL, 4 mmol) at 0°C. To the yellow solution thus obtained was added dropwise in 15 min, 1,6-heptadiyne (0.24 mL, 2 mmol) in 2 mL of 1,2-dichloroethane and 80 µL of dodecane at rt. After addition of 1,6-heptadiyne an aliquot was removed *via* syringe, hydrolyzed with water, extracted with ether and dried by passage through a short column of anhyd. $MgSO_4$-silica gel. The prepared aliquot was analyzed by gas chromatography. Aliquots were removed, worked up and analyzed every 15 min. The results are sumarized in Figure 5.

b. Experiment using 1,6-heptadiyne at 0.2 M and $ZrCp_2Cl_2$ in stoichiometric amount with respect to the alkyne: The procedure as described above in "a" was used with the following quantities of reagents: 0.58 g (2 mmol) of $ZrCp_2Cl_2$, 0.38 mL (4 mmol) of $AlMe_3$ in 8 mL of 1,2-dichloroethane. 0.24 mL (2 mmol) 1,6-heptadiyne, 80 µL of dodecane in 2 mL of 1,2-dichloroethane. The results are sumarized in Figure 7.

c. Experiment using 1,6-heptadiyne at 0.2 M and $ZrCp_2Cl_2$ in a stoichiometric amount with respect to the alkyne and $AlMe_3$ in excess: The procedure as described above in "a" was used with the following quantities of reagents: 0.58 g (2 mmol) of $ZrCp_2Cl_2$, 0.48 mL (5 mmol) of $AlMe_3$ in 8 mL of 1,2-dichloroethane. 0.24 mL (2 mmol) 1,6-heptadiyne, 80 µL of dodecane in 2 mL of 1,2-dichloroethane. The results are sumarized in Figure 6.

d. Experiment using 1,6-heptadiyne at 0.1 M and $ZrCp_2Cl_2$ as a catalyst: The procedure as described above in "a" was used with the following quantities of reagents: 0.06 g (0.2 mmol) of $ZrCp_2Cl_2$, 0.19 mL (2 mmol) of $AlMe_3$ in 8 mL of 1,2-dichloroethane. 0.12 mL (1 mmol) 1,6-heptadiyne, 80 µL of dodecane in 2 mL of 1,2-dichloroethane. The results are sumarized in Figure 8.

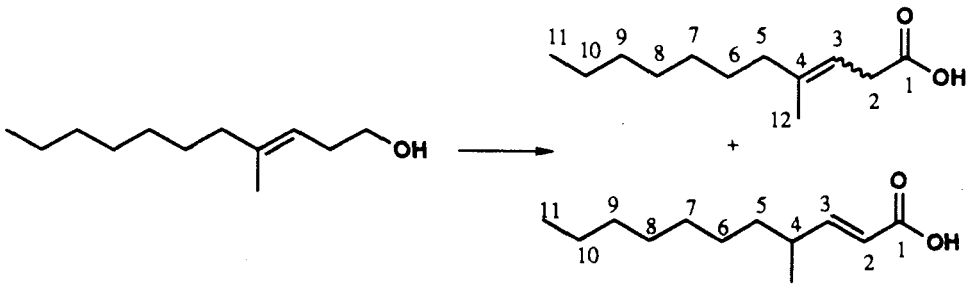
e. Experiment using 1,6-heptadiyne at 0.1 M and $ZrCp_2Cl_2$ in a stoichiometric amount with respect to the alkyne: The procedure as described above in "a" was used with the following quantities of reagents: 0.29 g (1 mmol) of $ZrCp_2Cl_2$, 0.19 mL (2 mmol) of $AlMe_3$ in 8 mL of 1,2-dichloroethane. 0.12 mL (1 mmol) 1,6-heptadiyne, 80 µL of dodecane in 2 mL of 1,2-dichloroethane. The results are sumarized in Figure 9.

f. Experiment using 1,6-heptadiyne at 0.2 M and $ZrCp_2Cl_2$ in a stoichiometric amount with respect to the alkyne and $AlMe_3$ in deficiency: The procedure as described above in "a" was used with the following quantities of reagents: 0.29 g (1 mmol) of $ZrCp_2Cl_2$, 0.10 mL (1 mmol) of $AlMe_3$ in 8 mL of 1,2-dichloroethane. 0.12 mL (1 mmol) 1,6-heptadiyne, 80 µL of dodecane in 2 mL of 1,2-dichloroethane. The results are sumarized in Figure 10.

Oxidation reactions.

Preparation of Jones' reagent: Chromium trioxide (7 g, 70 mmol) in 10 mL of water was cooled in an ice bath, and 11.2 g (6.1 mL, 0.1 mol) of concentrated (18 M) sulphuric acid was added. The salts which precipitate

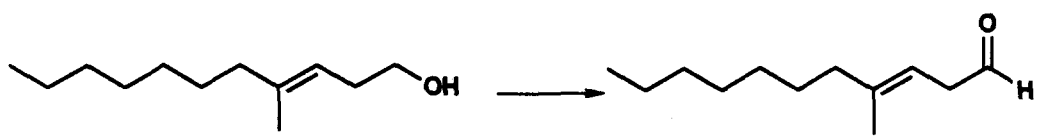
were dissolved by the addition of a minimum quantity of distilled water (CAUTION).



Oxidation of (*E*)-4-methyl-3-undecen-1-ol with Jone's reagent: A solution of 0.19 g (1 mmol) of (*E*)-4-methyl-3-undecen-1-ol in 1 mL of acetone was cooled to 0°C. The chromic acid oxidizing agent was added very slowly until an orange color persisted for 20 min (*ca.* 0.2 mL). The mixture was decanted and the residue rinsed with acetone. Isopropyl alcohol was added to destroy excess oxidizing agent and $NaHCO_3$ was added until the solution was pH neutral. The acetone was removed *in vacuo* and the residue extracted with ether (3 X 3 mL), the solvent was again removed *in vacuo*, the residue was dissolved in 5 mL of water and a solution of NaOH 0.1M was added dropwise until reaching pH 10. The alkaline solution was extracted with ether (3 X 3 mL), the remaining aqueous solution was acidified with a solution of 0.1 M HCl until pH 4. The aqueous solution was extracted with ether (3 X 3 mL), the organic phase was washed with water (2 X 2 mL) and dried over anhyd. $MgSO_4$. An aliquot of the isolated reaction crude was treated with diazomethane then analyzed by GC. Three major products with very similar retention times were observed. Analysis of the ^1H MNR showed the presence of the α-β unsaturated carboxylic acid and a mixture of the E and Z homocarboxylic acids in a ratio of 1.6:1:1.^1H NMR ($CDCl_3$, 100 MHz) of (E)-4-methyl-2-undecenoic acid: δ 9.62 (-OH: bs; 1H), δ 6.82 (H2: d, J = 15.6 Hz; 1H), δ 6.34 (H3: dd, J =

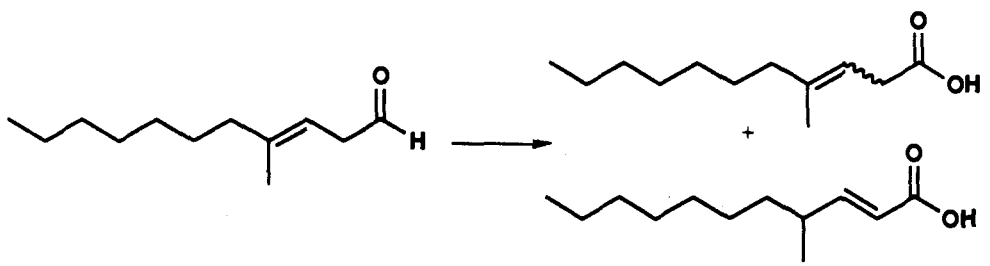
15.6, 6.25 Hz; 1H), δ 2.20(H4: m; 1H), δ 1.5-1.1 (m H5, H6, H7, H8, H9, H10, H12: m; 15H); δ 0.87 (H11: t, *J* = 6.25 Hz; 3H) ppm. ^{1}H NMR ($CDCl_3$, 100 MHz) of a mixture of E and Z-4-methyl-3-undecenoic acid: δ 9.56 (-OH: bs; 2H), δ 5.31 (H3: bt, *J* = 6.25 Hz; 1H), δ 5.10 (H3: bt, *J* = 6.25 Hz; 1H), δ 3.10 (H2: d, *J* = 6.25 Hz; 2H), δ 2.90 (H2: d, *J* = 6.25 Hz; 2H), δ 1.5-1.1 (m H5, H6, H7, H8, H9, H10, H12: m; 30H); δ 0.87 (H11: t, *J* = 6.25 Hz; 6H) ppm.

