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UNIVERSITY OF ALBERTA

FREE RADICAL METHODS FOR SYNTHESIS OF BIOLOGICALLY IMPORTANT COMPOUNDS

by

ANTONIO CARLOS JOUSSEF

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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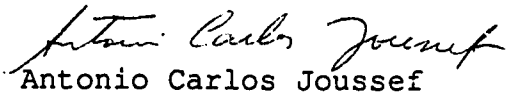


Antonio Carlos Joussef

PERMANENT ADDRESS:
Rua Teodoro Langard 443
Campinas, S. Paulo
Brasil
CEP: 13100

Date: 2nd November, 1990

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled FREE RADICAL METHODS FOR SYNTHESIS OF BIOLOGICALLY IMPORTANT COMPOUNDS submitted by ANTONIO CARLOS JOUSSEF in partial fulfillment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

Dr. D.L.J. Clive .....
(Supervisor)

Dr. W.A. Ayer .....

Dr. H.J. Liu .....

Dr. S. Fraga .....

Dr. F. Pasutto .....

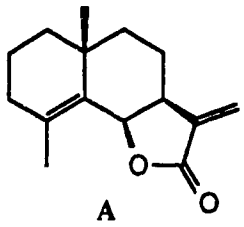
Dr. M. Majewski .....

Date: 2nd October, 1996

To my family

ABSTRACT

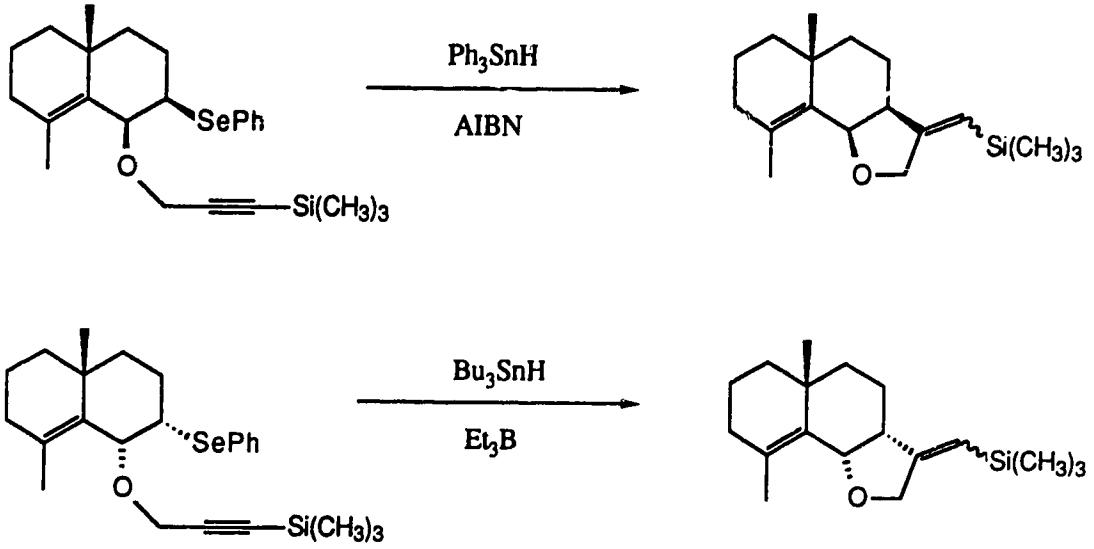
This thesis describes the synthesis of the allergy-producing sesquiterpene, (±)-frullanolide (**A**) by methodology involving radical cyclization [Clive, D.L.J.; Joussef, A.C. *J. Org. Chem.* **1990**, *55*, 1096]. The technique developed



A

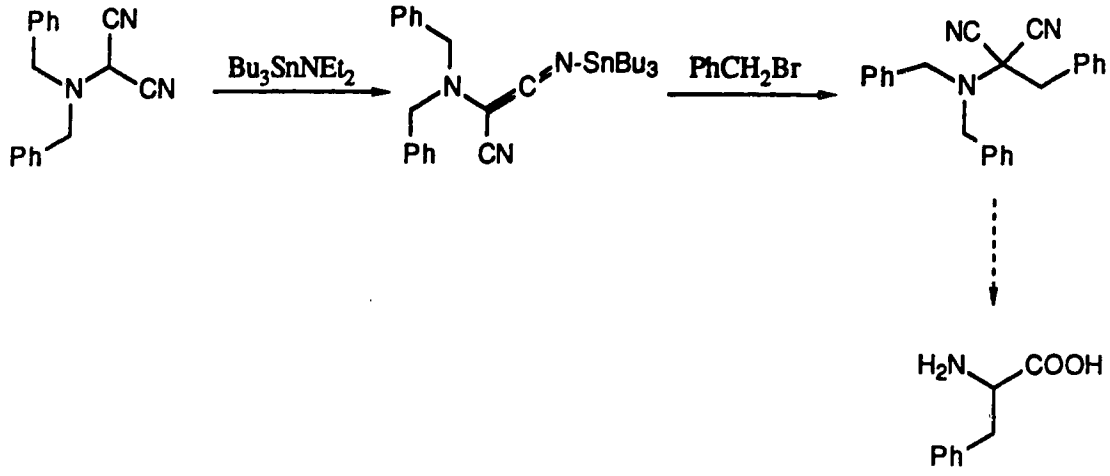
provides a method for attaching a ring to either face of an existing cyclic structure (see Scheme A). The second chapter

SCHEME A



of the thesis describes preliminary work on a new approach (see Scheme B) for the construction of α-amino acids via intermolecular radical chemistry.

SCHEME B



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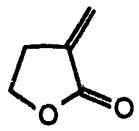
CHAPTER 1

Synthesis of (±)-Frullanolide

I. INTRODUCTION

A. Generalities

The α-methylene γ-butyrolactone substructure **1** is an integral building block of many natural products, especially the sesquiterpene lactones, which exhibit significant biological properties.[1] A book[2] published in 1979 lists



1

approximately 900 α-methylene γ-butyrolactones that have been fully characterized. Since then this number has risen to at least 2000 to 3000. If we consider that the number of structurally elucidated natural products has been estimated[3] to be only between 25000 and 30000, α-methylene γ-butyrolactones of the sesquiterpene type represent almost 10% of the total, and are the major class of known natural products.

B. Biosynthesis

The biosynthesis of the sesquiterpenoid α-methylene γ-butyrolactones is fairly simple.[2,4,5] The compounds are derived from *trans,trans*-farnesyl pyrophosphate (Scheme 1), which first cyclizes to give the strained cyclodecadiene skeleton of germacradiene (or germacratriene) and leads,

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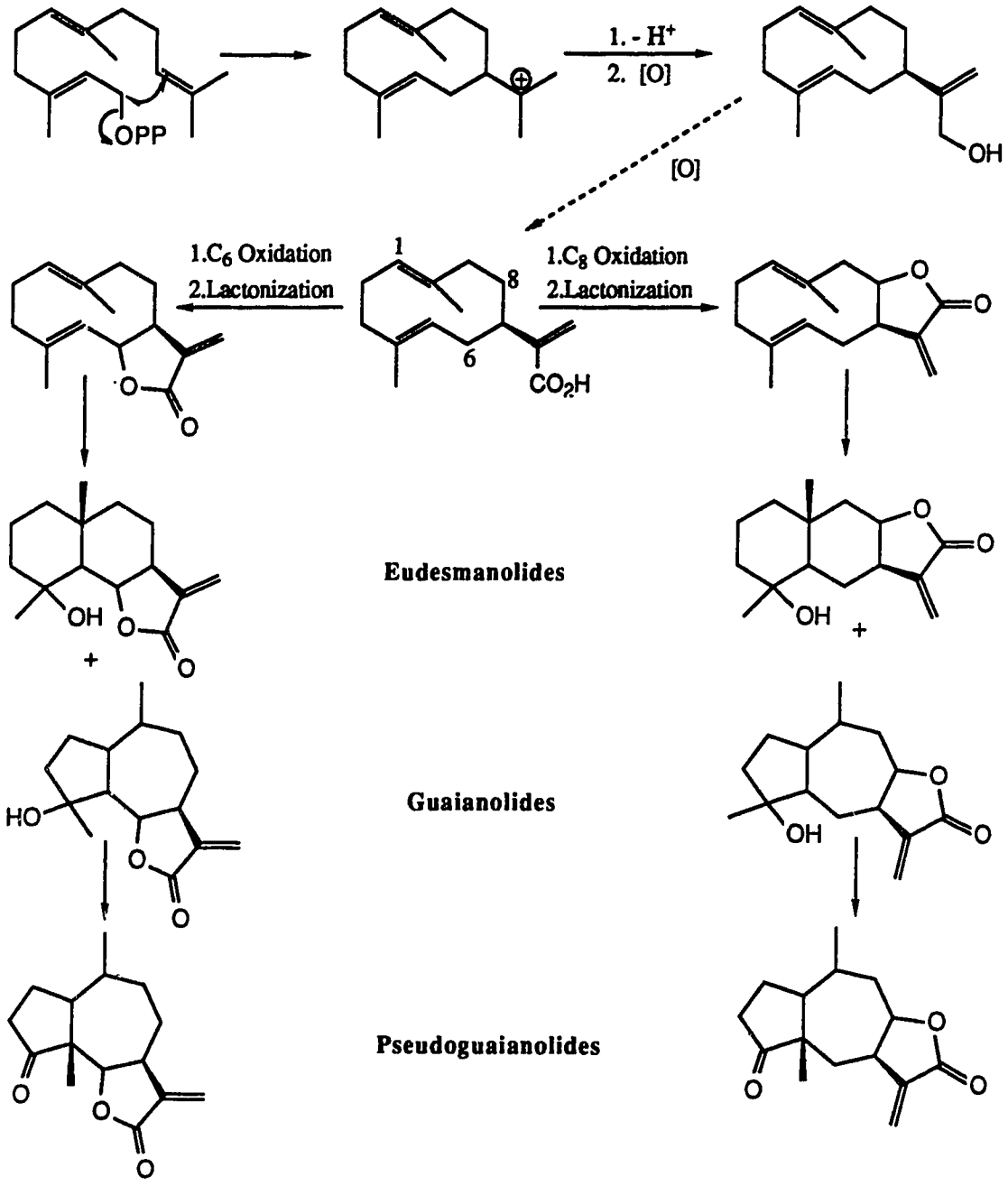


after a sequence of steps, to either a perhydroazulene system (e.g., guaiane and pseudoguaiane) or a decalin system (e.g., eudesmane). Many plants which belong to the large, species-

rich family *Compositae*[4b] (composites) contain sesquiterpene lactones as characteristic constituents. These compounds are colorless, lipophilic, often bitter-tasting, and are mainly present in the leaf tissue, where they can constitute up to 5% of the dry weight.

C. Important Biological Activities

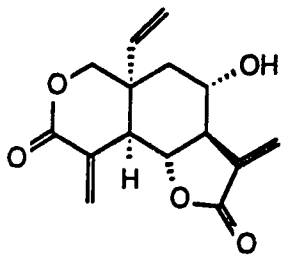
Studies on the relationship between biological activity and structure[6-10] have shown that α-methylene γ-butyrolactones act as alkylating agents because they undergo a Michael reaction with biological nucleophiles such as L-cysteine or thiol-containing enzymes (Enz-SH) (eq. 1). It is likely that these lactones inhibit incorporation of selected amino acids into proteins, i.e., they inhibit the metabolism at the cellular level, but they do not alkylate DNA.[8,11-15]

eq. 1

C.1. Antitumor and Cytotoxic Activity

A large number of biologically active sesquiterpene lactones, including vernolepin **2**,[16a] aromaticin **3**,[11] and elephantopin **4**[16b] have been isolated from plant extracts and show tumor-inhibiting activity.[17] It has been shown that almost all known cytotoxic sesquiterpene lactones possess an α,β-unsaturated lactone structure, and that the conjugated

double bond must be exocyclic. A cyclopentenone, or an additional α-methylene lactone moiety, enhances the cytotoxic activity; a hydroxy group can also cause an enhancement.



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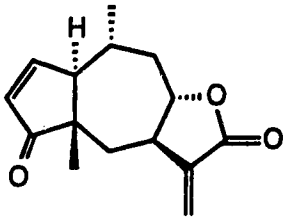

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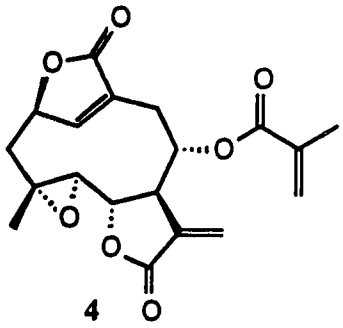

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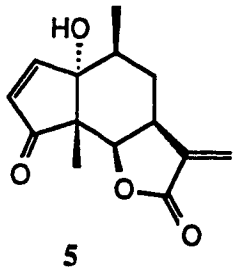
These supplementary features can have a variety of positions with respect to the α-methylene lactone unit. The high cytotoxicity of the sesquiterpene lactones is probably due to the inhibition of DNA synthesis and/or transcription.[15] However, protein synthesis is also partially impaired.[13,14] It should be mentioned, however, that at present there is no cytostatic sesquiterpene which is used clinically, apparently because of the relatively high toxicity of the compounds. Attempts to increase the activity by chemical modification have, so far, been unsuccessful.

C.2. Allergenic Activity

Many people suffer from an allergic contact dermatitis (ACD) which is caused by contact with the chemical constituents of plants.[18] Sesquiterpene lactones, which are sometimes present in the pollen, can cause this allergic

contact dermatitis even when the pollen is carried by the wind. The presence of an α-methylene γ-butyrolactone moiety is a sufficient requirement for the allergenic activity. For example, parthenin **5**, present in *Parthenium hysterophoros*, is a primary allergen of this widespread plant. The allergy thus caused represents a serious dermatological problem in India and neighboring countries.[19] Perfume oils extracted from the costus root (*Saussurea lappa*)[20] or from the laurel (*Laurus nobilis*),[21] cultivated since antiquity, can also cause dermatitis due to the germacranolide costunolide **6**, present in both mixtures. In order to obtain a perfume that is free from allergen, one passes the raw oil through a column



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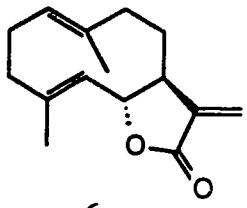
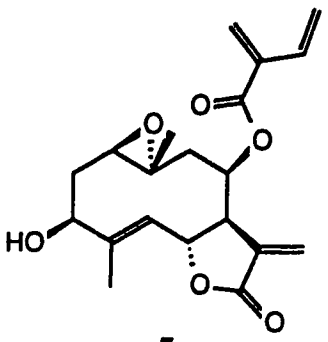


6

containing a nucleophile on a solid support, e.g., β-(amino-ethyl)polystyrene. In this way, the allergen is bound to the nucleophile.[18b] With respect to the pathogenesis of ACD, it is assumed that the α-methylene lactone becomes bonded to a skin protein via a Michael reaction, thus forming an antigen which causes the sensitization of the lymphocytes [19b] In view of the widespread occurrence of ACD, further research efforts can be expected in this area.

C.3. Phytotoxic and Antimicrobial Activities

In addition to the cytotoxic and allergenic activities described, phytotoxic activities are shown by a number of sesquiterpene lactones.[6,7] Thus, heliagin **7**, a germacranolide of the tuberous sunflower (*Helianthus tuberosus L.*, also called topinambur or Jerusalem artichoke), and vernolepin **2**, from *Vernomia hymenolepsis*, cause plant growth inhibition.[6,22] Xanthatin **8** is also used in the regulation of plant growth.[5]



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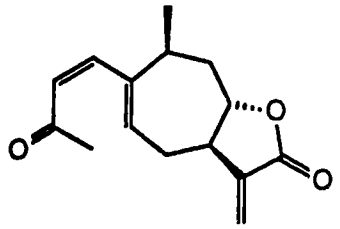

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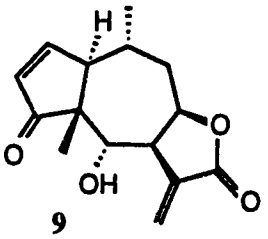
The α-methylene lactones present in the common sunflower (*Helianthus annus L.*) appear to be stress metabolites, i.e., they are formed during attack on the plant by pests, in periods of dryness, or overexposure to sunlight and heat. The compounds probably act mainly as chemical defenses against pests, especially microorganisms.[23] Other α-methylene lactones, such as helenalin **9**[24] and eremanthin **10**[25] show bactericidal, fungicidal, and anthelmintic properties.[26]

Not only highly functionalized and complex sesquiterpene lactones but also simple representatives of this compound class have been studied for their biological activity. Two



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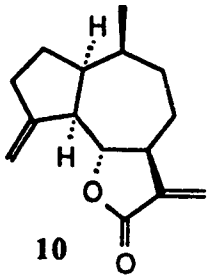

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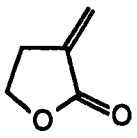
compounds with fungicidal properties have been isolated from tulip bulbs and identified:[27] tulipalin A **11**, which is the simplest α-methylene γ-butyrolactone possible, and its 4-hydroxy derivative, tulipalin B **12**,which is present in nature as the (*S*)-enantiomer. It appears certain that α-methylene



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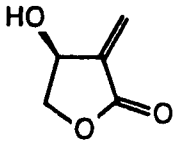

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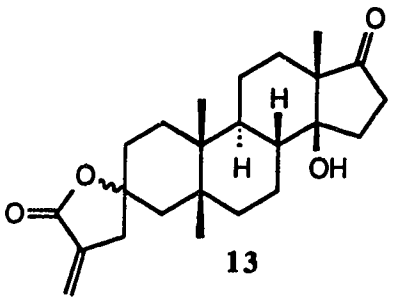
γ-butyrolactones, due to their high and selective antibiotic activities, afford important protection to plants. In the course of evolution, this fact, together with the outstanding adaptive and reproductive capabilities of *Compositae*, has contributed to a selective advantage in the survival of this plant family and also to its broad distribution all over the continents except Antarctica.

In the future, the study of α-methylene γ-butyrolactones related to the naturally-occuring examples[28] will become increasingly important. The steroidal spiro α-methylene lactones **13**, which are not found in nature, possess tumor-inhibiting activity.[10,29] Thus, α-methylene γ-lactones can serve as lead structures for the synthesis of biologically active compounds.

The structurally related α-methylene cyclopentanones pleurotellol (**14**, R = CH_2OH) and pleurotellic acid (**14**, R = CO_2H), have been found in fungi and show antibiotic



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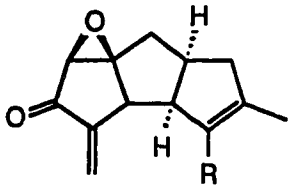
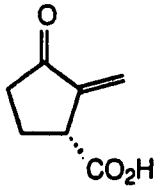


14 R = CH_2OH or CO_2H

activity.[30] Comparatively simple representatives of this type are cyclopentanoid antitumor agents such as sarkomycin **15**, methylenomycin A **16**, and xanthocidin **17**.[31]



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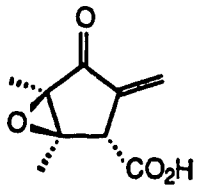

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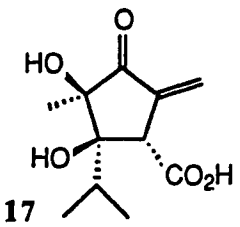

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Because of their broad range of biological activities and their interesting structural features, α-methylene γ-butyrolactones present a scientific challenge which is reflected in an increasing number of investigations and syntheses of these heterocycles.

D. General Routes to α-Methylene γ-butyrolactones

The synthesis of α-methylene γ-butyrolactones is a subject of continuing interest due, as mentioned before, to the biological activity of natural products containing this structural unit. Since 1975 up to the present, four reviews have been published concerning the synthesis of α-methylene γ-butyrolactones.[32] Methods used for the construction of this moiety can be classified generally into two groups:

1- Construction of the α-methylene lactone unit starting from an acyclic precursor bearing all the necessary functionalities.

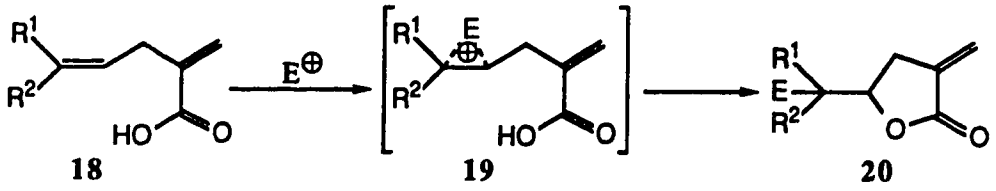
2- α-Methylenation of preformed γ-butyrolactone rings.

The first approach (1) is clearly attractive, since it offers a great variation of solutions, as well as a continuous challenge for a search for new methods. These methods are illustrated in the following sections (**D.1.** and **D.2.**).

D.1. Construction of the α-Methylene Lactone Unit from an Acyclic Precursor

D.1.1. Lactonization of α-Methylene γ,δ-Unsaturated Acids or Esters

α-Methylene γ,δ-unsaturated acids **18**, when treated with suitable electrophiles, are converted, via **19**, to the corresponding lactones **20** (eq. 2).

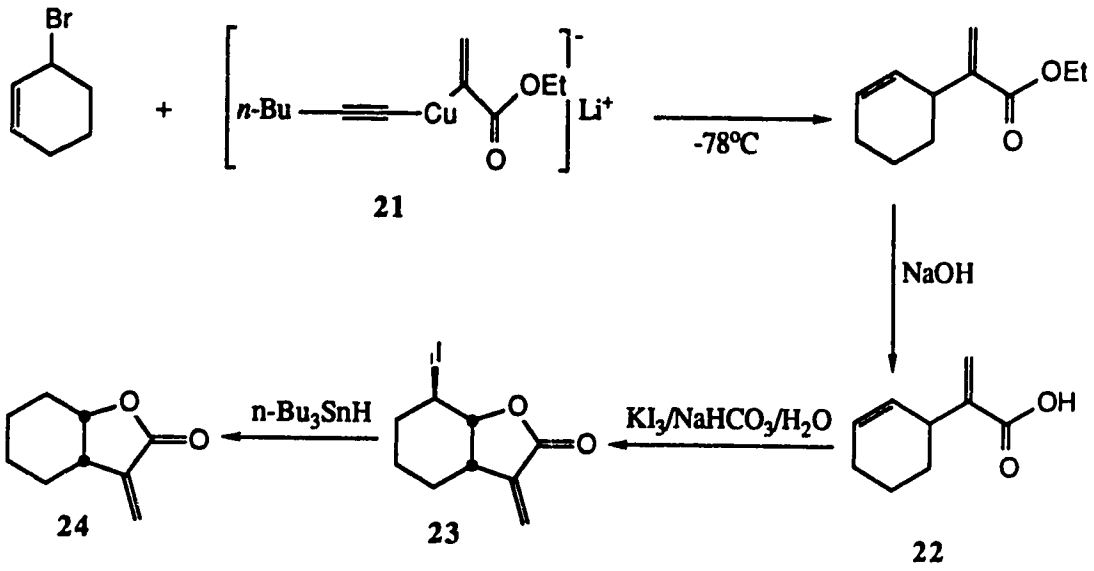


eq. 2

This general approach for the synthesis of α-methylene γ-butyrolactones will be outlined in this section, with emphasis on the diversity of methods employed to prepare the acid **18** (or its corresponding ester).

Marino and Floyd[33] have used α-(ethoxycarbonyl)vinylcuprate **21** (Scheme 2), which, due to the lack of reactivity of the acetylenic ligand, allows selective transfer of ethyl acrylate to allylic substrates. Reaction with 3-bromocyclohexene affords a product which possesses the necessary functionalities for subsequent conversion into an α-methylene γ-butyrolactone. Thus, the acid **22**, obtained from 3-bromocyclohexene, is easily converted to the *cis*-fused iodo lactone **23**, which, in turn, is reduced to the corresponding lactone **24**.

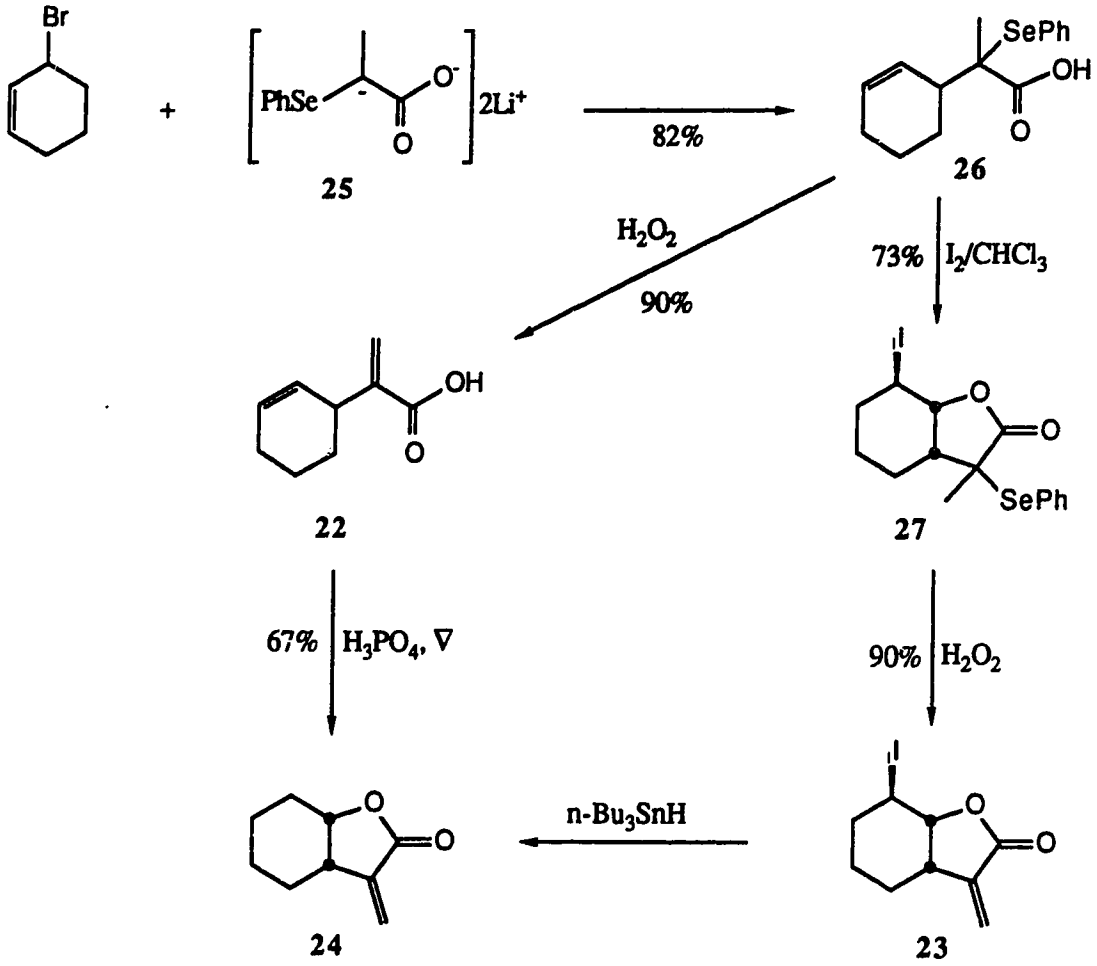
With regard to the stereochemistry of the cyclization reaction it must be pointed out that the selective formation of *cis*-fused lactones is a general result observed in the



iodolactonization,[34] as well as in the acid-promoted lactonization of γ,δ- and β,γ-unsaturated acids.

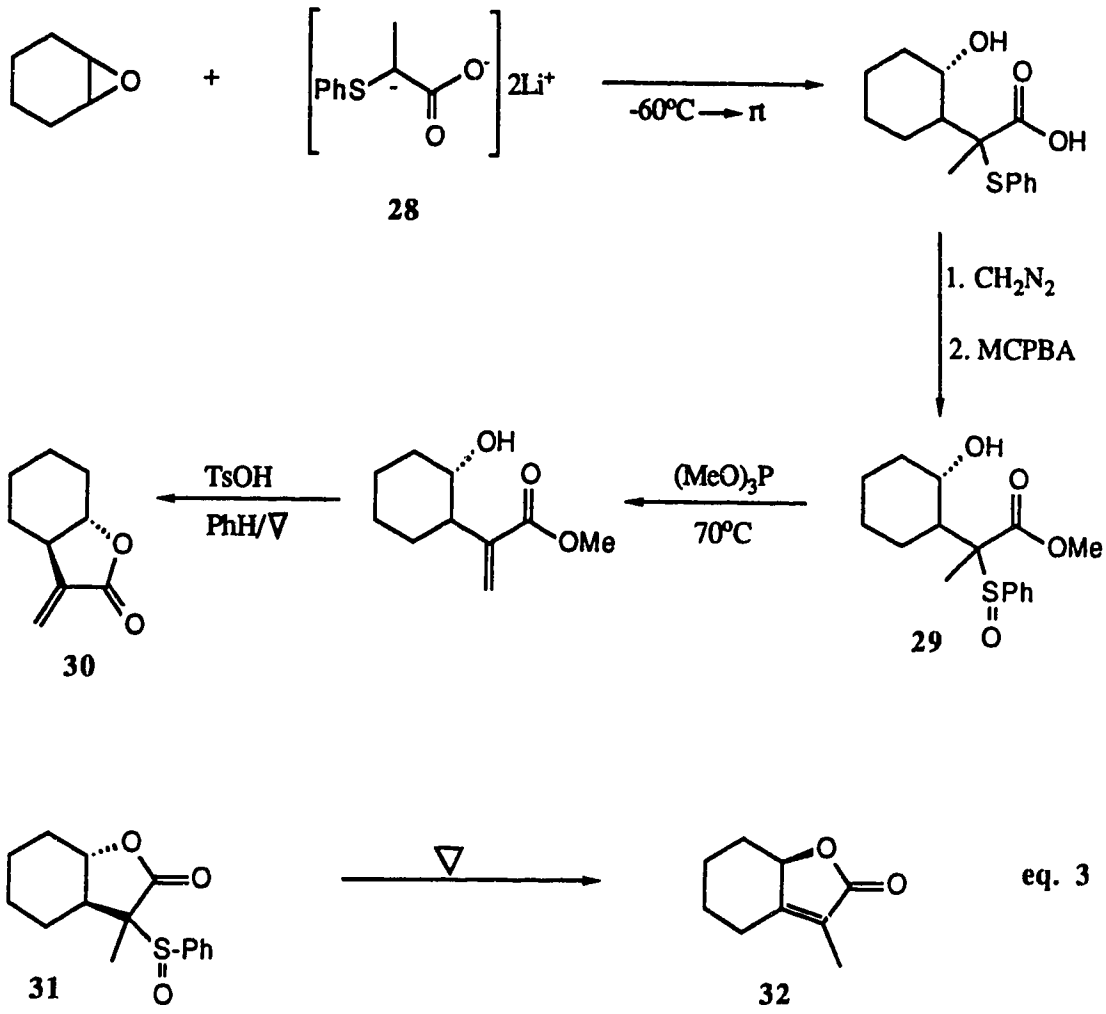
In 1978, Petragnani and Ferraz[35] explored the utility of selenium-containing reagents to introduce a masked acrylate unit, and they used 2-(phenylseleno)propanoic acid dianion **25** (Scheme 3), for the construction of the α-methylene γ-butyrolactone moiety. Thus, reaction of acid dianion **25** with 3-bromocyclohexene followed by oxidative *syn* elimination of the resulting selenide **26** furnished the α-methylene γ,δ-unsaturated acid **22**. The *cis*-fused α-methylene γ-butyrolactone **24** was obtained simply by heating **22** with phosphoric acid. Alternatively, **26** was iodolactonized affording the *cis*-fused iodo lactone **27**, which was then deselenated to the corresponding iodo lactone **23** (the same intermediate as in the vinylcuprate route of Scheme 2).

SCHEME 3



Trost and Leung[36] have employed (α-phenylthio)propanoic acid dianion **28** (Scheme 4) as a masked acrylate unit to convert cyclohexene oxide into *trans*-fused α-methylene γ-butyrolactone **30**. It must be pointed out that, in contrast, the sulfoxide-elimination performed with a cyclic equivalent of **29**, i.e., the sulfinyl lactone **31**, furnished exclusively the butenolide **32** (eq. 3).