Oxidation of (*E*)-4-methyl-3-undecen-1-ol with PDC: A solution of 0.188 g (1 mmol) of (*E*)-4-methyl-3-undecen-1-ol in 2.6 mL of DMF was mixed with 1.2 g of PDC (3 mmol) and stirred at rt for 7 h. After this time 10 mL of water were added and the reaction mixture was extracted with ether (3 X 10 mL). The work-up which followed was identical to that employed in the Jone's oxidation. GC analysis of the crude product which had been pretreated with diazomethane revealed two principal products. ^{1}H NMR ($CDCl_3$, 100 MHz) analysis revealed in the vinyl region a broad triplet in 5.20 ppm (*J* = 6.6 Hz) attributed to the homoallylic product, it also confirmed the presence of the α-β unsaturated carboxylic acid [δ 6.75 (d, *J* =14.1 Hz), δ 6.32 (dd, *J* = 14.1, 6.25 Hz)]. The products were present in a ratio of 2:1.



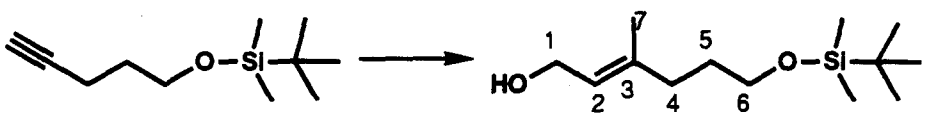
Oxidation of (*E*)-4-methyl-3-undecen-1-ol with chromic oxide: Chromic oxide (3.3 g, 15 mmol) was added to a mixture of pyridine (5.0 g, 35 mmol) and 85 mL of dichloromethane. After stirring 15 min at rt, 0.94 g (5 mmol) of (*E*)-4-methyl-3-undecen-1-ol was added in one portion. After stirring another 15 min. the solution was decanted and the residue washed with 20 mL of ether.

The combined ethereal extracts were applied to a short column of silica for dry chromatography. The eluate was washed with ice-cold 2 M HCl (25 mL), saturated $NaHCO_3$ (2 X 25 mL) and brine (25 mL), dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to give 0.47 g of (*E*)-4-methyl-3-undecenal (50%) yield. IR (film) 2926, 2855, 2718, 1726, 1693, 1466, 1379, 1117 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 9.64 (H1: t *J* =2.4 Hz; 2H), δ 5.31 (H3: bt, *J* = 7.1 Hz; 1H), δ 3.16 (H2: dt, *J* = 7.1, 2.4 Hz; 2H), δ 2.00 (H5: bt, *J* = 6.7 Hz; 2H), δ 1.67 (H12: s; 3H), δ 1.5-1.3 (H6, H7, H8, H9, H10: m; 10H); δ 0.89 (H11: t, *J* = 6.8 Hz; 6H) ppm.



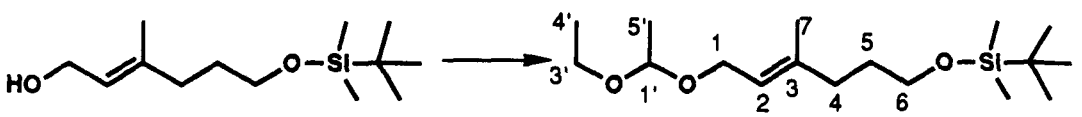
Oxidation of (*E*)-4-methyl-3-undecenal with AgO: A mixture of 94 mg (0.5 mmol) of (*E*)-4-methyl-3-undecenal, 2 mmol of AgO (0.48 g) and 5 mL of THF:water (9:1), was stirred at rt for 48 hr. The suspension was filtered, diluted with water, acidified with 2 M HCl and extracted with ether. The ethereal phase was washed successively with a saturated solution of $NaHCO_3$ and NaCl, then dried over anhyd. $MgSO_4$. The ^1H NMR spectrum of the isolated crude showed two broad bands at 6.80 and 6.30 ppm attributed to the α-β unsaturated carboxylic acid. Also present were two broad triplets at 5.5 and 5.2 ppm attributed to the E and Z carboxylic acids, respectively. The products were in a ratio of 1:1:1.

Oxidation of (*E*)-4-methyl-3-undecenal with Ag_2O: To a suspension of 0.17 g of Ag_2O (1 mmol) in 2 mL of water cooled with an ice bath, was added 0.2 g (4.8 mmol) of sodium hydroxide pellets. After stirring for 15 min, 0.188 g (1 mmol) of (*E*)-4-methyl-3-undecenal was added and stirring was continued for an additional 10 min. then the suspension was filtered and the residue washed with water. The aqueous solution was acidified and extracted with ether, the organic phase was washed with a saturated solution of $NaHCO_3$ and NaCl then dried over anhyd. $MgSO_4$. Analysis of the ^1H NMR spectrum showed the presence of the α,β–unsaturated carboxylic acid and a mixture of the E and Z homocarboxylic acids in a ratio of 2:0.5:0.5. The ^1H NMR of the isolated crude was very similar to the one obtained by Jones' oxidation.



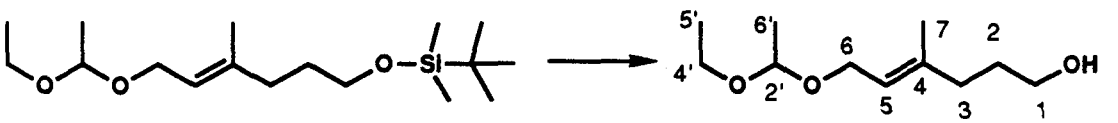
Preparation of (*E*)-3-methyl-2-hexen-6-(*tert* -butyldimethylsiloxyl)-1-ol (54): Alkyne **53** was prepared by treatment of an ice-cold solution of 4-pentyn-1-ol (2.3 g, 27 mmol) and imidazole (4.6 g, 67 mmol) in 8 mL of dry DMF with 4.9 g (32.5 mmol) of *tert*-butyldimethylchlorosilane. The ice bath was removed after 30 min and the reaction mixture stirred for 4 hr at 23°C. The reaction mixture was then poured into water (15 mL), extracted with pentane (4 X 10 mL) and washed with brine (3 X 5 mL). The isolated product was distilled (Vigreaux 10 mm) to give **53**; 5.2 g (98%); bp 60°C (3 mm Hg). To a solution of $ZrCp_2Cl_2$ (1.75 g, 6 mmol) in 50 mL of 1,2-dichloroethane was added trimethylaluminum (5.7 g, 7.6 mL, 79 mmol) at 0°C. The yellow solution thus obtained was stirred 15 min at rt. The solution was added dropwise **53** (5.2 g, 26 mmol) in 13 mL of 1,2-dichloroethane at 0°C. The mixture was stirred for 12

h at rt and volatile compounds were removed *in vacuo*. The organic compounds were extracted with hexane and separated from the solid by filtration under an inert atmosphere. To the hexane soluble intermediates was added at -78°C, n-butyllithium in hexane (10.4 mL, 2.5 M, 26 mmol). THF was added to dissolve the precipitate and paraformaldehyde (2.34 g, 78 mmol) was then added. The reaction mixture was stirred overnight, quenched with ice-cold water and extracted with ether. The extract was dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel using ether:hexane (1:5) to give 5.27 g (21.6 mmol) of **54** in 80% over two steps. IR (film) 3363, 2930, 2857, 1669, 1472, 1387, 1255, 1101, 1006, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.42 (H2: ttq, *J* = 7.0, 1.5, 1.5 Hz; 1H), δ 4.14 (H1: d, *J* = 7.0 Hz; 2H), δ 3.59 (H6: t, *J* = 6.4 Hz; 2H), δ 2.06 (H4: td, *J* = 7.2,1.5 Hz; 2H), δ 1.67 (H7: bs; 3H), δ 1.64 (H5: tt, *J* = 6.4, 7.2 Hz, 2H), δ 0.87 (Si-C-C$\underline{H}_3$: s, 9H), δ 0.03 (Si-C$\underline{H}_3$: s; 6H).ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 139.63 (C3), δ 123.42 (C2), δ 62.74 (C1), δ 59.41 (C6), δ 35.76 (C4), δ 30.96 (C5), δ 25.85 (Si-C-$\underline{C}H_3$), δ18.32 (Si-$\underline{C}$-CH_3), δ16.24 (C7),.δ -5.29 (Si-$\underline{C}H_3$) ppm. Anal. Calc. for $C_{13}H_{28}O_2Si$: C, 63.87%; H, 11.54%. Found: C, 63,82%; H, 11.42%.