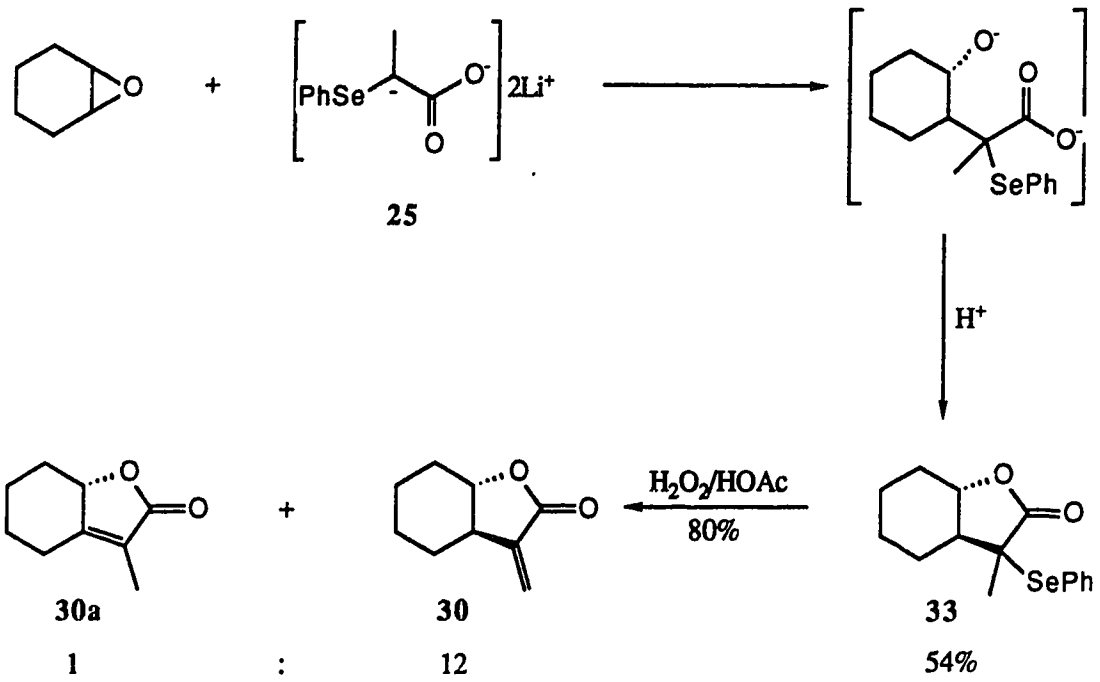
SCHEME 4



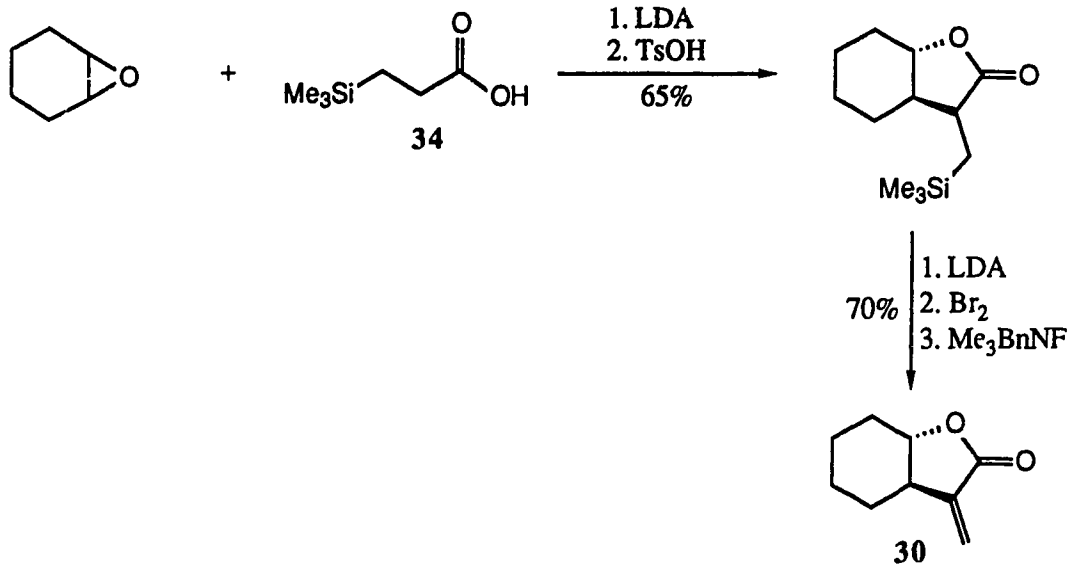
eq. 3

Petragnani and Ferraz[35] have also used (Scheme 5) the acid dianion **25**, to convert cyclohexene oxide into an α-methylene γ-butyrolactone. Here the approach is more convenient since a more direct two-step sequence and milder conditions are employed. Moreover, the selenoxide-elimination of **33** furnishes mainly the desired *trans*-fused α-methylene lactone **30**.

SCHEME 5



Similarly, Fleming and Goldhill[37] have used 3-(trimethylsilyl)propanoic acid **34** (eq. 4) as a masked acrylate

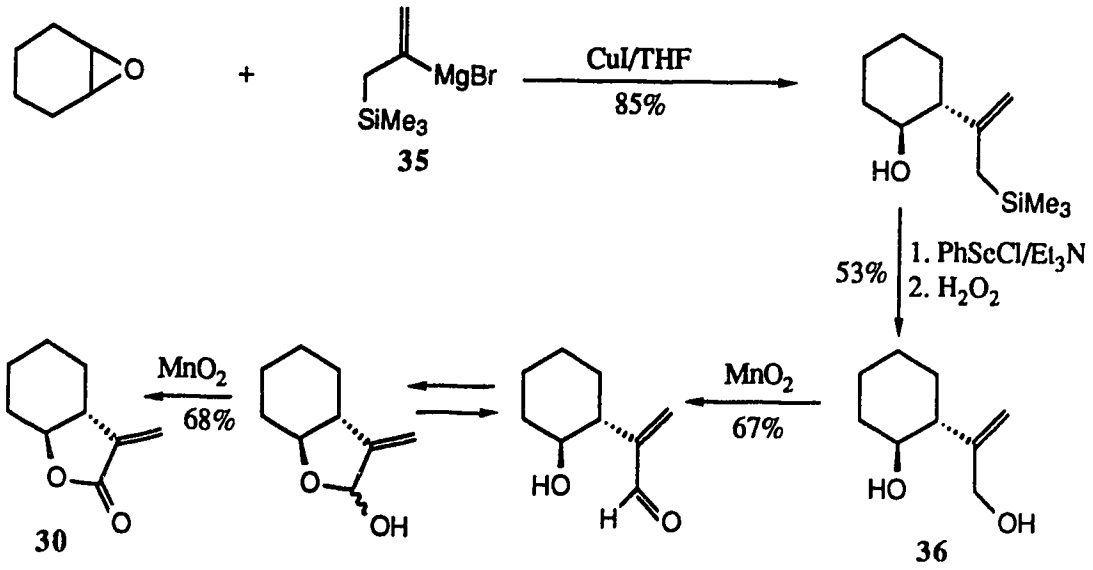


eq. 4

synthon, from which, after cyclization, the silicon group can be eliminated with regeneration of the double bond.

In 1982, Itoh and co-workers[38] employed the allyl silane **35** (Scheme 6) as a masked acrylic acid and it was allowed to react with cyclohexene oxide to give the functionalized

SCHEME 6

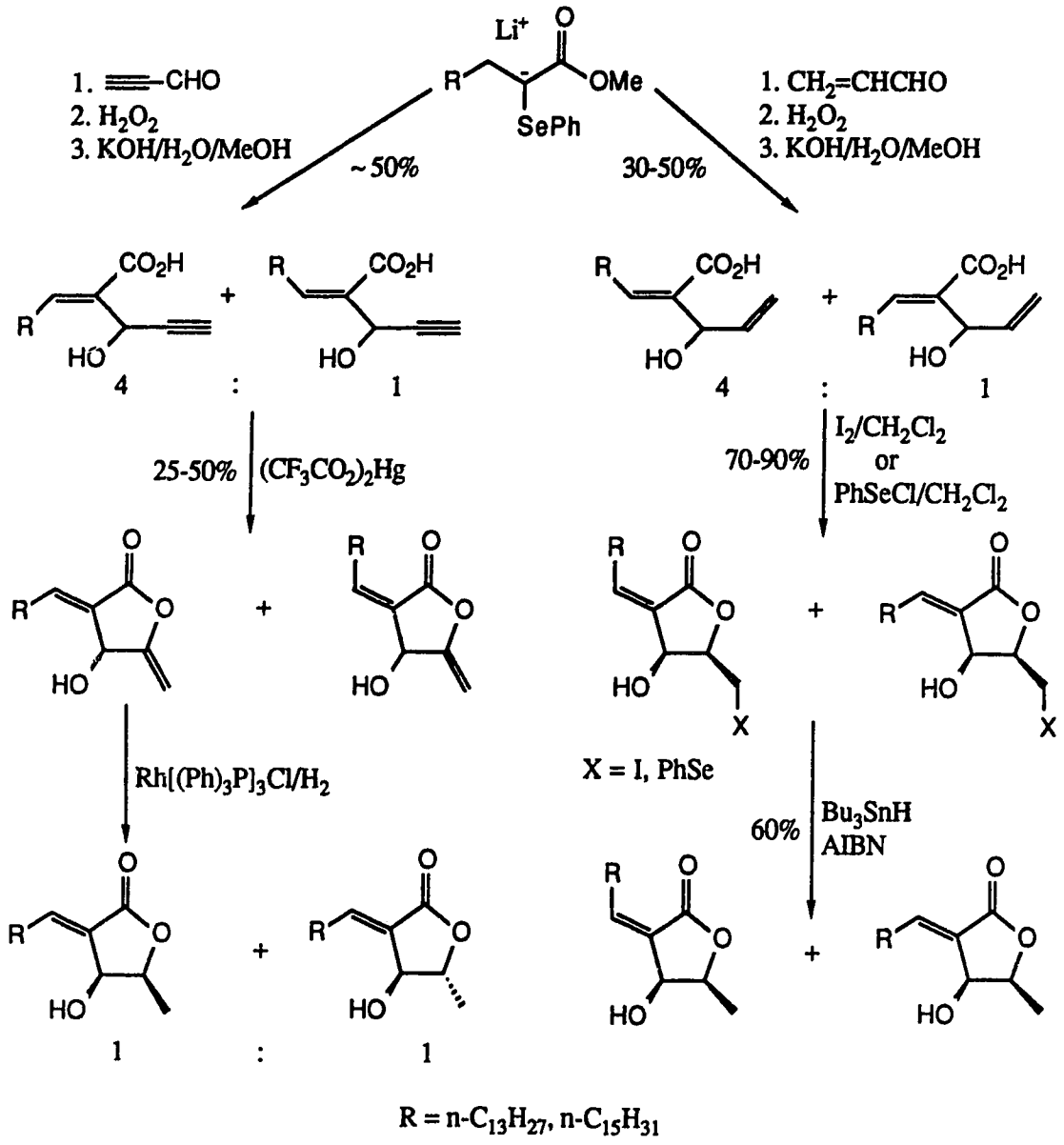


homoallylic alcohol shown. This alcohol, in turn, reacted with phenylselenenyl chloride and subsequently with hydrogen peroxide (desilylating oxidation via allyl selenide and oxidative rearrangement) to give allyl alcohol **36**. The α-methylene γ-lactone **30** was then assembled by oxidation of **36** with manganese dioxide.

Another synthetic sequence, in which 2-(phenylseleno) alkanoic esters[39] are employed as acrylate equivalents, leads

to α-alkylidene-β-hydroxy-γ-methylene (or γ-methyl) butyrolactones[40] (Scheme 7). These compounds are present in

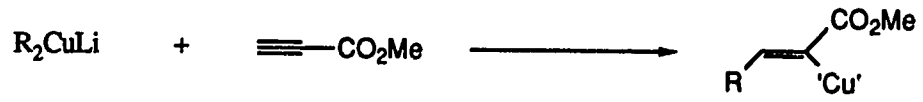
SCHEME 7



R = n-$C_{13}H_{27}$, n-$C_{15}H_{31}$

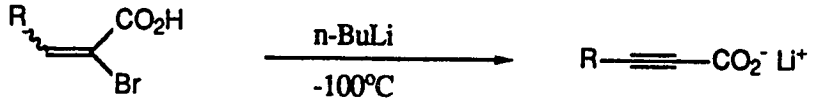
Lauracea species. It must be pointed out that the generation of α-acrylate anions by conjugate addition of dialkylcuprates

to propynoic esters (eq. 5) is of limited use,[32d] since this addition is known to occur only in a *syn*-manner. Attempts to generate α-acrylate anions at low temperature by lithium-



eq. 5

halogen exchange of α-bromo acrylic acid failed,[32d] since in this system, with a β-hydrogen, β-elimination is the predominant reaction (eq. 6).



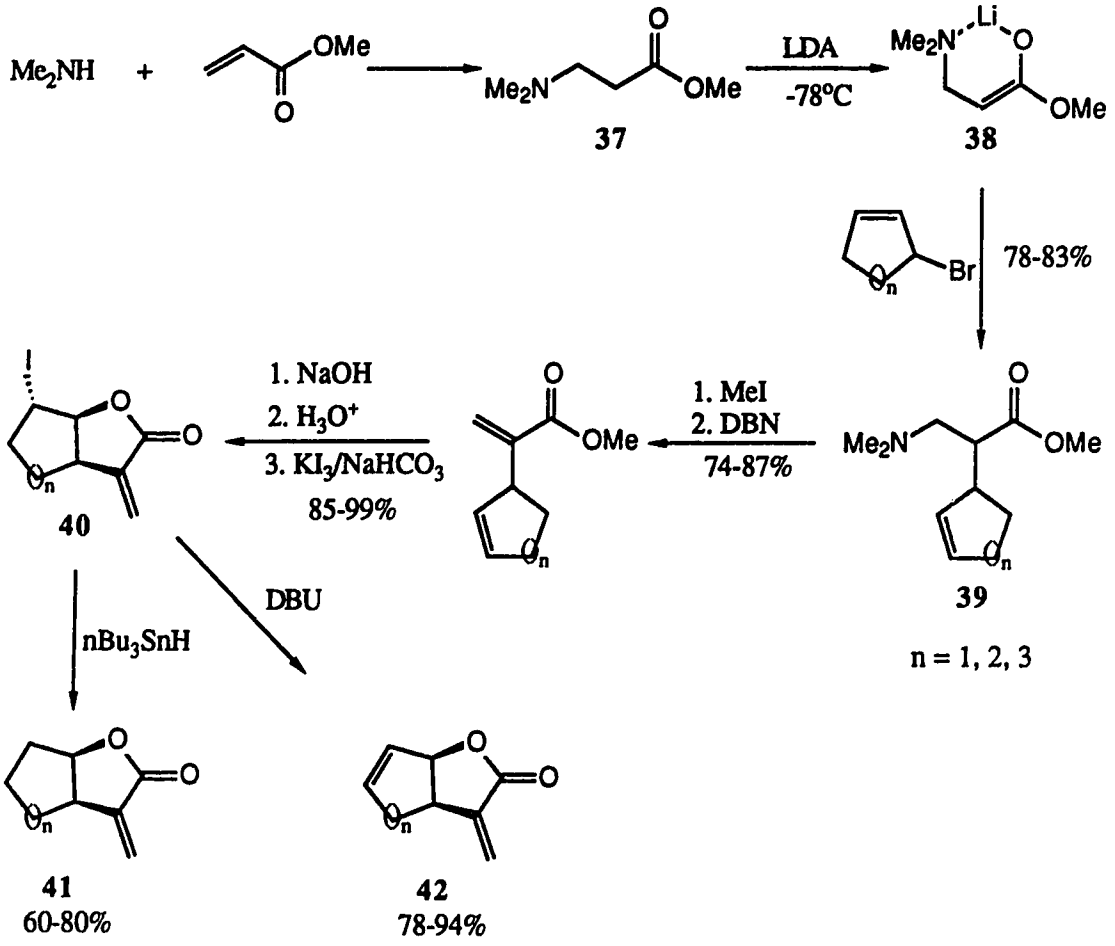
eq. 6

Helquist and Yu[41] used methyl 3-(dimethylamino)propionate **37**. This reagent is readily available via Michael addition of dimethylamine to acrylic ester. Deprotonation gives enolate **38**, which is stable at room temperature, probably due to a chelate structure. The enolate reacts with allyl bromides giving the desired γ,δ-unsaturated esters **39**. Elimination of the amino group and iodolactonization yields **40** which, under elimination or reduction conditions leads, respectively, to **41** and **42**, as shown in Scheme 8.

In this regard, the lack of utility of other β-substituted acrylate equivalents should be mentioned: 3-(mercapto)-propanoic acid and derivatives undergo alkylation at sulfur

or elimination,[41a] and 3-(phenylseleno)propanoic acid undergoes β-elimination under strongly basic conditions.[32d]

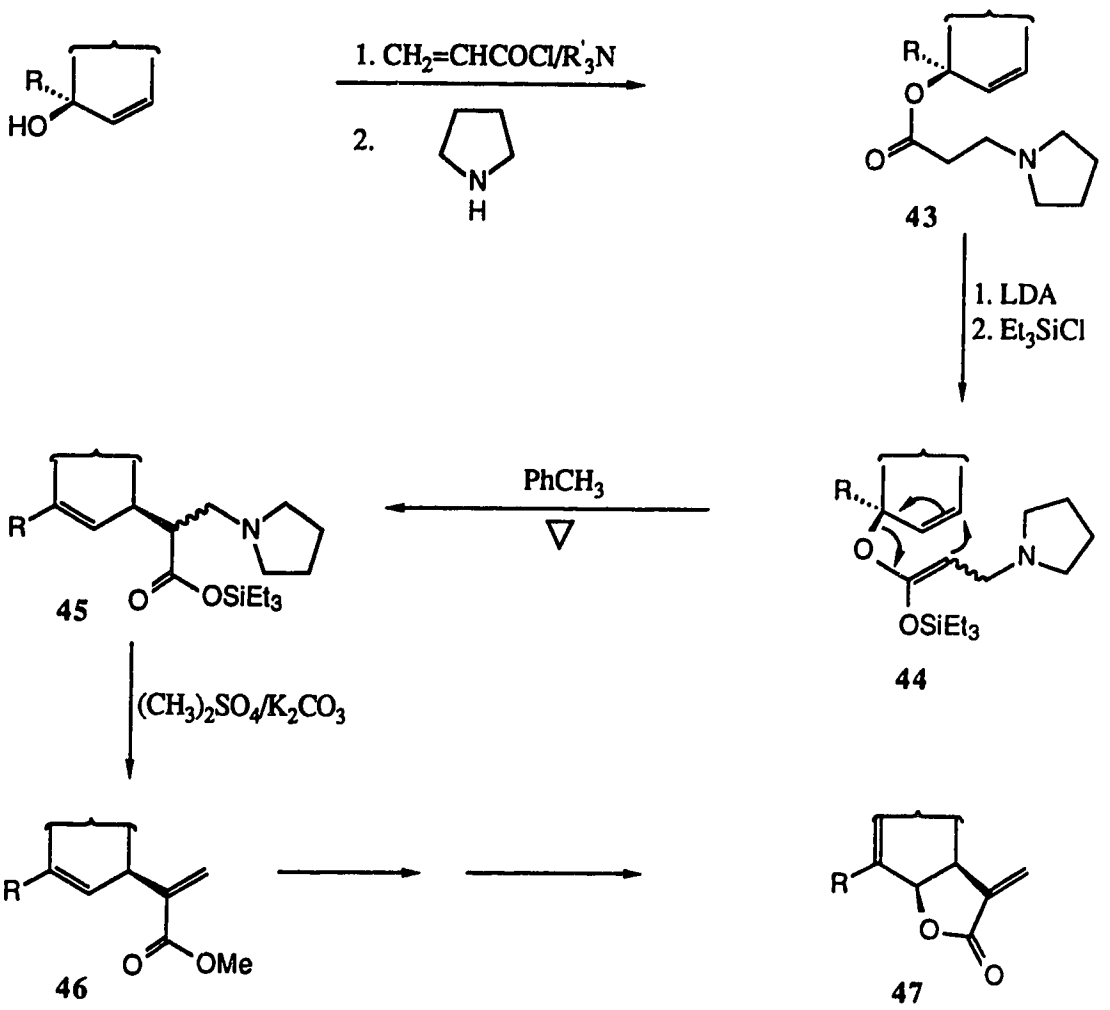
SCHEME 8



Still and Schneider[42] have developed a very interesting approach (Scheme 9) for the synthesis of α-methylene γ,δ-unsaturated acids, substrates for a subsequent lactonization reaction based on the Ireland modification of the Claisen rearrangement. This multi-step route can be performed in a one-pot procedure and involves acylation of an allylic

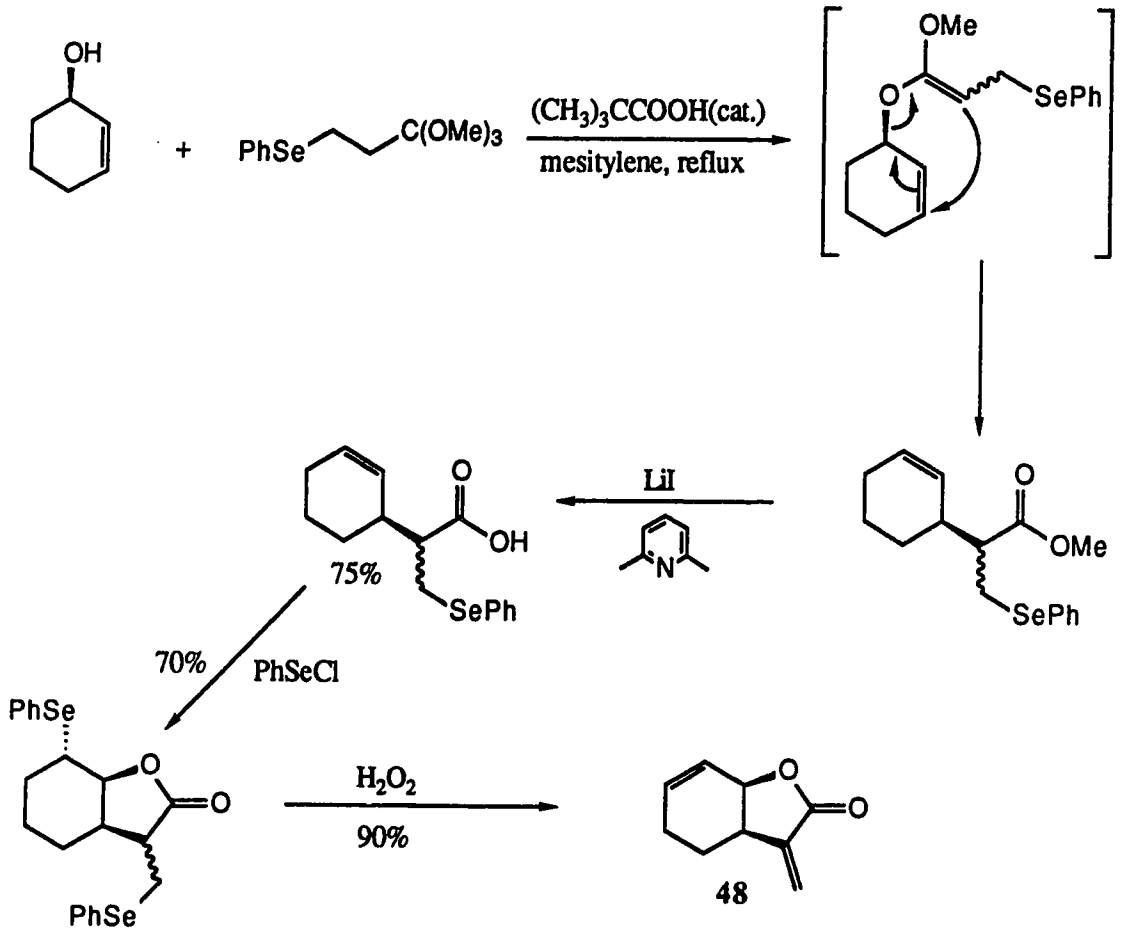
alcohol with acryloyl chloride, and then reaction with pyrrolidine to give the masked acrylate **43**. Conversion of **43** to the corresponding silyl ketene acetal **44** and rearrangement to **45**, promoted by heating in toluene, followed by removal of the protective pyrrolidine group gave **46**. The synthesis was completed by iodolactonization-elimination to the desired lactone **47**.

SCHEME 9



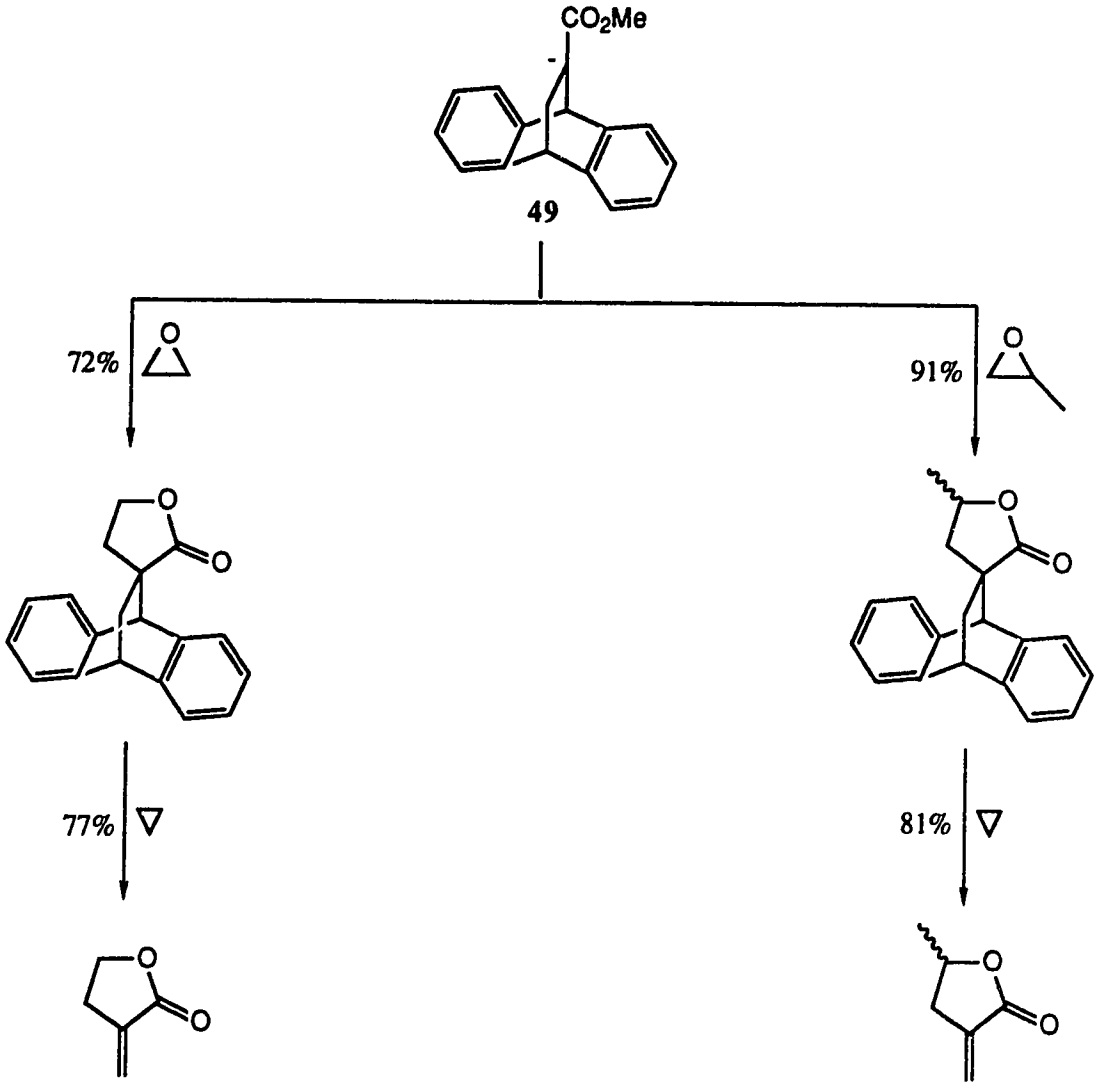
In 1979, Raucher and co-workers[43] applied a procedure strictly related to the previous one, by making use of the Claisen orthoester rearrangement (Scheme 10). This method leads directly to the desired arrangement of carboxyl group and terminal carbon-carbon double bond, i.e., to a γ,δ-unsaturated carboxylic acid or 4-pentenoic acid. Cyclization was accomplished via selenolactonization. Oxidation of the selenium group and spontaneous elimination gave the lactone **48**.

SCHEME 10



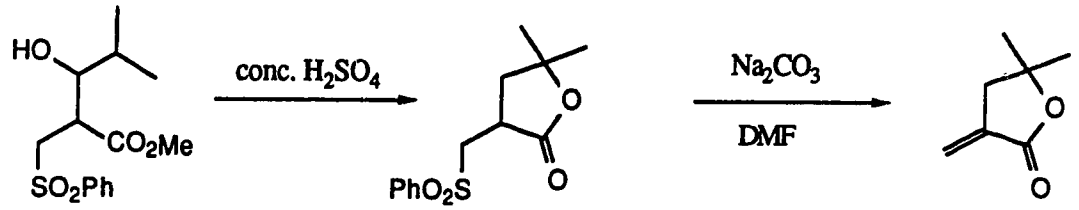
In view of the reversibility of the Diels-Alder reaction, the enolates of Diels-Alder adducts **49** have been employed as masked acrylates.[44] After deprotonation, they react with epoxides at room temperature to give the corresponding lactone adducts. These are then decomposed, by heating, into anthracene and α-methylene γ-butyrolactones (Scheme 11).

SCHEME 11

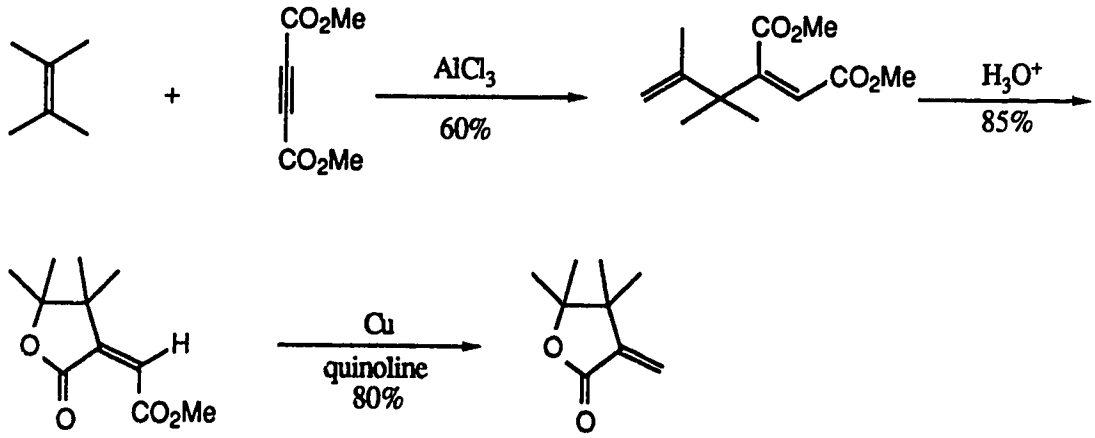


The methods of Shono and co-workers[45] (Scheme 12) and McCulloch and McInnes[46] (Scheme 13) are mechanistically interesting but not generally applicable because of the drastic reaction conditions. The former applies a method for lactone formation described by Dobrev and Ivanov[47] to the synthesis of α-methylene lactones, and the latter (Scheme 13) begins with an aluminium chloride-catalyzed ene reaction[48] of the strongly enophilic dimethyl acetylenedicarboxylate.

SCHEME 12



SCHEME 13

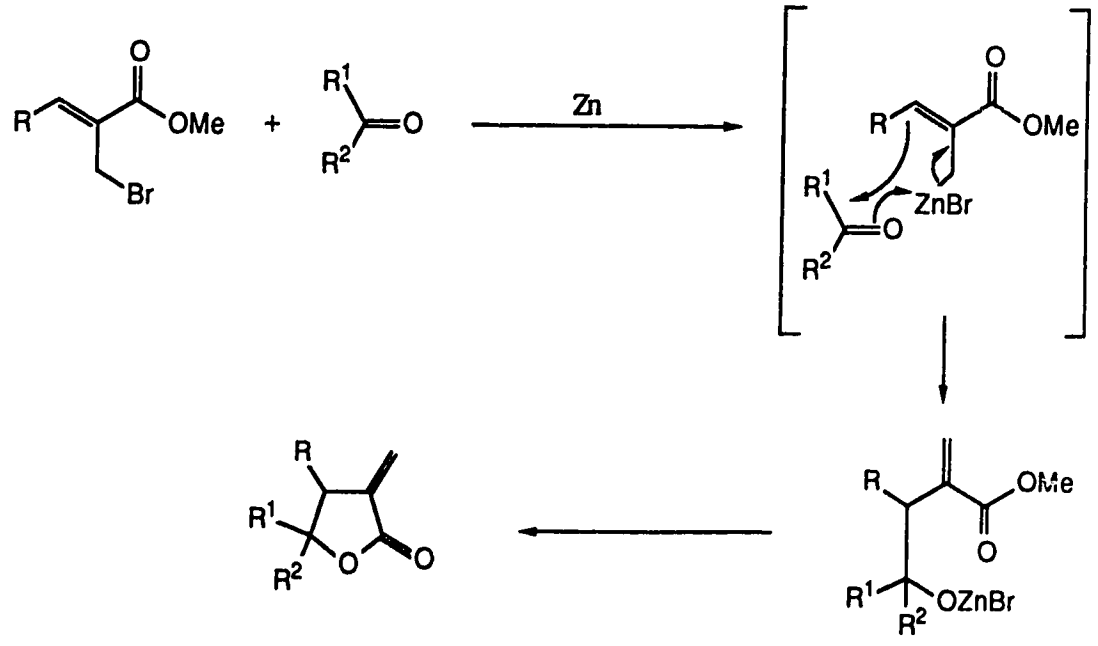


After acid-catalyzed lactonization, the ester function is removed by reductive treatment with copper in quinoline. Since the reduction is only successful for highly substituted five-membered rings, the range of application of the reaction is limited.