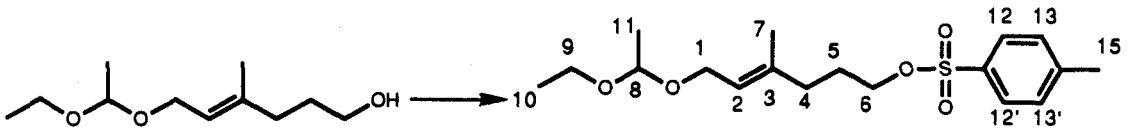
Preparation of (*E*)-3-methyl-6-(*tert*-butyldimethylsiloxyl)-2-hexenyl-1'-ethoxy ethyl ether (55): A solution of (*E*)-3-methyl-2-hexen-6-(*tert*-butyldimethylsiloxyl)-1-ol, **54** (4.0 g, 16.4 mmol) and ethyl vinyl ether (1.74 g, 24.3 mmol) in dry methylene chloride containing PPTS (0.2 g, 1.6 mmol) was

stirred for 8 hr at -22°C. Concentration *in vacuo* followed by dilution with ether gave a suspension which was filtrated through Celite. Concentration *in vacuo* followed by Kugelrohr distillation gave 5.13 g of **55** (99%). IR (Film) 2930, 2858, 1670, 1472, 1440, 1386, 1360, 1255, 1101, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.33 (H2: ttq, *J* = 6.9, 1.1, 1.1 Hz; 1H), δ 4.72 (H2': q, *J* = 5.4 Hz; 1H), δ 4.08 and 3.98 (H1: dd, *J* = 11.64, 6.9 Hz; 2H), δ 3.62 and 3.47 (H4': qd, *J* = 7.1, 9.Hz, 2H), δ 3.57 (H6: t, 6.5 Hz; 2H), δ 2.04 (H4: bt, *J* = 7.3 Hz, 2H), δ 1.65 (H7: bs; 3H), δ 1.40 (H5: m; 2H); δ 1.29 (H6': d, *J* = 5.4 Hz, 3H), δ 1.19 (H5': t, *J* = 7.1 Hz; 3H), δ 0.86 (Si-C-C$\underline{H}_3$: s, 9H), δ 0.01 (Si-C$\underline{H}_3$: s; 6H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 139.63 (C3), δ 120.90 (C2), δ 98.86 (C1'), δ 62.75 (C6), δ 61.72 (C1), δ 60.29 (C3'), δ 35.77 (C4), δ 30.91 (C5), δ 25.91 (Si-C-$\underline{C}H_3$), δ 19.87 (C5'), δ 18.27 (Si-$\underline{C}$-CH_3), δ 16.32 (C7),.δ 15.30 (C4'), δ -5.32 (Si-$\underline{C}H_3$) ppm. Anal. Calc. for $C_{17}H_{36}O_3Si$: C, 64.50%; H, 11.46%. Found: C, 64.59; H, 11.36%.



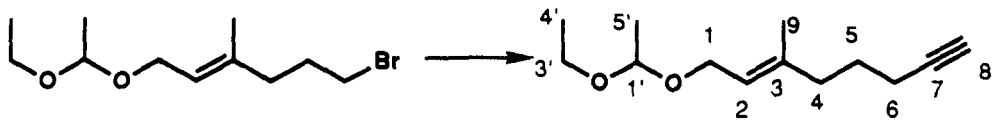
Preparation of (*E*)-4-methyl-6-(1',3'-dioxa-2'methyl-pentyl)-4-hexenol (56): To a solution of **55** (5.13 g, 16.23 mmol) in THF (22 mL) was added 33 mL of *tetra*-n-butylammonium fluoride (33 mmol, 1 M solution in THF). The reaction mixture was stirred at 0°C for 5 min and at 25°C for 1 hr. Then, it was diluted with 100 mL of water, extracted with ether (3 X 50 mL) and the organic extract washed with brine (2 X 50 mL). Kugelrohr distillation gave 2.95 g of **56**. IR (film) 3420, 2937, 1667, 1868, 1445, 1381, 1339, 1128, 945 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (H5: ttq, *J* = 6.9, 1.1, 1.1 Hz; 1H), δ 4.70 (H2': q, *J* = 5.4 Hz; 1H), δ 4.10 and 3.97 (H6: dd, *J* = 11.6, 6.6 Hz; 2H), δ 3.60 and

3.45 (H4': qd, J = 7.0, 9.4Hz; 2H), δ 3.60 (H1: t, 6.5 Hz; 2H), δ 2.10 (H3: bt, J = 7.0 Hz; 2H), δ 1.67 (H7: bs; 3H), δ 1.40 (H2: m; 2H), δ 1.30 (H6': d, J = 5.4 Hz; 3H), δ 1.15 (H5': t, J = 7.0 Hz; 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 139.45 (C4), δ 121.00 (C5), δ 98.83 (C2'), δ 63.75 (C6), δ 61.72 (C1), δ 60.31 (C4'), δ 35.65 (C3), δ 30.92 (C2), δ 19.80 (C6'), δ 16.45 (C7), δ 15.30 (C5') ppm. Anal. Calc. for $C_{11}H_{22}O_3$: C, 65.31%; H, 10.96%. Found: C, 65.32%; H, 11.15%.

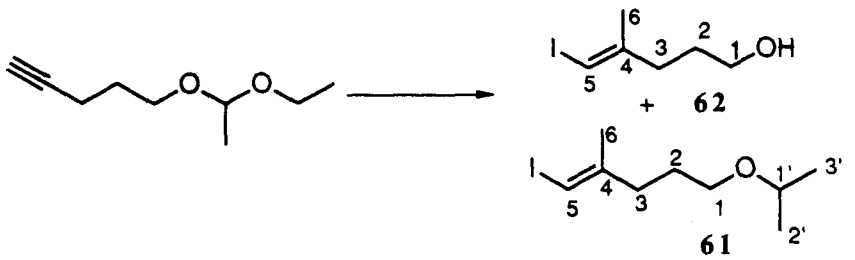


Preparation of (*E*)-3-methyl-6-(*p*-toluensulfonyl)-2-hexenyl-1'-ethoxy ethyl ether: To a stirred solution of **44** (2.9 g, 14.35 mmol) in pyridine (4.5 mL) and methylene dichloride (75 mL) at 0°C was added *p*-TosCl (3.0 g, 15.7 mmol). The reaction was stirred for 10 hr at 0°C and poured into ice-water (100 mL) and extracted with ether (3 X 50 mL). The extracts were combined and washed with an ice-cold 2 M HCl followed by saturated $NaHCO_3$, dried over anhyd. $MgSO_4$. Concentration *in vacuo* gave a yellowish oil (5.1 g) containing the tosylate (80% by GC). The crude product was taken to the next step. IR (Film) 2930, 2858, 1670, 1472, 1440, 1386, 1360, 1255, 1101, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 7.79 (H Ar-ortho: d, J = 7.9 Hz; 2H), δ 7.34 (H Ar-meta: d, J = 7.9 Hz; 2H), δ 5.22 (H2: t, J = 6.8 Hz; 1H), δ 4.75 (H1': q, J = 5.6 Hz; 1H), δ 4.10 (H6: t, J = 7.0 Hz; 2H), δ 3.55 (H3', H1: m; 4H), δ 2.54 (Ar-para-methyl: s; 3H), δ 2.10 (H4: bt, J = 7.0 Hz; 2H), δ 1.65 (H7: s; 3H), δ 1.40 (H5: m; 2H), δ 1.30 (H5': d, J = 5.6 Hz; 3H), δ 1.20 (H4': t, J = 7.0 Hz; 3H) ppm.