D.1.2. Metal-Promoted Reaction of Aldehydes and Ketones with Methacrylate Anions or Equivalents

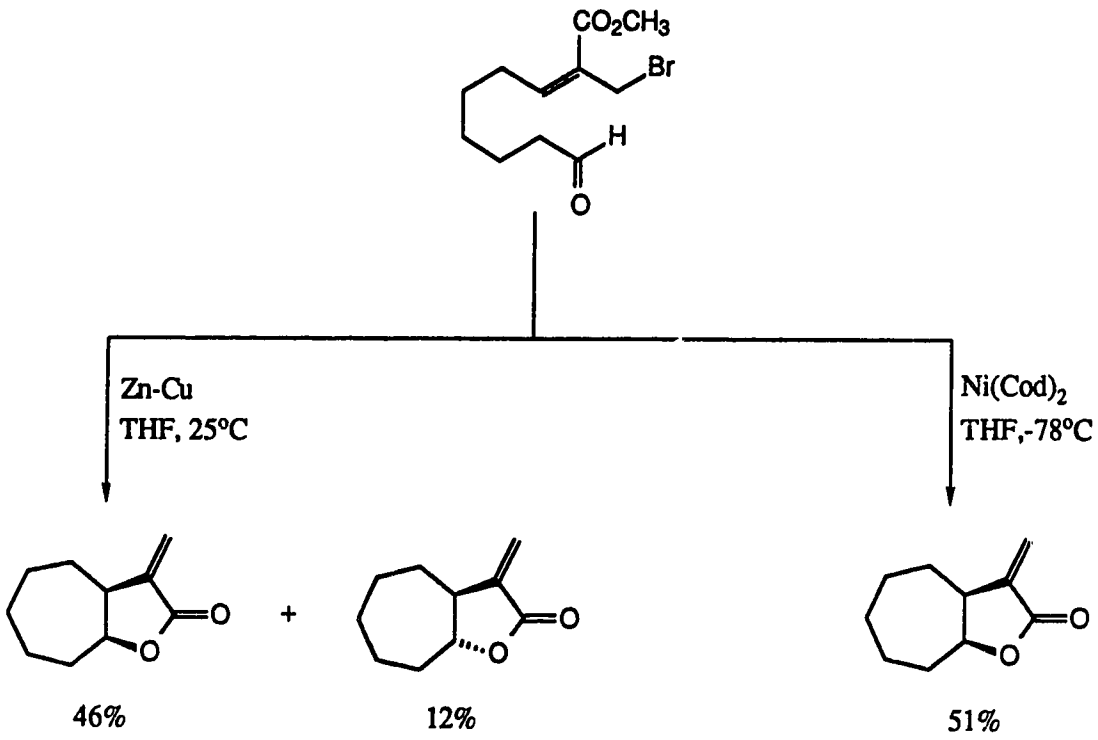
In this method (Scheme 14), developed by Dreiding and co-workers[49] and Schmidt and co-workers,[50] a Reformatzky-type reaction between α-(bromomethyl) acrylic esters and carbonyl compounds is employed, followed by lactonization using a simple, one-step technique. The so-called Dreiding-Schmidt reaction has been very useful in the synthesis of monocyclic and spiro α-methylene lactones.[10,51]

SCHEME 14



A useful strategy for the simultaneous construction of the α-methylene lactone unit and a carbocyclic ring (Scheme 15), starting from an acrylic substrate, involves the intramolecular coupling of an allylic metal species with an aldehyde unit, followed by spontaneous lactonization.[52]

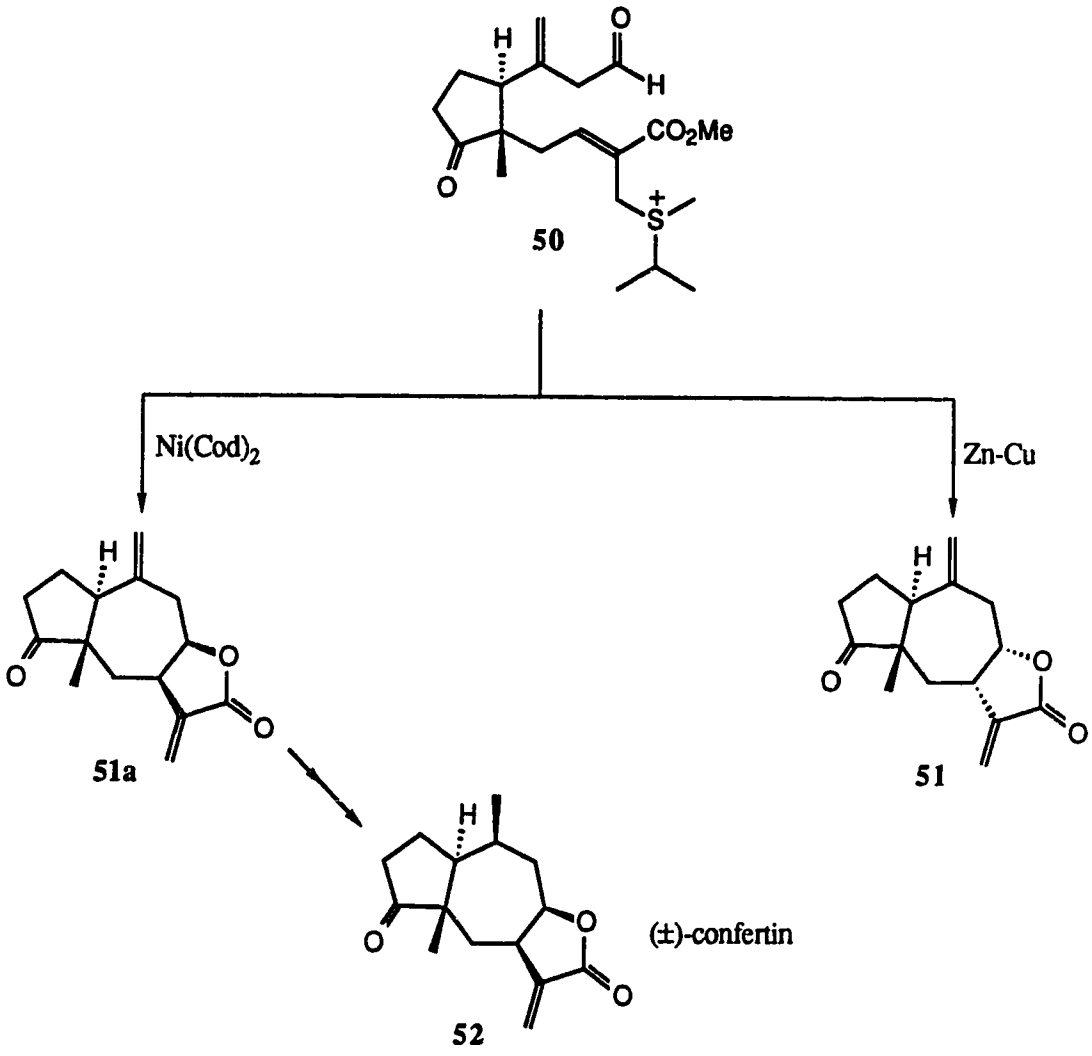
SCHEME 15



In this fashion, Semmelhack and co-workers[53] successfully synthesized (±)-confertin **52** in 1978 (Scheme 16) employing a sulfonium salt **50** instead of a bromide. They obtained the isomer **51** by zinc-promoted cyclization, whereas

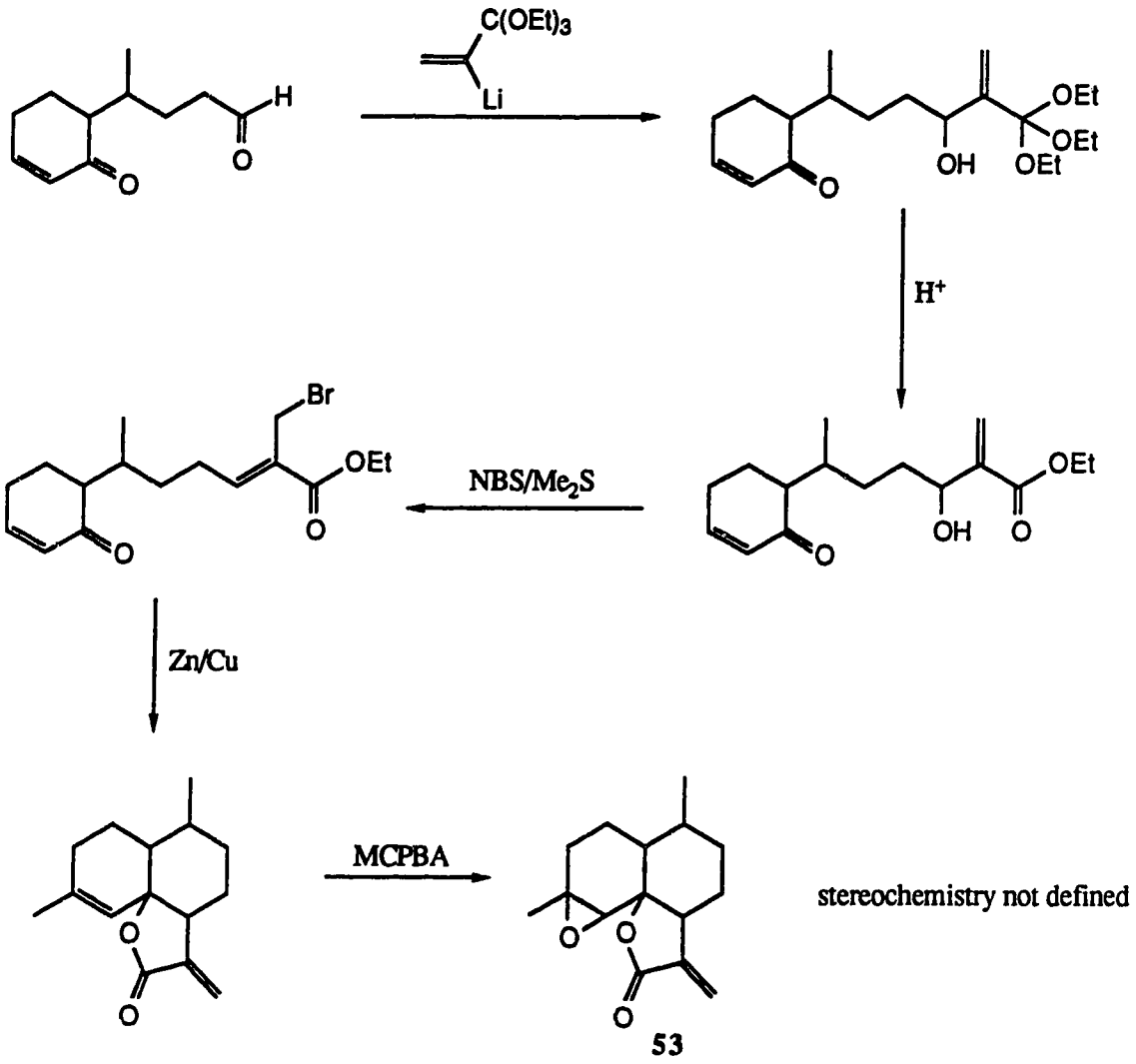
nickel-promoted cyclization yielded the isomer **51a** with the appropriate configuration to carry on the next step.

SCHEME 16



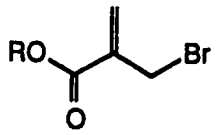
Dreiding and co-workers[54] have also used metal-promoted cyclization to synthesize compounds of the arteanuin type **53** (Scheme 17).

SCHEME 17

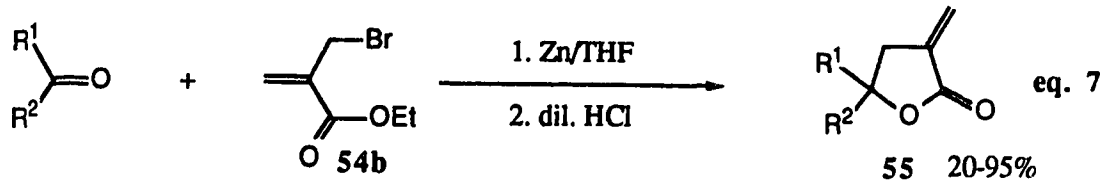


Perhaps the most important building blocks in the synthesis of γ-monosubstituted and γ,γ-disubstituted α-methylene γ-butyrolactones are the 2-(bromomethyl) acrylic ester **54a** and the ethyl ester **54b**. The synthesis of **54a** and **54b** have been reported[55] in three and two steps, respectively. Benezra and co-workers,[10] starting from **54b**, have

reported the synthesis (eq. 7) of more than thirty lactones (**55**),[55] some of which are structurally quite complex.



54 a; R = Me
b; R = Et
c; R = H

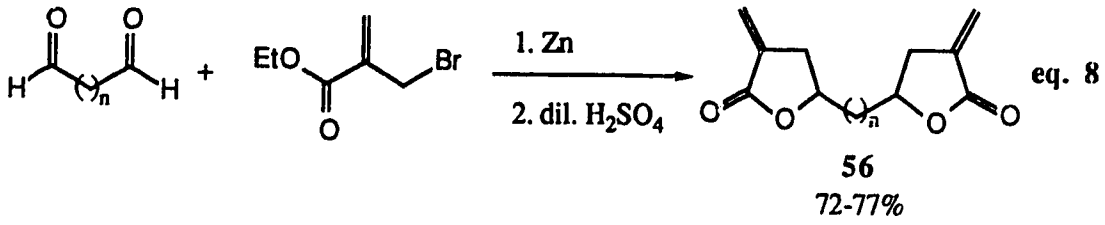


54b

55 20-95%

eq. 7

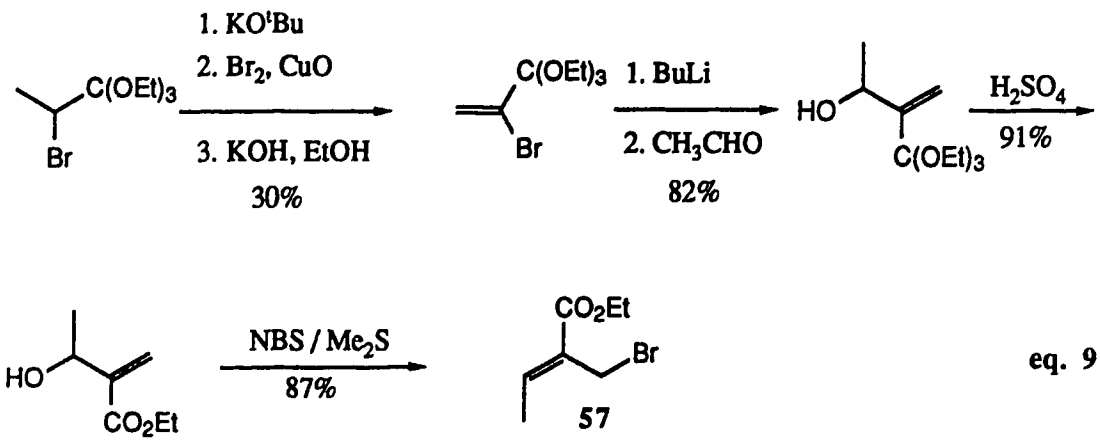
In the same fashion, Cassady and co-workers[56] have prepared bislactones **56** from dialdehydes (eq. 8). Others have reported similar work.[29,57]



56
72-77%

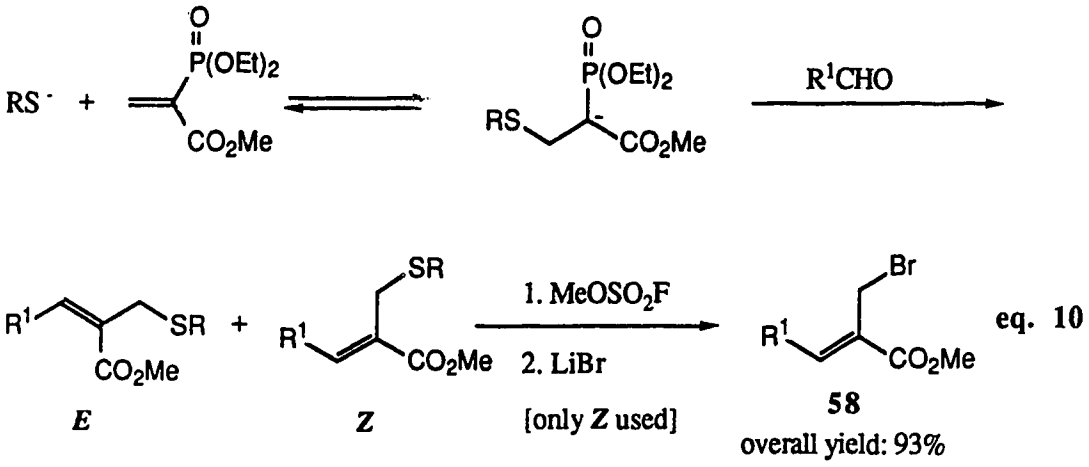
eq. 8

A problem in the metal-promoted cyclization to give bicyclic α-methylene lactones lies in the synthesis of the functionalized methacrylic acid used as starting material. Dreiding and Goldberg[58] have synthesized the substituted allyl bromide **57** in several steps as shown in eq. 9.



eq. 9

The synthesis of the allylic sulfur compound **58**, used by Semmelhack and co-workers,[59] also requires several steps and is not (*Z*)-selective. The last step (see eq. 10), conversion of the allylic sulfide into the bromide **58**, required extensive development work.

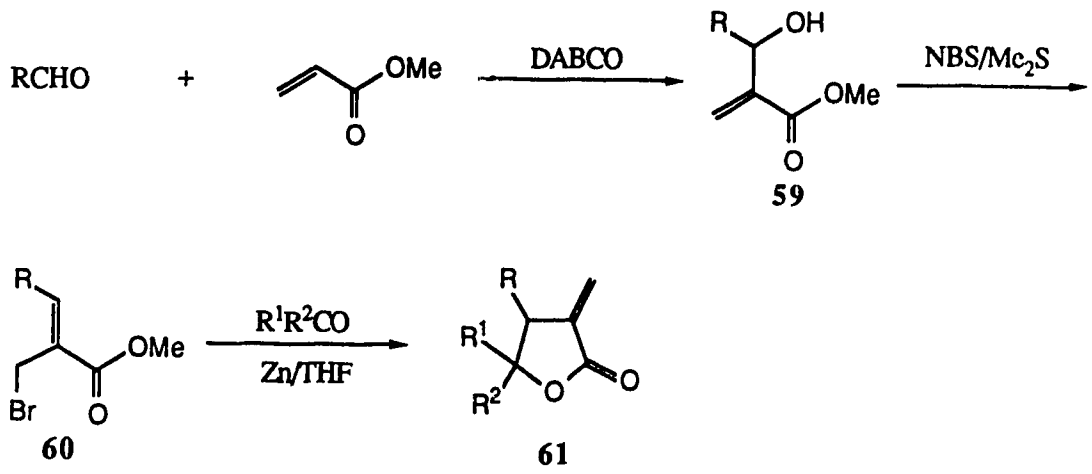


eq. 10

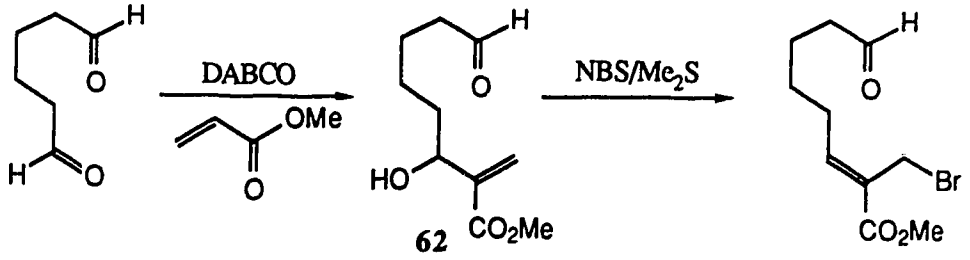
In connection with the synthesis of a wide range of allylic alcohols and their precursors, which are further functionalized on the central carbon atom,[60] Hoffmann and

Hennig[60] have used DABCO-catalyzed coupling of acrylic esters and aldehydes to yield **59** (Scheme 18), which, in turn was used to prepared allylic bromides **60** in excellent yields, via replacement of the hydroxyl group by bromine accompanied by allylic rearrangement.[61] Metal-induced coupling of **60** with carbonyl compounds allowed ready access to β-substituted α-methylene lactones **61**.

SCHEME 18



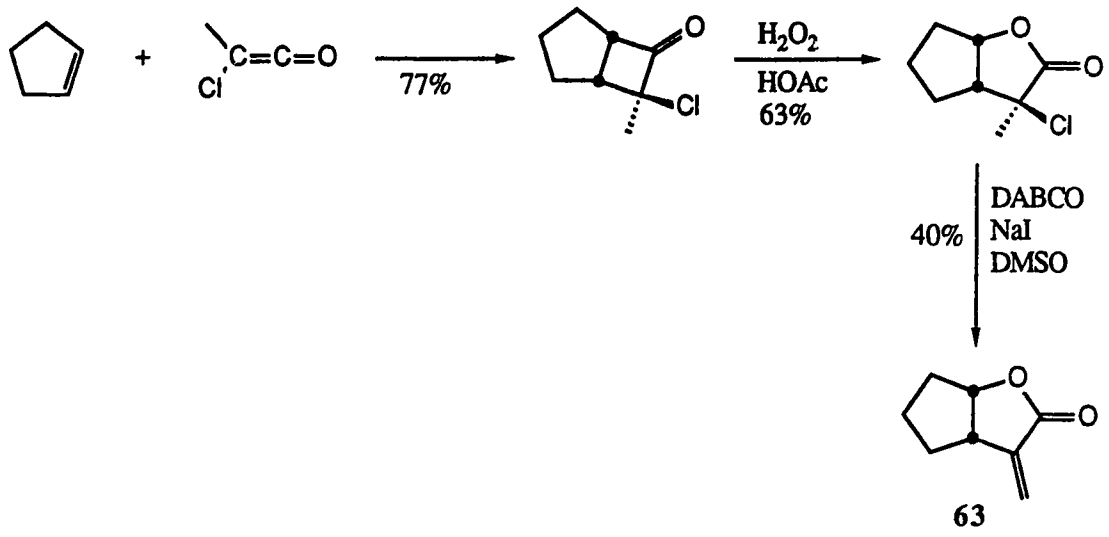
Similarly, acrylic ester **62** can be manipulated as shown and in high yield even in the presence of an additional aldehyde group.(eq. 11).



eq. 11

There are only a few examples of the synthesis of α-methylene butyrolactones by Baeyer-Villiger oxidation.[62] The approach, shown in Scheme 19, begins with a [2+2]-cycloaddition of halo ketenes to reactive double bonds to form a functionalized cyclobutanone. Baeyer-Villiger oxidation, which occurs regioselectively, and subsequent elimination of hydrogen halide, yields the desired lactone **63**. It remains to be seen whether this route can be applied to the synthesis of natural products. A limitation of the cycloaddition step is that only *cis*-fused lactones can be formed.

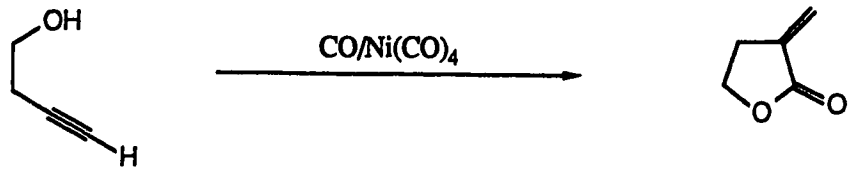
SCHEME 19



63

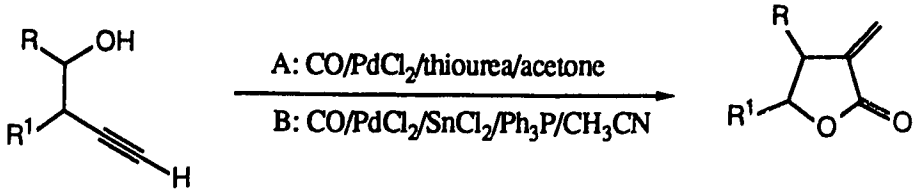
D.1.3. Cyclocarbonylation Reactions

An attractive approach for the synthesis of α-methylene lactones is the ring closure of ethynyl alcohols with carbon monoxide, a process commonly named cyclocarbonylation. The first example of cyclocarbonylation was the low yield conversion of 3-butyn-1-ol into α-methylene lactone (eq. 12) by means of nickel tetracarbonyl, reported in 1950.[63]



eq. 12

In 1975, Norton and co-workers[64] successfully introduced a palladium(II)-catalyzed cyclocarbonylation procedure employing palladium(II) chloride and thiourea in acetone as solvent. Later in 1981, a comparison of catalytic systems showed that palladium(II) chloride with one equivalent of anhydrous tin(II) chloride and two equivalents of a tertiary phosphine in dry acetonitrile is a superior system[65] (eq. 13). Mechanistic studies[66] indicated that the reaction

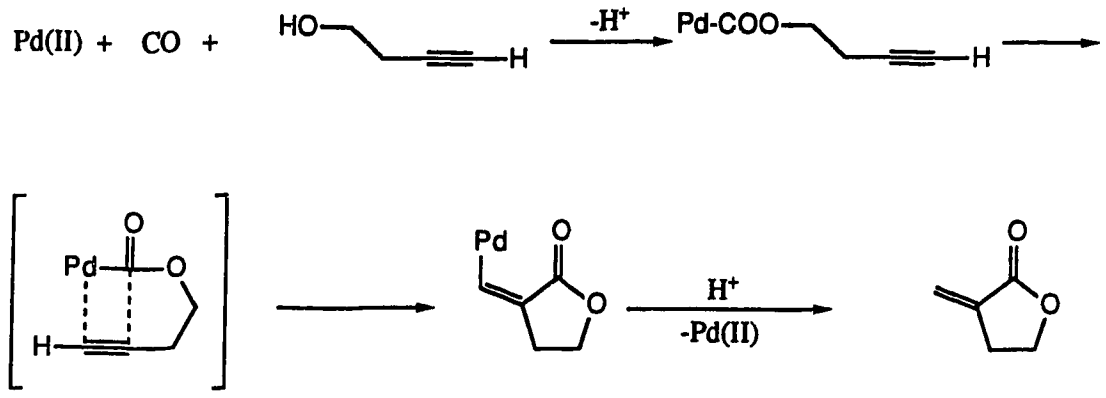


eq. 13

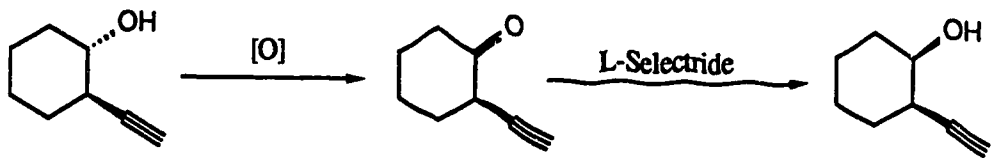
	method	yield %
$R = R^1 = H$	A	21
	B	31
$R, R^1 = -(CH_2)_4-$	A	53
	B	85

starts (Scheme 20) with formation of an alkoxycarbonyl species from palladium(II), carbon monoxide, and the acetylenic alcohol, followed by intramolecular acetylene insertion (*cis* addition to the triple bond). Protonolysis of the resulting vinyl-palladium bond completes the sequence as shown in Scheme 20.

SCHEME 20



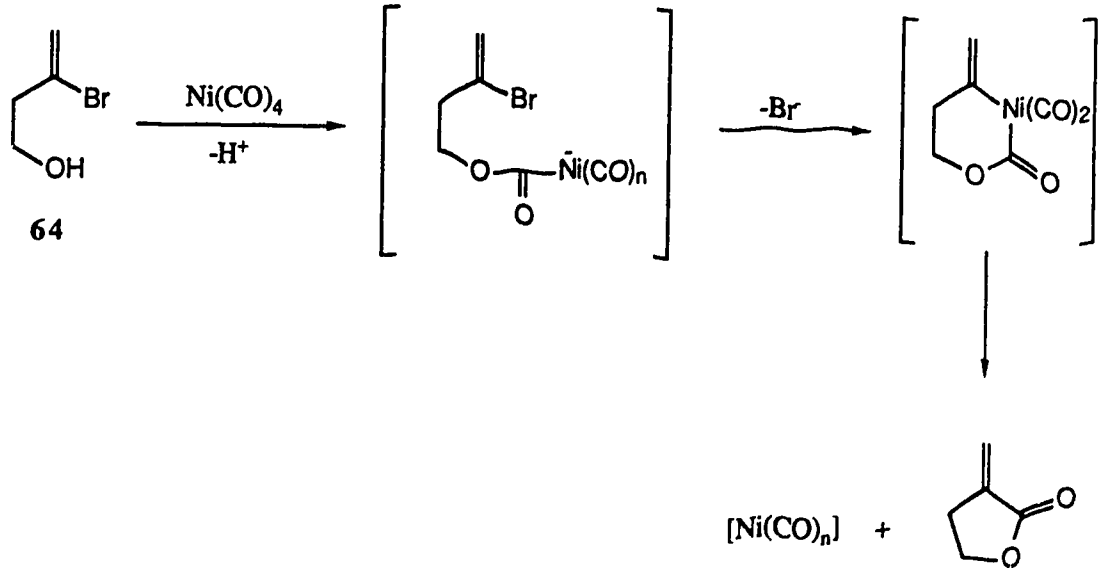
Trans-2-Ethylcycloalkanols have been prepared by ethynylation of epoxides, and are potential general substrates for lactonization reactions catalyzed by Pd(II) and leading to *trans*-fused α-methylene lactones. The same catalytic procedure can be applied to *cis*-2-ethynylcycloalkanols giving *cis*-fused α-methylene lactones. The starting materials are easily prepared by submitting the *trans*-isomer to an oxidation/reduction sequence as illustrated in eq. 14.



eq. 14

Hydroxy-substituted vinyl halides are also suitable starting materials for cyclocarbonylation. In recent years a variation[67,68] of the intramolecular version of the transition metal-catalyzed carbonylation originally described by Corey and Hegedus[69] has been used for the synthesis of α-methylene lactones. Zero-valent transition metal compounds, usually of nickel or palladium, function as catalysts and reagents. Scheme 21 shows the proposed mechanism[68] of the nickel-induced reaction, in which the bromo homoallylic alcohol **64** has been employed as the starting compound.

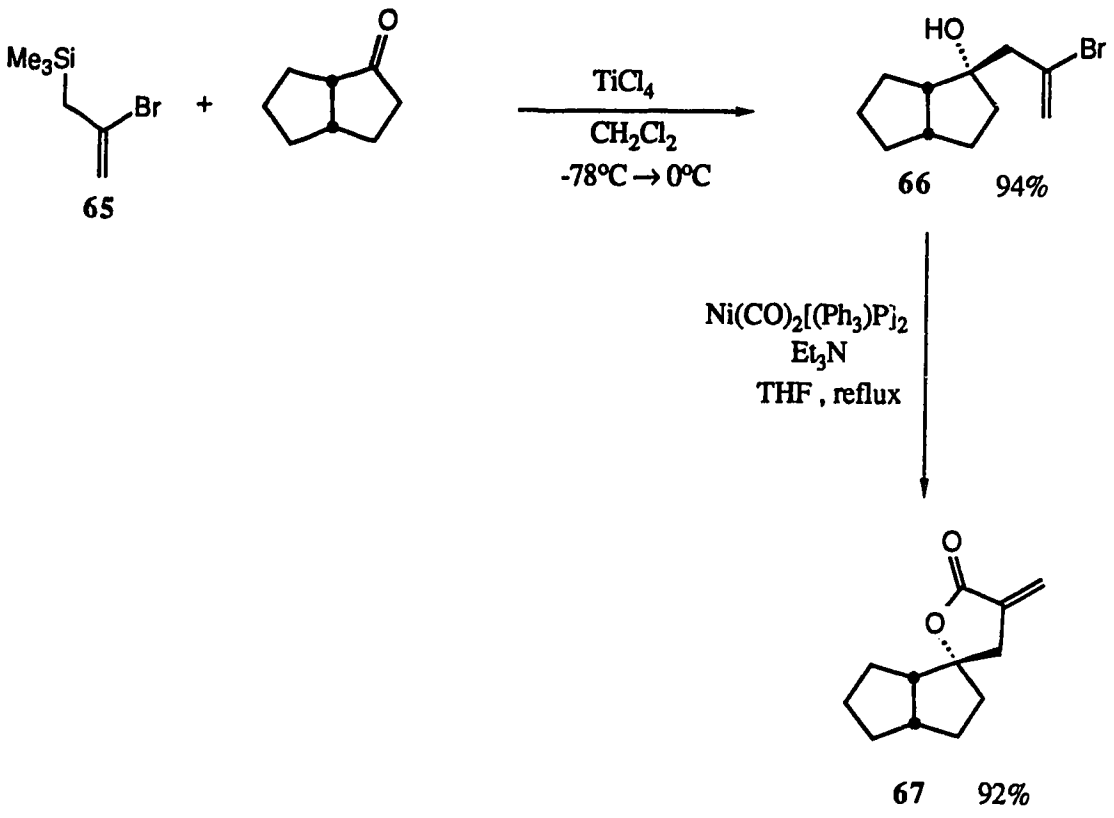
SCHEME 21



Semmelhack and Brickner[68] have shown that better results are obtained using $Ni(CO)_2[(C_6H_5)_3P]_2$ in the presence of triethylamine instead of nickel tetracarbonyl.