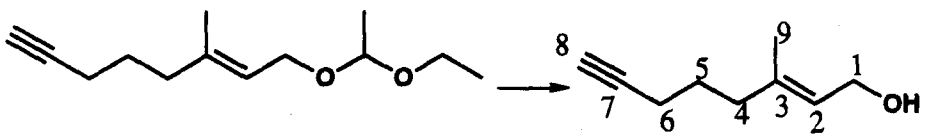
Preparation of(*E*)-6-bromo-3-methyl-2-hexenyl-1'-ethoxy ethyl ether (57): (*E*)-3-Methyl-6- (*p*-toluensulfonyl)-2-hexenyl-1'-ethoxy ethyl ether (4.1 g, 11.5 mmol) and lithium bromide (3.0 g, 34.5 mmol) were refluxed in dry acetone (115 mL) with stirring and protection from moisture. The acetone was removed *in vacuo* and the oily residue was dissolved in ether. The ether was washed with water and brine then dried over anhyd. $MgSO_4$. Purification of the crude product *via* silica gel chromatography using ether:hexane (1:1) as the eluant gave pure **57** (2.81 g) in 75% yield from **56**. IR (film) 2976, 2933, 1669, 1442, 1379, 1338, 1270, 1245, 1129 cm^{-1}. 1H NMR $CDCl_3$, 400 MHz) δ 5.38 (H2: bt, *J* = 6.9 Hz; 1H), δ 4.70 (H1': q; *J* = 5.3 Hz; 1H), δ 4.10 and 4.01 (H1: dd, *J* = 11.7, 6.9 Hz; 2H), δ 3.60 and 3.53 (H3': qd, *J* = 7.1, 8.7 Hz, 2H), δ 3.38 (H6: t, 7.0 Hz; 2H), δ 2.18 (H4: bt, *J* = 7.0 Hz, 2H), δ 1.95 (H5: tt, 7.0, 7.0 Hz, 2H), δ 1.67 (H7: s; 3H), δ 1.32 (H5': d, *J* = 5.3 Hz, 3H), δ 1.21 (H4': t, *J* = 7.1 Hz; 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 137.79 (C3), δ 122.00 (C2), δ 98.98 (C1'), δ 61.60 (C1), δ 60.40 (C3'), δ 37.77 (C4), δ 33.10 (C6), δ 30.70 (C5), δ 19.87 (C5'), δ 16.28 (C7), δ 15.32 (C4') ppm. Anal. Calc. for $C_{11}H_{21}O_2Br$: C, 49.82%; H, 7.98%. Found: C, 49.60; H, 7.80%.



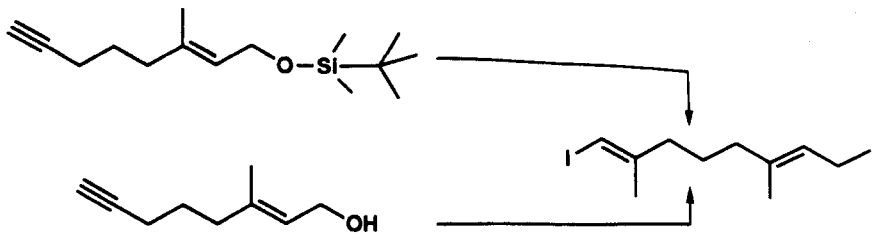
Preparation of (*E*)-3-methyl-2-ene-7-octynyl-1'-ethoxy ethyl ether (58): Under argon atmosphere with magnetic stirring, acetylene (0.6 g ,21.5 mmol) was introduced into dry THF (5.3 mL) cooled to -78°C. n-Butyllithium (4.8 mL, 2.5 M, 12 mmol) was added dropwise in such a manner that the temperature did not exceed -50°C. Then, the temperature was allowed to reach 0°C and (E)-6-bromo-3-methyl-2-hexenyl-1'-ethoxy ethyl ether, **57** (2.81 g, 10.8 mmol) dissolved in 12 mL of dry HMPA was added. The mixture was stirred for 30 min at rt. Ice-cold water was added and extracted with ether (3 X 15 mL). The organic layer was washed with water and dried over anhyd. potassium carbonate. The residue was chromatographed on silica gel using ether:hexane (2:3) as the eluant to give 2.15 g of **58** (96%). IR (Film) 3299, 2937, 2117, 1670, 1440, 1380, 1338, 1129, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.36 (H2: ttq, J = 6.8, 1.1, 1.1 Hz; 1H), δ 4.70 (H1': q, J = 5.3 Hz), δ 4.10 and 4.01 (H1: dd, J = 7.0, 11.3 Hz; 2H), δ 3.63 and 3.49 (H3': qd, J = 7.1, 9.0 Hz, 2H), δ 2.16 (H6: td, J = 7.3, 2.6 Hz; 2H), δ 2.04 (H4: bt, J = 7.3 Hz, 2H), δ 1.95 (H8: t, J = 2.6, 2H), δ 1.67 (H9: bs, 3H), δ 1.60 (H5: m; 2H), δ 1.32 (H5': d, J = 5.3 Hz, 3H), δ 1.21 (H4': t, J = 7.1 Hz; 3H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 138.75 (C3), δ 121.67 (C2), δ 98.95 (C1'), δ 84.31 (C7), δ 68.40 (C8), δ 61.70 (C1), δ 60.39 (C3'), δ 38.43 (C4), δ26.52 (C5), δ 19.91 (C5'), δ 17.99 (C6), δ 16.26 (C9), δ 15.34 (C4') ppm. Anal. Calc. for $C_{13}H_{22}O_2$: C, 74.24%; H, 10.54%. Found: C, 73.95; H, 10.61%.



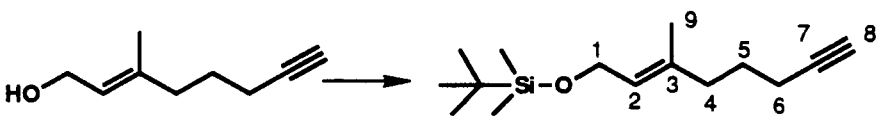
Preparation of (*E*)-5-iodo-4-methyl-4-pentenyl-isopropyl ether (61) and (*E*)-5-iodo-4-methyl-4-penten-1-ol (62): The procedure employed was identical to that used in the preparation of **67**. The reaction was conducted on a scale of 2 mmol in alkyne. The crude product was purified by chromatography on silica gel using ether:hexane (15:85) as the eluant to give **61** and **62** in a ratio of 2:1. ^{1}H NMR ($CDCl_3$, 100 MHz) of **61**: 5.91 (H5: bs; 1H); 3.65 (H1': q, J = 6.5 Hz; 1H), 3.55 (H1: t, J = 6.7 Hz; 2H), 2.23 (H3: t, J = 6.9 Hz; 2H), 1.70 (H6: s; 3H), 1.50 (H2: m; 2H), 1.18 (H2',H3': d, J = 6.7 Hz; 6H) ppm. ^{1}H NMR ($CDCl_3$, 100 MHz) of **62**: 6.03 (H5: bs; 1H); 4.32 (H1: t, J = 6.3 Hz; 2H), 2.29 (H3: t, J = 6.7 Hz; 2H), 2.20 (OH: s; 1H), 1.70 (H6: s; 3H), 1.54 (H2: m; 2H) ppm.



Preparation of (*E*)-3-methyl-2-ene-7-octyn-1-ol (63): A solution of the ether (0.5 g, 2.4 mmol) and PPTS (63 mg, 0.2 mmol) in ethanol (20 mL) was stirred at rt for 12 hr. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ether to give a suspension which was filtered. Removal of the solvent *in vacuo* afforded pure **51** (0.3 g, 100%).^{1}H NMR ($CDCl_3$, 100 MHz) 5.54 (H2: t, J = 6.1 Hz; 1H), 4.13 (H1: d, J = 6.1 Hz; 2H), 2.17 (H6, H4, -OH: m; 5H), 1.90 (H8: t, J = 2.5 Hz; 1H), 1.67 (H9: s; 3H), 1.50 (H5: m; 2H) ppm.



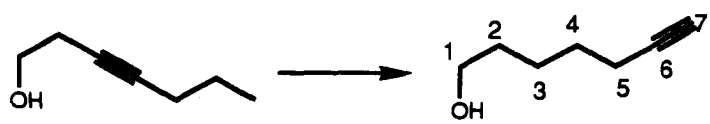
Preparation of (*E*,*E*)-1-iodo-2,6-dimethyl-1,6-nonadiene (64): The procedure employed was the same as the one used in the preparation of **56**. Purification by column chromatography on silica gel using ether:hexane (1:1) as the eluant afforded, quantitatively, the iodide, **52**. ^{1}H NMR ($CDCl_3$, 100 MHz) 5.89 (H1: bs,1H), 2.25-2.10 (H3,H5, H8: m; 6H), 1.70 (H10: bs; 3H), 1.67 (H11: bs; 3H), 1.55 (H4: m, 1H), 1.01 (H9: t: *J*=6.7; 3H) ppm.



Preparation of (*E*)-3-methyl-2-ene-1-(*tert*-butyldimethylsiloxyl)-7-octynyl ether (65): An ice-cold solution of **63** (0.138 g, 1 mmol) and imidazole (0.17 g, 2.5 mmol) in 0.3 mL of dry DMF was added 0.2 g (1.2 mmol) of *tert*-butyldimethylchlorosilane. The ice bath was removed after 30 min and the reaction mixture stirred for 4 hr at 23°C. The reaction mixture was then poured into water (0.6 mL), extracted with pentane (4 X 0.3 mL) and washed with brine (3 X 0.2 mL). The product was passed through a short column of silica gel using ether:hexane (7:93) as the eluant to give 0.22 g of **65** (60%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.45 (H2: bt; *J* = 7.1 Hz; 1H), δ 4.14 (H1: d; *J* = 7.0Hz; 2H), δ 2.13 (H6: td; *J* = 6.7, 2.5 Hz; 2H), δ 2.06 (H4: t; *J* = 6.9 Hz; 2H), δ

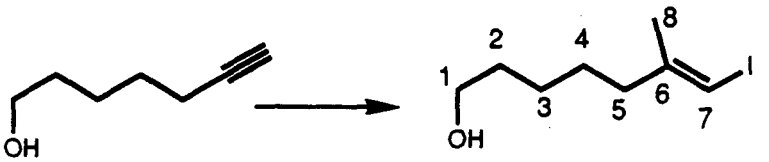
1.97 (H8: t; J = 2.5 Hz, 2H), δ 1.70 (H5: m; 2H), δ 1.67 (H9: s, 3H), δ 0.93 (Si-C-C$\underline{H}_3$: s, 9H), δ 0.03 (Si-C$\underline{H}_3$: s; 6H).ppm.

Carbocupration of (*E*)-3-methyl-2-ene-7-octynyl-1'-ethoxy ethyl ether (46): A solution of dimethyl sulphide complex of cuprous bromide (0.82 g, 4 mmol), ether (5 mL) and dimethyl sulphide (4 mL) under argon, was cooled to -45°C at which temperature a white solid formed. A 3.0 M solution of methyl magnesium bromide (1.2 mL, 4 mmol) was added dropwise over a period of 2 min. After the resulting suspension of a yellow solid was stirred at -45°C for 2 h, (*E*)-3-methyl-2-ene-7-octynyl-1'-ethoxy ethyl ether, **46** (0.720 g, 3.5 mmol) was added over 1 min and the mixture was stirred at -18°C for 120 h. The dark green reaction mixture was quenched with 2 mL of saturated ammonium chloride (buffered to pH 8 with ammonia). The maximum consumption of the starting material observed was 10 % (by GC analysis)



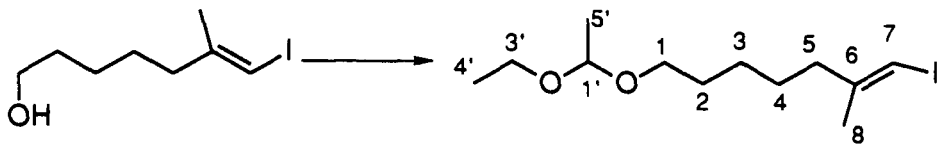
Preparation of 6-heptyn-1-ol (66): Under a slight pressure of argon, lithium (0.42 g, 60 mmol, washed free of mineral oil with hexane) was added to 1,3-diaminopropane (30 mL). The mixture was heated and stirred at 70°C for approximately 2 h until the blue color had discharged and a milky white suspension of the lithium salt formed. The mixture was cooled to rt and potassium *tert*-butoxide (3.9 g, 36 mmol) was added at once, affording a pale

yellow solution. After stirring for 30 min addition of 3-heptyn-1-ol (0.9 g, 8 mmol) in one portion resulted in an orange reaction with a suspended white solid. Stirring was continued for further 2 h and the mixture poured into water. The product was extracted with chloroform (4 X 20 mL). The combined organic phases were washed successively with water, 2 M HCl, $NaHCO_3$ saturated and NaCl solutions, then dried over anhyd. $MgSO_4$. Removal of the solvent *in vacuo* gave an oil (0.75 g, 80%) of sufficiently high purity (96%) to use in the next step. ^1H NMR ($CDCl_3$, 100 MHz) δ 3.60 (H1: t, J = 6.5 Hz; 2H), δ 2.15 (H5: td, J = 7.0, 2.6 Hz; 2H), δ 1.95 (H7: t, J = 2.6 Hz; 1H), δ 1.55-1.45 (H2 ,H3, H4, OH: m; 7H) ppm.

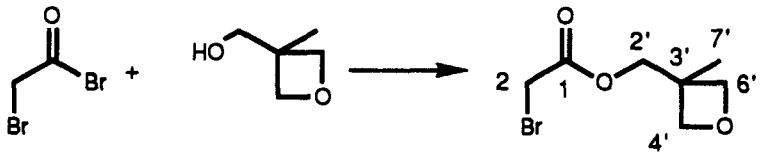


Preparation of (*E*)-7-iodo-6-methyl-6-hepten-1-ol (67): To a solution of $ZrCp_2Cl_2$ (0.47 g, 1.6 mmol) in 15 mL of 1,2-dichloroethane was added trimethylaluminium (1.5 g, 21 mmol) at 0°C. The yellow solution thus obtained was stirred 15 min at rt then to it was added dropwise **66** (0.7 g, 7 mmol) in 3.5 mL of 1,2-dichloroethane at 0°C. The mixture was stirred for 12 hours at rt then treated with iodine (2.18 g, 8.4 mmol) in 7 mL of THF at -30°C, warmed to 0°C and stirred for 2 h and hydrolyzed with saturated aqueous K_2CO_3. The heterogenous mixture was extracted with hexane (4 X 5 mL), ether (2 X 10 mL) and the extract was dried over anhyd. $MgSO_4$. Concentration *in vacuo* gave 1.35 g of product (purity of 88% by GC) which was taken to the next step without further purification. ^1H NMR ($CDCl_3$, 100 MHz) δ 5.89 (H7: bs; 1H), δ 3.59 (H1: t,

J = 6.5 Hz; 2H), δ 2.26 (H5: t, J = 7.0 Hz; 2H), δ 1.80 (H8: s; 3H), δ 1.55-1.45 (H2, H3, H4, OH: m; 7H) ppm.

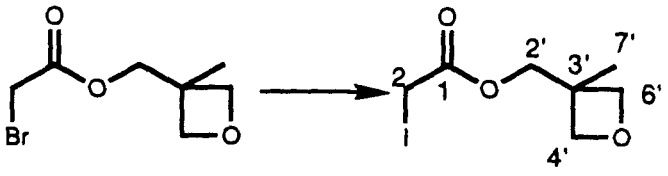


Preparation of (*E*)-7-iodo-6-methyl-6-hexenyl-1'-ethoxy ethyl ether (68): The procedure was identical to that used for the preparation of **55**. Kugelrohr distillation gave 1. 57 g of **68**, 61 % yield from 3-heptyn-1-ol. IR (Film) 2981, 2933, 1667, 1455, 1379, 1339, 1132, 1150, cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 5.80 (H7: bs, 1H), δ 4.75 (H1': q, J = 5.2 Hz; 1H), δ 3.80-3.20 (H1, H3': m, 4H), δ 2.15 (H5: t, J = 6.7 Hz), δ 1.65 (H8: s; 3H), δ 1.55-1.45 (H2 ,H3, H4: m; 6H); δ 1.35 (H5': d, J = 5.2 Hz; 3H), δ 1.27 (H4': t, J = 7.0 Hz; 3H) ppm.

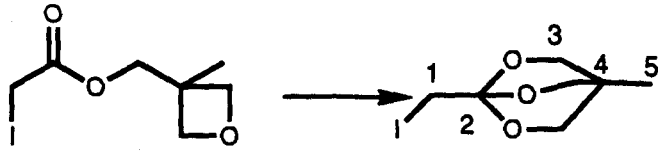


Preparation of 2-bromo-3'-methyl-3'-hydroxymethyloxetane acetate (69): To a solution of commercially available 3-methyl-3-hydroxymethyl-oxoethane (2.0 g, 20 mmol) and 1.62 mL (20.0 mmol) of pyridine in 12 mL of dichloromethane at 0°C was added 4.02 g (20 mmol) of bromoacetyl bromide and the mixture was stirred for 1.5 h at 0°C. Extractive work-up (dichloromethane) followed by Kugelrohor distillation (9 °C/0.04 mm Hg), gave **69** in 90 % yield. ^1H NMR ($CDCl_3$, 100 MHz) δ 4.46 (H4', H6': dd, 6.0 Hz; 4H), δ

4.27 (H2': s; 2H), δ 3.88 (H2: s; 2H), δ 1.36 (H7': s; 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 167.0 (C1), δ 79.0 (C4',C6'), δ 69.9 (C2'), δ 38.9 (C3'), δ 25.0 (C2), δ 20.67 (C7') ppm.