Routes to α-methylene lactones using transition metal-catalyzed carbonylation have been explored in many laboratories and the key intermediate is the functionalized homoallylic alcohol[66] which is required for insertion of the carbonyl group.[67,70] An illustrative example is Trost's[71] route to the tricyclic spiro α-methylene lactone **67**, which is formed stereoselectively and in high yield (Scheme 22).

SCHEME 22

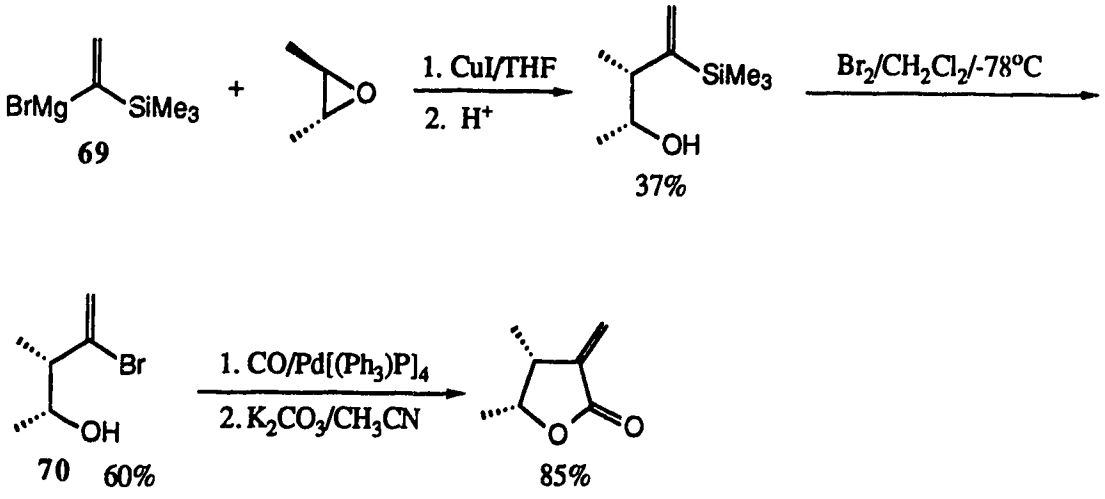


The Grignard reagent derived from **65** can also be combined with epoxides to establish the desired 1,4-relationship of functional groups[38] such as in **66** (see also Scheme 6). The possibility of storing the carbanion reactivity of **65**, while selectively activating the allyl silane (with titanium tetrachloride) and subsequently metallating the bromide (with magnesium), makes **65** a valuable equivalent for the hypothetical dianion **68**.

68

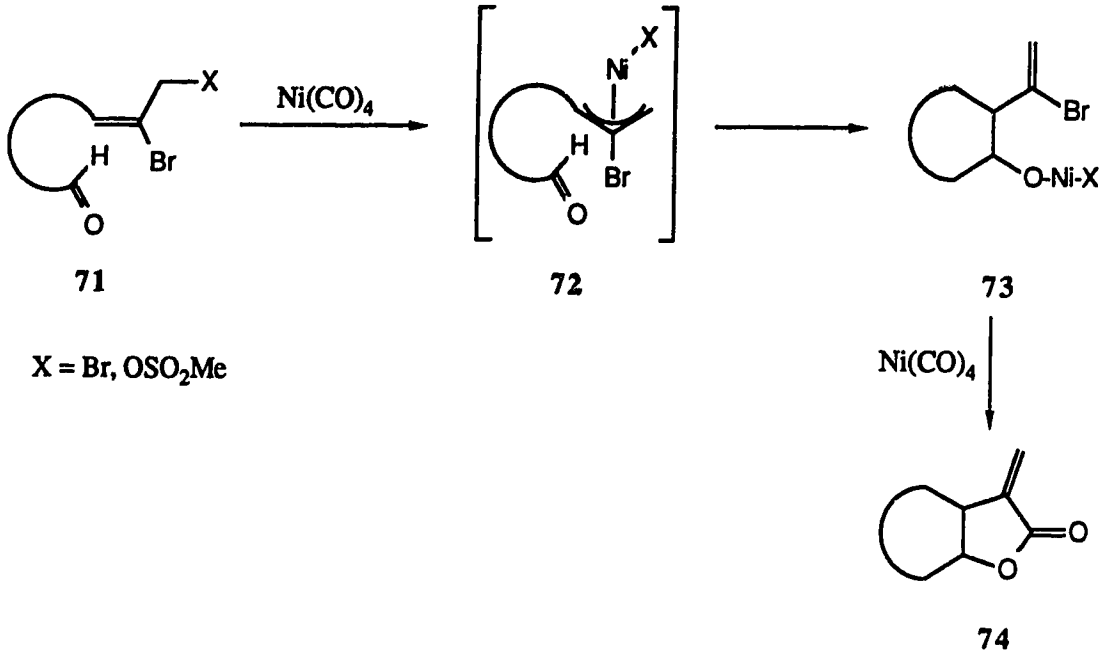
Stille and Martin[72] have employed the vinylic Grignard compound **69** for reaction with epoxides in order to obtain, after further transformation, the desired homoallyl bromide **70** required for carbonylative cyclization[72] (Scheme 23).

SCHEME 23



In 1981 Semmelhack[73] developed a combination of intramolecular coupling[52] (Scheme 15) with cyclocarbonylation of hydroxylated vinyl bromides. The procedure is illustrated in Scheme 24.

SCHEME 24

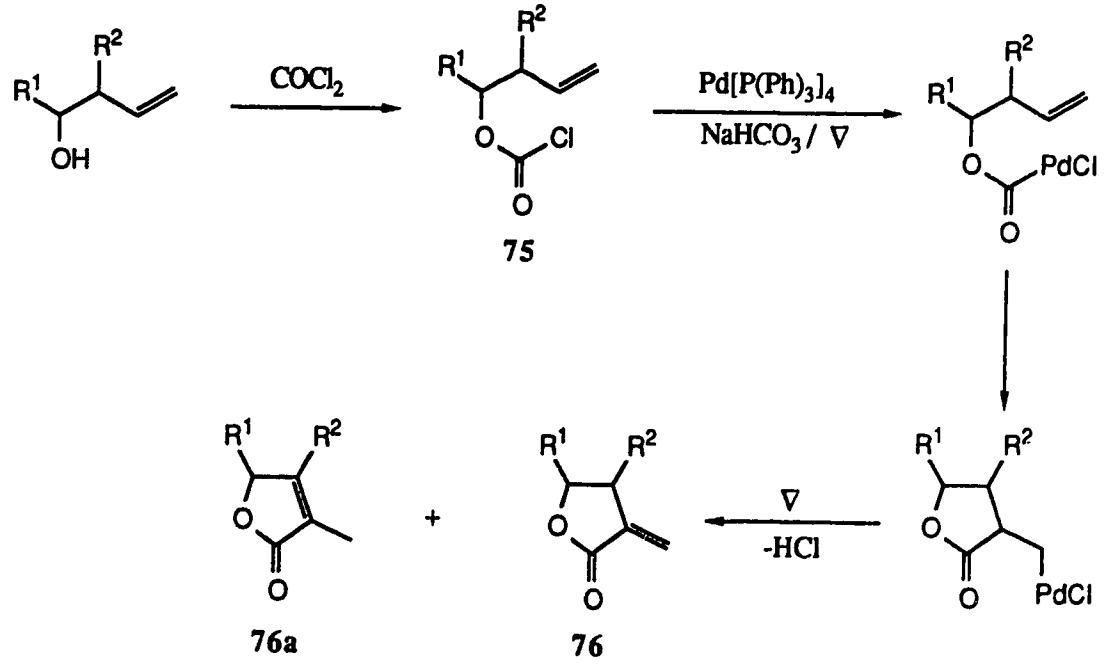


The allylic system in **71** can first be activated as the π-allyl nickel complex **72** and cyclized with the aldehyde function to give **73** (potentially a *cis/trans* mixture). In the next step, nickel tetracarbonyl functions as a carbonylating reagent to form the α-methylene lactone **74**. The yield of **74** is very poor (X = Br, 9%; X = CH_3-SO_2-O-, 2%), the major product being **73** (ONi-X = OH). More complete

conversion to the final product **74** was achieved (58%) upon long heating (95 h at 65°C) of **71** (X = CH_3-SO_2-O-) with periodical addition of nickel tetracarbonyl. Experimentally, a very high selectivity is observed for the formation of a *cis*-fused lactone as well as for the syn-orientation of the lactone ring with respect to the angular methyl group[73] (see later, Scheme 41). The reasons for these stereochemical results are not yet clear.

In 1983, Henin and Pete[74] presented a variant of the transition metal-catalyzed cyclization using carbonochloridates **75**, prepared from the corresponding alcohols and phosgene, to furnish α-methylene lactones **76** in accordance with Scheme 25. Compound **76a** is also obtained when the

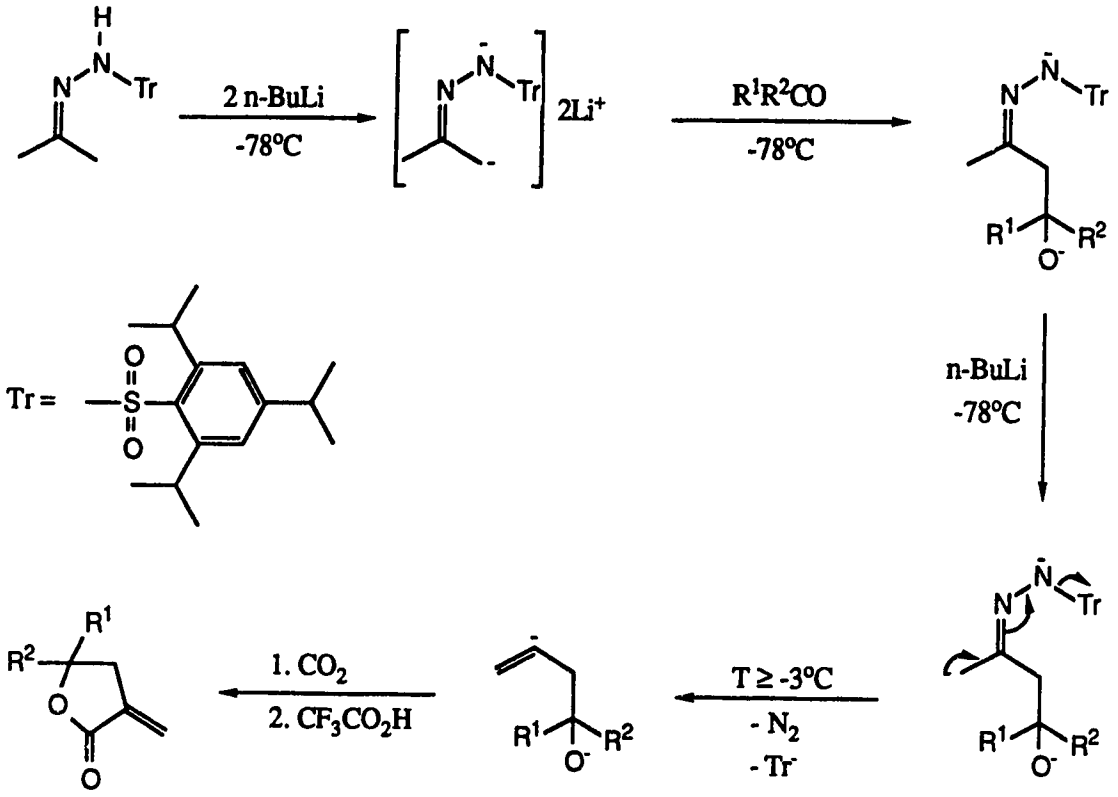
SCHEME 25



catalyst is not associated to triphenylphosphine, otherwise **76** is formed exclusively.

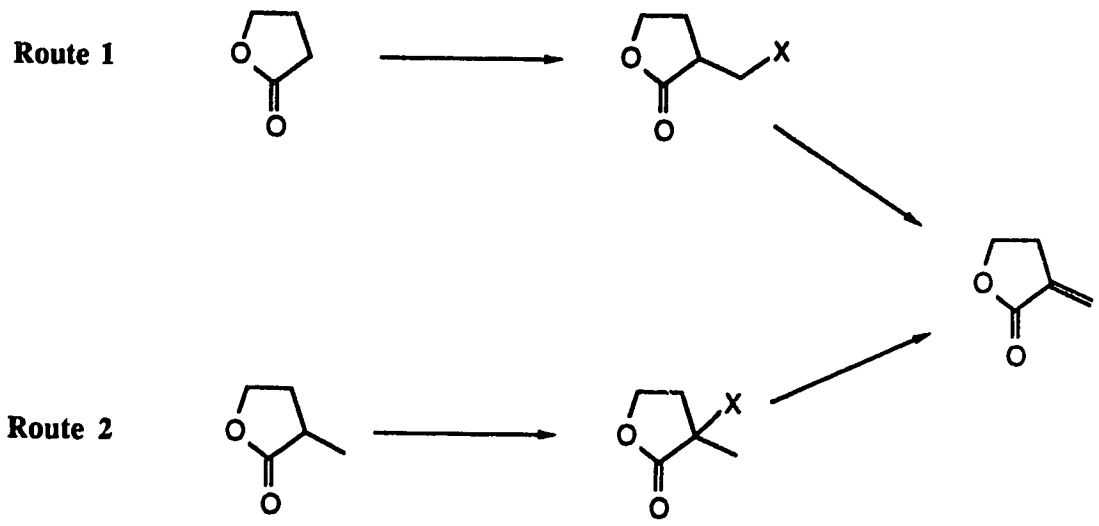
A further variant is the insertion of carbon dioxide, according to Barrett et al.,[75] via Shapiro reaction, in which case carbon dioxide functions as CO unit (Scheme 26). This reaction sequence requires strongly basic conditions, which are not always tolerated by highly functionalized molecules.

SCHEME 26



D.2. α-Methylenation of Preformed γ-Butyrolactone Rings

The incorporation of the α-methylene group into a preformed lactone has been used for many years in the synthesis of α-methylene γ-lactones. The introduction of a leaving group and subsequent elimination to generate the α-methylene moiety can be done by two different routes:



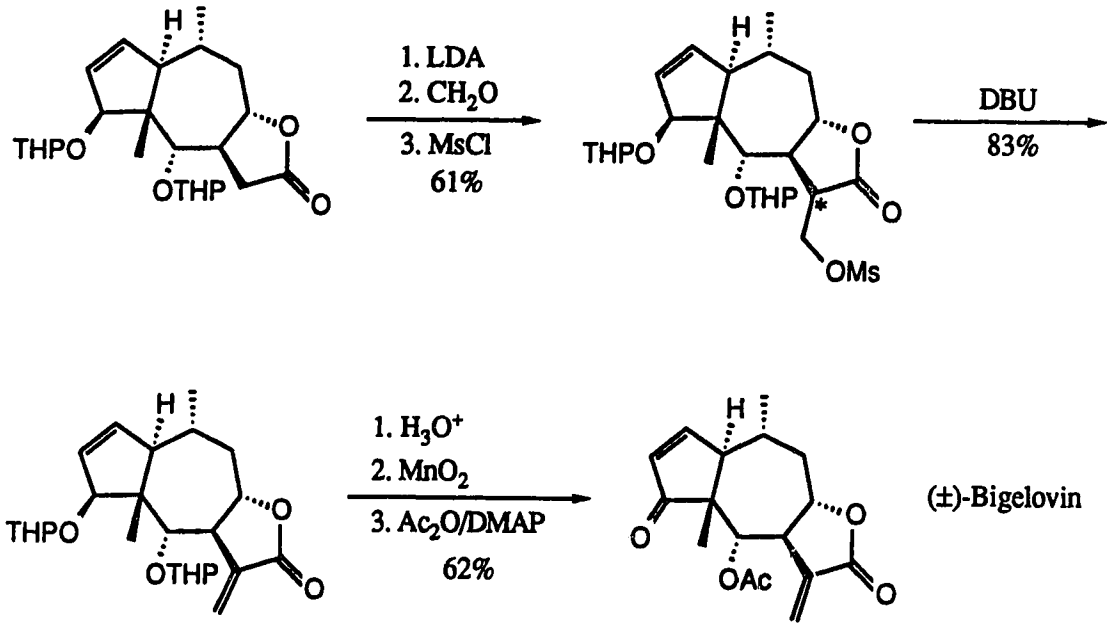
Route 1 is better because, in route 2, the introduction of a leaving group α to the carbonyl and subsequent elimination can lead either to an exocyclic double bond or an endocyclic double bond, or a mixture of both.[76]

In contrast, a leaving group placed β to the carbonyl group (route 1) avoids the possibility of formation of an endocyclic double bond.