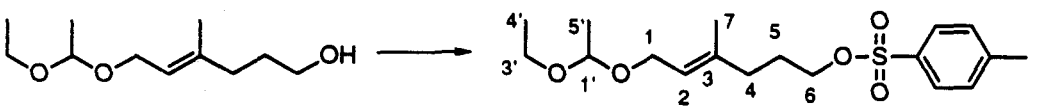


Preparation of 2-iodo-3'-methyl-3'-hydroxymethyloxetane acetate (70): A mixture of **69** (1 g, 4.5 mmol) and NaI (1 g, 6.25 mmol) in acetone (10 mL) was stirred for 12 h at rt. Removal of the solvent *in vacuo* left a residue which was dissolved in ether (30 mL), washed with water (2 X 10 mL) and dried over anhyd. $MgSO_4$. Kugelrohor distillation (100°C/0.04 mm Hg) quantitatively gave **70** (1.15 g). ^1H NMR ($CDCl_3$, 100 MHz) δ 4.50 (H4', H6': dd, 6.0 Hz; 4H), δ 4.27 (H3': s; 2H), δ 3.85 (H2: s; 2H), δ 1.15 (H7': s; 3H) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 168.0 (C1), δ 78.9 (C5', C6'), δ 69.7 (C2'), δ 38.9 (C3'), δ 20.0 (C7'), δ -6.2 (C2) ppm.



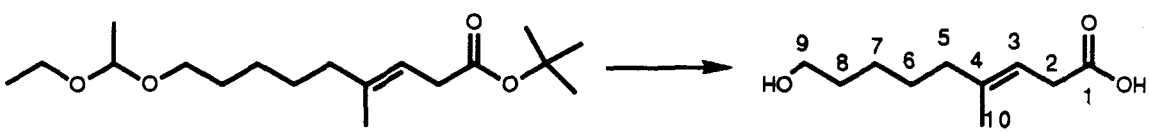
Preparation of 1-iodo-methylene-4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (71): To a solution of 1.15 g of **70** (4.25 mmol) in 5 mL of dry dichloromethane at -15°C was added with stirring 1.5 g (1.2 mmol) of distilled boron trifluoride-etherate. After stirring at -15°C for 8 h the starting material had

been consumed (GC analysis) and the reaction mixture was quenched by the addition of 4.3 mmol of triethylamine. The resulting mixture was diluted with ether and filtered to remove the amine-BF_3 complex. The filtrate was concentrated *in vacuo* and filtered through silica gel column using CH_2Cl_2 as the eluant to give 0.8 g of pure **71** (70%). ^1H NMR ($CDCl_3$, 100 MHz) δ 3.95 (H3: s; 6H), δ 3.35 (H1: s; 2H), δ 0.82 (H5: s; 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 107.9 (C2), δ 73.4 (C3), δ 30.8 (C4), δ 14.2 (C5), δ 4.0 (C1) ppm.



Preparation of *tert*-butyl-(*E*)-4-methyl-9-oxa-(1'ethoxy ethyl)-3-nonenate (73): A flask equipped with septum inlet and magnetic stirring was maintained under positive argon pressure and charged with 0.218 g (1 mmol) of anhydrous nickel (II) bromide and 1 mL of THF. The flask was immersed in a dry ice/acetone bath and 0.2 mmol (0.10 mL) of a 2.0 M solution of n-butyllithium in hexane was added *via* syringe. The resultant black suspension was stirred for 5 min, then 1 mmol (0.328 g) of (E)-7-Iodo-6-methyl-6-hexenyl-1'-ethoxy ethyl ether, **68**, was added *via* syringe, followed by 3 mmol of lithium *tert*-butyl acetate (Note 1) in THF. The solution was allowed to reach rt and stirred for 12 h. The cooling bath was the reapplied and the reaction mixture was quenched by addition of 0.6 mL of 2 M HCl. Pentane was added and the mixture was stirred at rt until the organic layer was nearly colorless. The organic layer was then separated, washed with $NaHCO_3$ and NaCl solutions and dried over anhyd. K_2CO_3. Evaporation of the solvent gave a green oil, purified by chromatography on silica gel using ether:hexane (1:4) as the eluant to give 0.31 g of pure **73** (80%).

Note 1: The ester enolate was prepared by the addition of 1.2 mL of a solution of n-butyllithium 1.45 M in hexane (3 mmol) to 0.42 mL (3 mmol) of diisopropylamide in 8.1 mL of THF at -35°C. The mixture was stirred for 10 min then cooled to -78°C and 0.4 mL (3 mmol) of *tert*-butyl acetate was added. The mixture was stirred 30 min at -78°C then transferred to the catalyst suspension *via* canula. IR (Film) 2979, 2933, 1716, 1652, 1568, 1529, 1456, 1368, 1316, 1254, 1150, 953, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 5.38 (H3: t, *J* = 6.9 Hz; 1H), δ 4.75 (H1': q, *J* = 4.8 Hz; 1H), δ 3.80-3.20 (H9, H3': m; 4H), δ 2.90 (H2: d, *J* = 7.0 Hz; 2H), δ 2.10 (H5: t, *J* = 7 Hz; 2H), δ 1.67 (H10: s; 3H), δ 1.50 (H6 ,H7, H8: m; 6H), δ 1.40 (O-C-C<u>H</u>3: s; 9H); δ 1.35 (H5': d, *J* = 4.7 Hz; 3H), δ 1.27 (H4': t, *J* = 7.0 Hz; 3H) ppm.



Preparation of (*E*)-4-methyl-3-nonen-9-hydroxy carboxylic acid (74): A solution of 0.29 g (1 mmol) of the *tert*-butyl ester and 45 mg of TosOH in 2 mL of benzene was heated at 40°C for 4 h. The mixture was cooled to RT and washed with water, dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to give 0.13 g (70%) of the hydroxyacid. IR (Film) 3500, 2930, 1715, 1660, 1384, 996 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 9.0-8.0 (bs; 1H), δ 5.38 (H3: bt; 6.9 Hz; 1H), δ 4.55 (H9: t, *J* = 6.8 Hz; 2H), δ 2.95 (H2: d, *J* = 6.9 Hz; 2H), δ 2.11 (H5: t; *J* = 6.6 Hz; 2H), δ 2.03 (-OH: s; 1H), δ 1.67 (H10: s; 3H), δ 1.55-1.45 (H6 ,H7, H8: m; 6H) ppm.

REFERENCES

1. Beroza, M. *Toxicol. and Appl. Pharmacol.* **1975**, 31, 421-429.

2. Banfield, M. *An Analysis of the Semiochemical Industry in North America.* **1988,** MBA Thesis, Simon Fraser University.

3. Norbom, A. *List of Reported Host Plants of Species of Anastrepha (Diptera:tephritidae)* . **1988**, APHIS: U.S.A., 52-81.

4. Sharp, J. *J.Econ. Entomol.* **1990,** 83, 1468-70.

5. Sarma, R.; Kitto, B.; Bercholer, S.; Bush, G. *Arch. Insect Biochem.* **1987**, 4, 271-86.

6. Stokes, J.B.; Uebel, E.C.; Warthen, J.D., Jr.; Jacobson, M.; Flippen-Anderson, J.L.; Gilardi, R.; Spishakoff, L.M.; Wilzer, K.R. *J. Agric. Food Chem.* **1983**, 31, 1162-7.

7. Benschoter, C.A. *J. Econ. Entomol.* **1979**, 72, 401-2.

8. Danse, L.H.J.; van Velsen, F.L.; van Der Heijden, C.A. *Toxicol. and Appl. Pharmacol.* **1984**, 27, 262-71.

9. (a) Shell, C.R.; Klag, N.G.; Burditt, A.K. *Pesticide Sience.* **1988**, 23, 41-9.
   (b) King, J.R.; Benschoter, C.A.; Burditt, A.K. *J. Agric. Food Chem.* **1981**, 29, 1003-5.

10. Castro, C.E.; Belser, N.O. *J. Agric. Food. Chem.* **1981**, 29, 1005-8.

11. Weber, J.D.; Carroll, J.F.; Hayes, D.K. *J. Stored Prod. Res.* **1987**, 23, 1-7.

12. (a) Sharp, J.; Hallman, G.L. *J. Econ. Entomol.* **1992**, 85, 168-71.
    (b) Sharp, J.L.; Gaffeney,J.J.; Moss, J.I.; Gould, W. P. *J. Econ. Entomol.* **1991**, 84, 520-7.

13 (a) Hallman, G.J. *J. Econ. Entomol.* **1990**, 83, 2331-4.
   (b) Hallman, G.J.; Sharp, J.L. *J. Econ. Entomol.* **1990**, 83, 2320-3.

(c) Hallman, G.J.; Sharp, J.L. *J. Econ. Entomol.* **1990**, 83, 1471-4

14. Hallman, G.J.; Gaffney, J.J.; Sharp, J.L. *J. Econ. Entomol.* **1990**, 83, 1475-78.

15. Sharp, J.; Gould, W.P. *J. Econ. Entomol.* **1990**, 83, 2324-6.

16. Perdomo, A.; Nation, J.L.; Baranowski, R.M. *Envirol. Entomol.* **1976**, 5, 1208-10.

17. Nation, J.L. *Envirol. Entomol.* **1975**, 4, 27-30.

18. Battiste, M.A.; Strekowoski, Lucjan, Vanderbilt, D.P.; Visnick, M.; King, R.W.; Nation, J.L. *Tetrahedron Lett.* **1983**, 24, 2611-4.

19. Chuman, T.; Sivinski, J.; Heath, R.R.; Calkis, C.O.; Tumlinson, J.H.; Battiste, M.A.; Wyndra, R.L.; Nation, J.L. *Tetrahedron Lett.* **1988**, 29, 6561-6564.

20. Rocca, J.; Nation, J.L.; Strekowski, L.; Battiste, M.A. *J. Chem. Ecol.* **1992**, 18, 223-43.

21. Esponda-Glaxiola, R.E. Contribucion al estudio quimica del atrayente sexual de la mosca Mexicana de la fruta, *Anastrepha ludens* (Loew). **1977**, Unpublished thesis. Instituto tecnologico y de estudios Superiores de Monterrey, Mexico. **cited by:** Stokes, J.B.; Uebel, E.C.; Warthen, J.D., Jr.; Jacobson, M.; Flippen-Anderson, J.L.; Gilardi, R.; Spishakoff, L.M.; Wilzer, K.R. *J. Agric. Food Chem.* **1983**, 31, 1162-7.

22. a) Robacker, D.C.; Chapa, B.E.; Hart, W.G. *Entomol. Exp. Appl.* **1986**, 40, 123-7.
b) Robacker, D.C.; Hart, W.G. *Ann. Entomol. Soc. Am.* **1987**, 80, 508-12.
c) Robacker, D.C. *J. Chem. Ecol.* **1988**, 14, 1715-26.

23. (a) Kemp, T.R.; Knavel, D. E.; Stoltz, L.P. *Phytochemistry.* **1974**, 13, 1167-70.
(b) Kajiwara,T.; Sekiya, J.; Odake, Y.; Hatanaka, A. *Agric. Biol. Chem.* **1977**, 41, 1481-4.

24. (a) For α-farnesene see: Negishi, E.I.; Matsushita, H. *Org. Synth.* **1990**, Col. Vol. VII, 245-8.
(b) For β-bisabolene see: Manjarrez, A.; Guzmán, A. *J. Org. Chem.* **1966**, 31, 348-9.
(c) For α-bergamotene see: Larsen, S.D.; Monti, S.A. *J. Amer. Chem. Soc.* **1977**, 99, 8015-20.
(d) For limonene see: Elphimoff-Felkin, I.; Sarda, P. *Org. Synth.* **1976**, 56,101-7.

25. Saito, A.; Matsushita, H.; Kaneko, H. *Chem. Lett.* **1984**, 729-30

26. Battiste, M.A.; Strekowski, L.; Coxon, J.M.; Wyndra, R.L.; Harden, D.B. *Tetrahedron Lett.* **1991**, 32, 5303-4.

27. Battiste,.M.A.; Rocca, J.R., Wyndra, R.L.; Tumlinson, J.H.; Chuman, T. *Tetrahedron Lett.* **1988**, 29, 6565-8.

28. Mitsunobu, O. *Synthesis*, **1981**, 1-28.

29. May, R.G. *A Synthesis of (E,E) Suspensolide.* **1990**, MSc. Thesis, Chemistry Department, Simon Fraser University.

30. Wyndra, R.L.; Harden, D.B.; Strekowski, L.; Battiste, M.A.; Coxon, J. *Tetrahedron Lett.* **1990**, 48, 3485-94.

31. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* 3rd Ed. John Wiley and Sons, New York, 1985, 305.

32. a) Cardillo, G.; Orena, M.; Sandri; S. *Synthesis* **1976**, 394-8.
b) McKillop, A; Young, D.W. *Synthesis* **1979**, 401-22.

33. Millar, J.G.; Oehlschlager, A.C. *J. Org. Chem.* **1984**, 49, 2332-8.

34. a) Blackman, A.J.; Wells, R.J. *Tetrahedron Lett.* **1976**, 2729-30.
b) Nakata, T.; Schimid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, 100, 2933-5.
c) Corey, E.J.; Katzenellenbogen, J.A.; Gilman, N.W.; Roman, S.A.; Erickson, B.W. *J. Am. Chem. Soc.* **1968**, 90, 5618-20.

35. a) Faulkner, D.J. *Synthesis* **1971**, 175-89.
b) Mafart, A.; McGuirk, P.R.; Kramer, R.; Helquist, P. *J. Am. Chem. Soc.* **1977**, 99, 253-5.

36. Normant, J.F.; Alexakis, A. *Synthesis* **1981**, 841-70.

37. van Horn, D.E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, 100, 2252-4.

38. Alexakis, A.; Normant, J.; Villierras, J. *Tetrahedron Lett.* **1976**, 3461-2.

39. Negishi, E., van Horn, D.E.; Yoshida, D. *J. Am. Chem. Soc.* **1985**, 107, 6639-47.

40. Alexakis, A.; Normant, J.F. *J. Organometallic Chem.* **1975**, 96, 271-85.

41. a) For aluminum see: Okukado, N.; Negishi, E.I. *Tetrahedron Lett.* **1978**, 2357-60.
b) For copper see: Normant, J.F.; Cahiez, G.; Chuit, C. *J. Organometallic Chem.* **1974**, 77, 281-7.

42. a) For aluminum see: Negishi, E.I.; van Horn, D.E.; King, A.O.; Okukado, N. *Synthesis* **1979**, 501-3.
b)For copper see: Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth* **1984**, 62, 1-9.

43. a) For aluminum see: Kobayashi, M.; Valente, L.F.; Neghisi, E.I. *Synthesis* **1980**, 1034-5.
b) For copper see: Alexakis, A.; Cahiez, G.; Normant, J.F. *Tetrahedron* **1980**, 36, 1961-9.

44. a) For aluminum see: Negishi, E.I.; Rand, C.L.; Jadhav, K.P. *J. Org. Chem.* **1981**, 46, 5040-3.
b) For copper see: Iyer, R.S.; Helquitst, P. *Org. Synth.* **1985**, 64, 1.

45. a) For aluminum see: Wirpf. P.; Smitrovich, J. H.; Moon, C. *J. Org. Chem.* **1992**, 57, 3178-6.
b) For copper see: 6(b).

46. Mafart, A.; McGuirk, P.R.; Helquist, P. *Tetrahedron Lett.* **1978**, 16, 1363-6.

47. Yoshida, T.; Neghisi, E.I. *J. Am. Chem. Soc.* **1981**, 103, 4985-7.

48. a) Breitmaier, E., Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd Ed., VHC:West Germany, **1987**.
b) Silverstein, R.M.; Bassler, G.C.; Morrill, T.C.; *Spectrometric Identification of Organic Compounds.* 4th Ed., John Wiley & Sons: New York, **1981**, 263.

49. Neuman, H.; Seebach,D. *Chem. Ber.* **1978**, 111, 2785-92.

50. Leznoff, C.C. *Acc. Chem. Res.* **1978**, 11, 327.

51. a) Trost, B.M.; Verhoeven, T.R. *J. Am. Chem. Soc.* **1980**, 102, 4743-63.
b) Ikeda, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1984**, 25, 5177-80.

52. Mc Dougal, P.G.; Rico, J.G.; Oh, Y.; Condon, B.D. *J. Org. Chem.* **1986**, 51, 3388-90.

53. Picard, P.; Leclercq, D.; Bats, J.P.; Moulines, J. *Synthesis* **1981**, 550-1.

54. Kanjolia , R.K.; Gupta, V.D. *Naturforsh.* **1980**, 35b, 767-70.

55. Cossy, J.; Pale, P. *Tetrahedron Lett.* **1987**, 28, 6039-40.

56. Corey, E.J.; Kim, C.U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339-42.

57. a) Olah, G.A.; Balaram, B.G.; Malhotra, R.; Narang, S.C. *J. Org. Chem.* **1980**, 45, 1638-9.
b) Morita, T.; Yoshida, S.; Okamoto, Y.; Sakurai, H. *Synthesis* **1979**, 379.

58. Greene,T.W.; Wuts, P.G. *Protective Groups in Organic Synthesis*, 2nd Ed., John Wiley: New York, **1991**, 68-73, 87.

59. Bestmann, H.J.; Gunawardena, N.E. *Synthesis* **1992**, 1239-40.

60. Calzada, J.; Hooz J. *Org. Synth.* **1976**, 54, 63-6.

61. Oehlschlager, A.C.; Pope, P.; Thakore, A.N. *Tetrahedron* **1971**, 27, 2617-26.

62. a) Allen, H. *Org. Synth.* **1941**, Coll. Vol. I, 156-7
b) Kendall, E.C.; McKenzie, B. *Org. Synth.* **1941**, Coll. Vol. I, 256-258.
c) Supniewski, J.V.; Salzberg, P.L. *Org. Synth.* **1941**, Coll. Vol. I, 46-7.
d) Adams, R.; Thal, A.F. *Org. Synth.* **1941**, Coll. Vol. I, 107-9.

63. a) Zubrick, J.W.; Dunbar, B.I.; Durst, H.D. *Tetrahedron Lett.* **1975**, 71-4.
b) Cook, F.L.; Bowers, C.W.; Liotta, C.L. *J. Org. Chem.* **1974**, 39, 3416-8.

64. Compagnon, P.L.; Miocque, M. *Ann. Chim.* **1970**, 5, 11-22.

65. Ruhoff, J.R. *Org. Synth.* **1943**, Coll. Vol. II, 292-4.

66. a) Fuson, R.C. *Org. Synth* **1963**, Coll. Vol. IV, 496-8
b) Allen, F.H.; Johnson, H.B. *Org. Synth* **1963**, Coll. Vol. IV, 804-6.

67. Hoye, T.R.; Kurth, M.J. *J. Org. Chem.* **1978**, 43, 3639-44.

68. James, F.; Bryan, W. *J. Am. Chem. Soc.* **1958**, 23, 1225-7.

69. Prout, F.S.; Hartman, R.J.; Huang, E.P. *Org. Synth* **1963**, Coll. Vol. IV, 93-8.

70. Aristoff, P.; Johnson, P.D.; Harrison, A.W. *J. Am. Chem. Soc.* **1985**, 107, 7967-74.

71. Reference 31, p. 788.

72. Cacchi, S.; Misti, D. *Synthesis* **1980**, 243-4.

73. a) Steiger, R.E. *Org. Synth.* **1955**, Coll. Vol. III, 66-70.
b) Steiger, R.E. *Org. Synth.* **1955**, Coll. Vol. III, 88-92.

74. Newman, N.S.; Wise, R.M. *J. Am. Chem. Soc.* **1956**, 78, 450-4.

75. Vaughan, H.L.; Robbins, M.D. *J. Org. Chem.* **1975**, 40, 1187-9.

76. Gassman, P.G.; Hodgson, P.K.; Balchunis, R.J. *J. Am. Chem. Soc.* **1976**, 1275-6.

77. Benardy, K.F.; Floyd, M.B.; Poletto, J.F.; Weiss, M.J. *J. Org. Chem.* **1979**, 44, 1438-47.

78. Czyzewska, E.; Oehlschlager, A.C. *Studies in Natural Products Chemistry.* Vol 8. Elsevier: Amsterdam, **1991**, 219-262.

79. Reference 31, p.184-6.

80. For reaction of potassium and cesium carboxylate see:
a) Kruizinga, W.H.; Kellogg, R.M. *J. Am. Chem. Soc.* **1981**, 103, 5183-9.
b) Galli, C.; Mandolini, L. *J. Org. Chem.* **1991**, 56, 3045-7.
c) Bram, B. G.; Decodts, G.; Loupy, A.; Orange, C.; Petit, A. *Synthesis* **1985**, 40-5.
For variations of double activation reagents see:
d) Kim, S.; Kim, S. *Synthesis* **1986**, 1017-9.
e) Takeda, K.; Tsuboyama, K.; Takayanagi, H.; Ogura, H. *Synthesis* **1987**, 560-2.
For reaction with 2-halo pyridinium salts see:
f) Mukaiyama, T.; Usui, M. Saigo, K. *Chem. Lett.* **1976**, 49-50.
g) Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 885-8.
h) Mukaiyama, T.; Narasaka, K.; Kikuchi, K. *Chem. Lett.* **1977**, 441-4.
For tin, copper, zirconium, silicon-mediated esterification see:
i) Steliou, K.; Poupart, M. *J. Am. Chem. Soc.* **1983**, 105, 7130-8.
j) Kuno, H.; Shibagaki, M.; Takahashi, K.; Honda, I.; Matsushita, H. *Chem. Lett.* **1992**, 571-4.
k) Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shina, I. *Chem. Lett.* **1993**, 907-10.

81. Corey, E.J.; Nicolaou, K.C. *J. Am. Chem. Soc.* **1974**, 96, 5614-16.

82. Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, 97, 3515-6.

83. Inanaga, J.; Hirata, K.; Sacki, H.; Katsuki, T.; Uamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989-93.

84. Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455-8.

85. Corey, E.J.; Nicolau, K.C.; Melvin, L.S. Jr.*J. Amer. Chem. Soc* **1975**, 97, 654-8.

86. Corey, E.J.; Brunelle, D.J. *Tetrahedron Lett.* **1976**, 3409-12.

87. Masamune, S.; Bates, G.S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, 33, 585-602.

88. House, H.O. *Modern Synthetic Reactions* 2nd Ed. W.A. Benjamin: New York, **1972**, 387-96.

89. Paterson, I.; Laffan, D.P.; Rawson, D.J. *Tetrahedron Lett.* **1988**, 1461-5.

90. Mitsunobu, O.; Euguchi, M. *Bull. Chem. Jpn.* **1971**, 44, 3427-30.

91. Baker, J.B.; Heath, R, R. *J. Entomol. Chem.* **1993**, 19, 1511-1519.

92. Seebach, D. *Synthesis*, **1969**, 17-33.

93. Seebach, D. *Angew. Chem. Int. Edit.* **1967**, 6, 442-4.

94. Corey, E.J.; Erickson, B.W. *J. Org. Chem.* **1971**, 36, 3553-60.

95. Grobel, B.-T.; Seebach, D. *Synthesis*, **1977**, 357-402.

96. Guss, C.O.; Rosenthal, R. *J. Amer. Chem. Soc.* **1955**, 77, 2549.

97. Corey, E.J.; Natarajan, R. *Tetrahedron Lett.* **1983**, 24, 5571-4.

98. Rand, C.L.; van Horn, D. E.; Negishi, E.I. *J. Org. Chem.* **1981**, 46, 4093-6.

99. Eisenbraun, E.J. *Org. Synth.* **1973**, Coll. Vol. IV, 310-14.

100. Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399-402.

101. Corey, E.J.; Gilman, N.W.; Ganem, B.E. *J. Am. Chem. Soc.* **1968**, 90, 5616-7.

102. Pear, I.A. *Org. Synth.* **1973**, Coll. Vol. IV, 972-3

103. Corey, E.I.; Venkateswarlu, A.; *J. Amer. Chem. Soc.* **1972**, 94, 6190-1.

104. Negishi, E.I.; Yoshida, T. *J. Am. Chem. Soc.* **1981**, 103, 4985-7.

105. Miyashita, N.; Yoshikoshi, A., Grieco, P. *J. Org. Chem.* **1977**, 42, 3772-4.

106. a) Feixas, J.; Capdevila, A.; Camps, F.; Guerrera, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1451-3
b) Corey, E.J.; Yi, K. *Tetrahedron Lett.* **1992**, 33, 2289-90.

107. Wilt, J.W.; Massie, S.N.; Dabek, R.B. *J. Org. Chem.* **1970**, 35, 2803-5.

108. Beckmann, W.; Doerjer, G.; Logemann, E.; Merkel, G.; Zucher, S.C. *Synthesis* **1975**, 423-4.

109. Abrams, S.R. *Can. J. Chem.* **1984**, 62, 1333-4.

110. Millard, A.A.; Rathke, M.W. *J. Am. Chem. Soc.* **1977**, 4833-5.

111. Anderson, G. W.; Callahan, F. M. *J. Amer. Chem. Soc.* **1960**, 82, 3359-63.

112. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923-5.

113. Watson, S.C.; Eastman J.F.; *J. Organometallic Chem.* **1967**, 9, 165-8.