Two methods are used most frequently at present to place the leaving group β to the carbonyl:

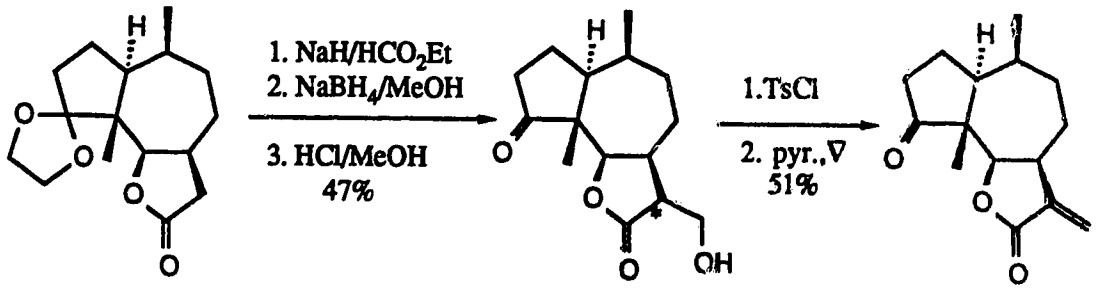
1. The lactone is converted into the enolate and subsequently trapped with formaldehyde to give the hydroxymethyl derivative. Alternatively, the anion is trapped with formic esters and reduced to the hydroxymethyl derivative. After conversion of the hydroxy group into a tosylate or mesylate, elimination is easily carried out with a base. The two methods can be illustrated in the following examples of the synthesis of (±)-bigelovin[77] (Scheme 27) and of (±)-damsin[78,79] (Scheme 28).

SCHEME 27



* stereochemistry not known

SCHEME 28

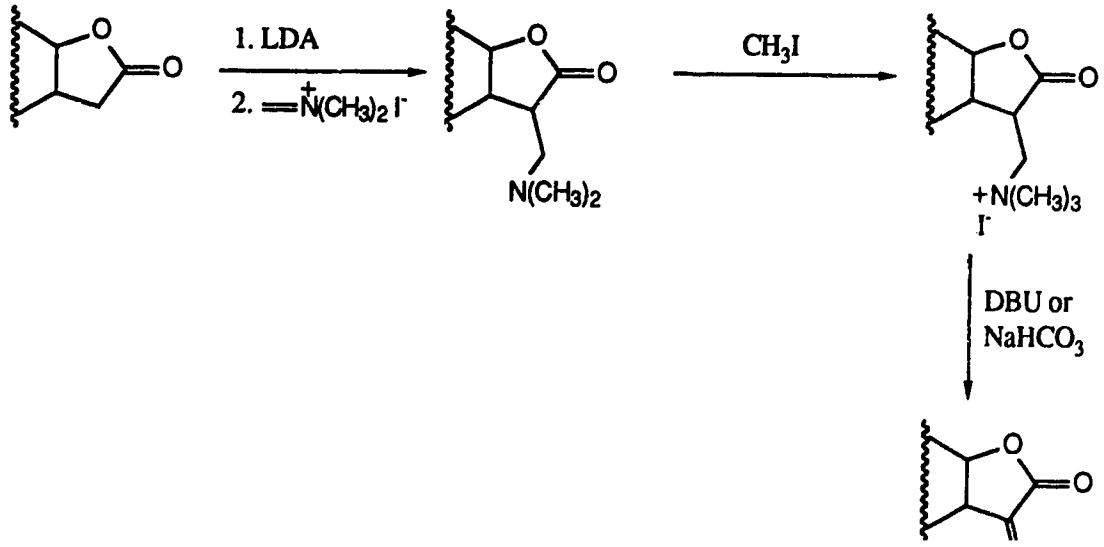


(±)-Damsin

* stereochemistry not known

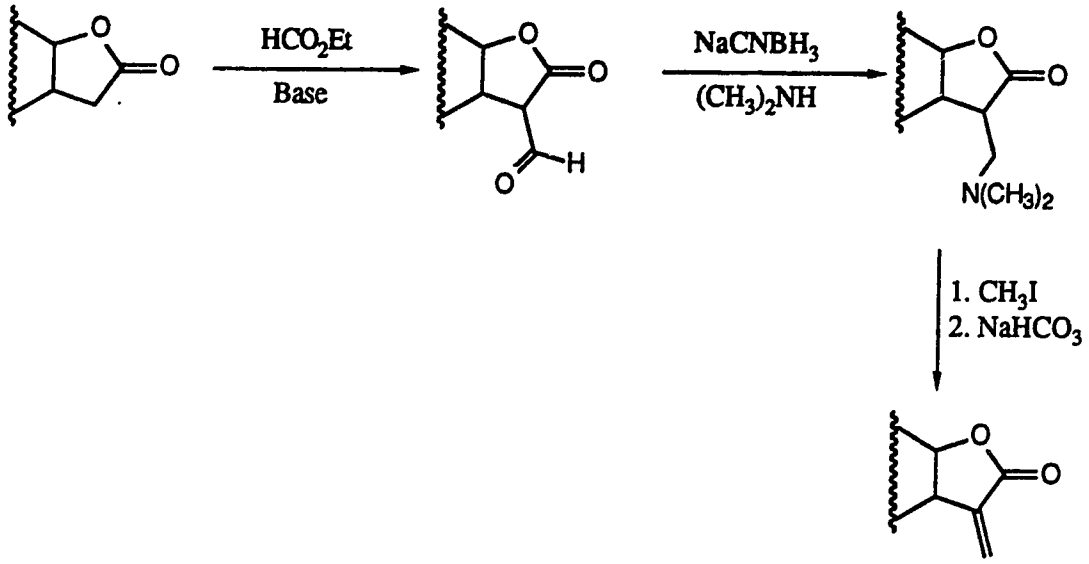
2. Another valuable method for introducing the α-methylene substructure uses the trialkylammonium unit as a leaving group. This can be introduced by trapping the enolate of the lactone with the Eschenmoser reagent. After quaternization of the nitrogen, elimination affords the double bond[80] (Scheme 29).

SCHEME 29

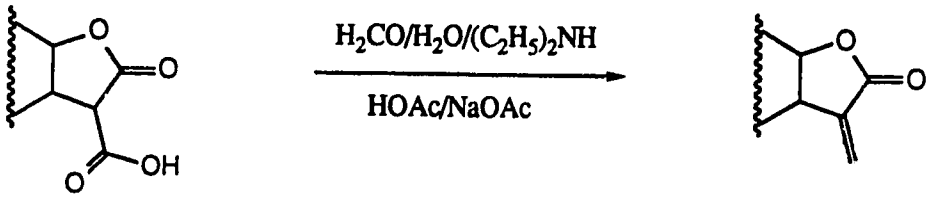


Several α-methylene γ-lactones were synthesized by the reductive amination of α-formyl lactones with sodium cyanoborohydride and dimethylamine[81] (Scheme 30).

SCHEME 30



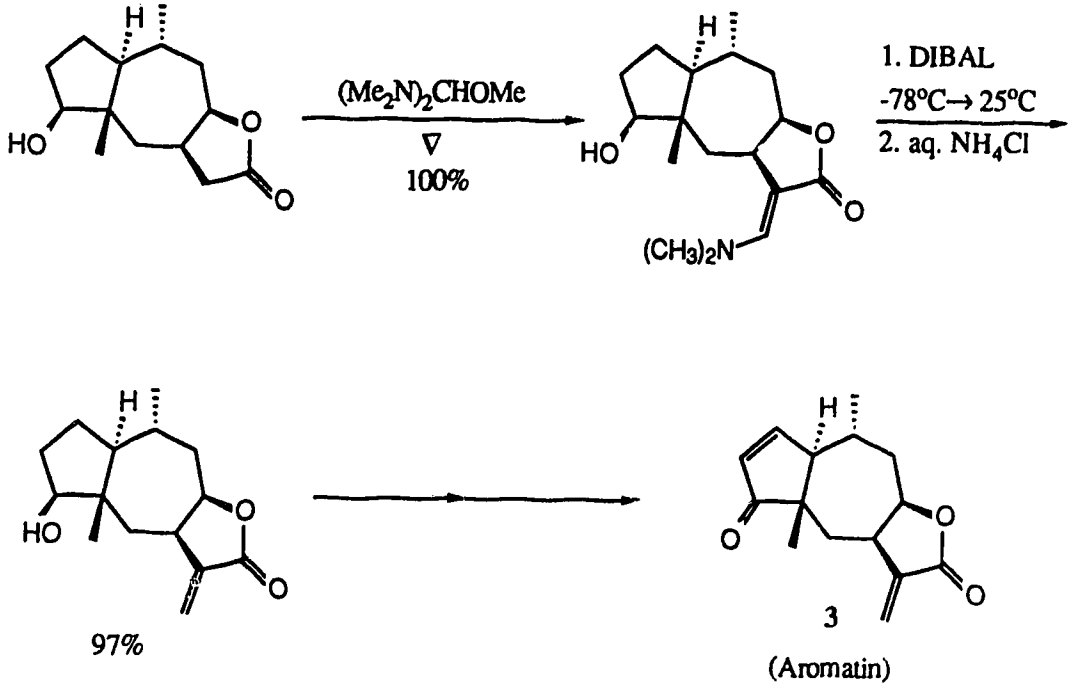
In a number of examples, the exocyclic double bond has been introduced α to the lactone ring by means of a decarboxylative methylenation reaction[82] as illustrated in eq. 15.



eq. 15

A disadvantage of many methods described so far is the need for strong bases for generating the lactone enolate. In this respect the introduction of the Bredereck reagent[83] by Ziegler et al.[84] has brought about an improvement. Using this reagent (Scheme 31), one prepares the vinylogous carbamate in the first step. This is reduced to the α-methylene γ-lactone selectively and in high yield with diisobutylaluminum hydride. The use of strong bases, which are otherwise necessary for generating the lactone enolate, is thus avoided.

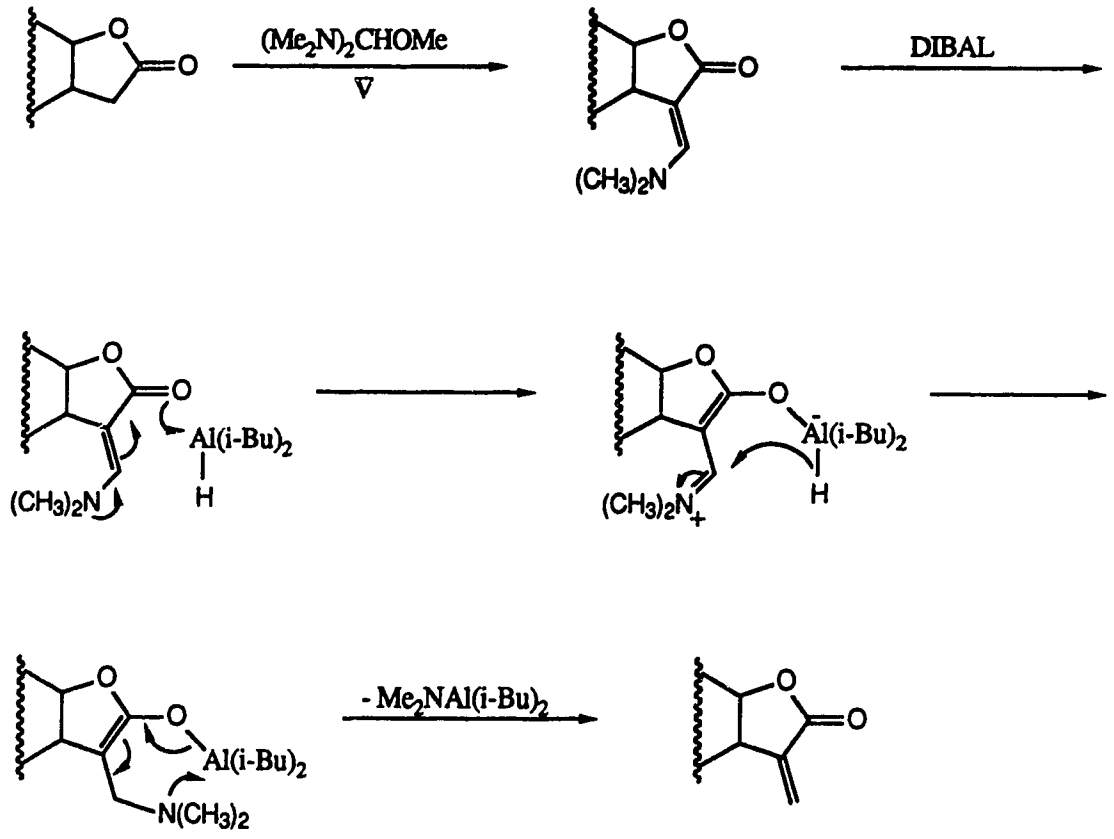
SCHEME 31



The reaction mechanism proposed[32c] (Scheme 32) suggests that deuteration of the methylene position should be feasible by

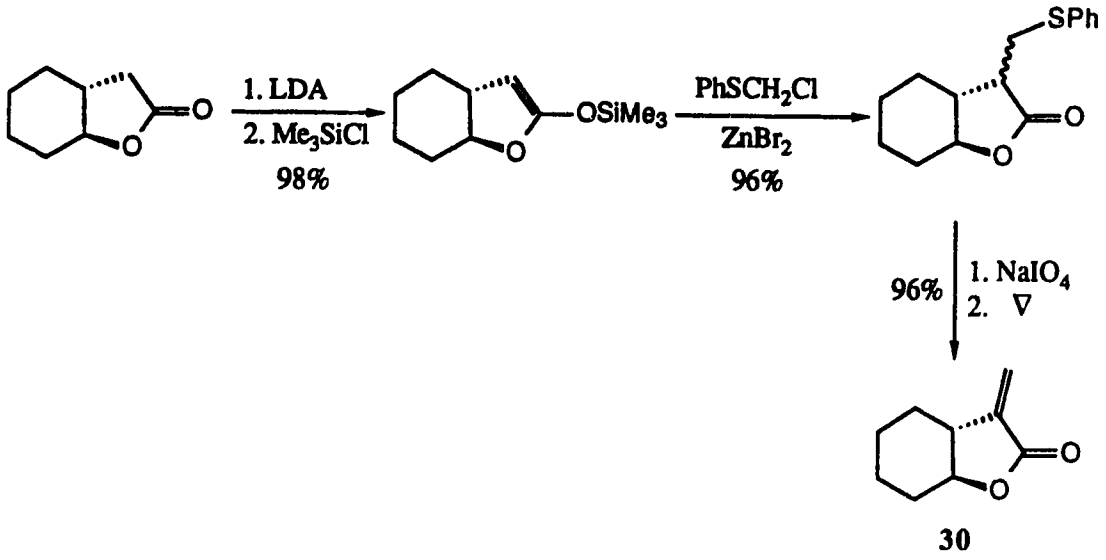
reduction of the vinylogous carbamate with diisobutylaluminum deuteride, but this does not appear to have been tried.

SCHEME 32



Sulfur and especially selenium have also served as leaving groups. The following synthesis (Scheme 33), in which sulfur is incorporated in the exocyclic β-position was described by Paterson and Fleming.[85] The sulfur is removed, after being oxidized to the sulfoxide, by a pericyclic reaction promoted by heating.

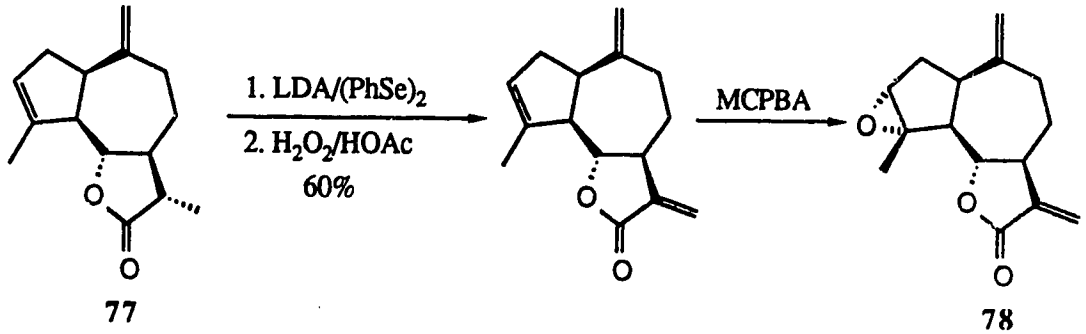
SCHEME 33



30

The incorporation of the phenylseleno group in **77** via electrophilic diphenyl diselenide and its elimination to give the *exo*-double bond are illustrated below in the synthesis of estafiantin[86] **78** (Scheme 34).

SCHEME 34



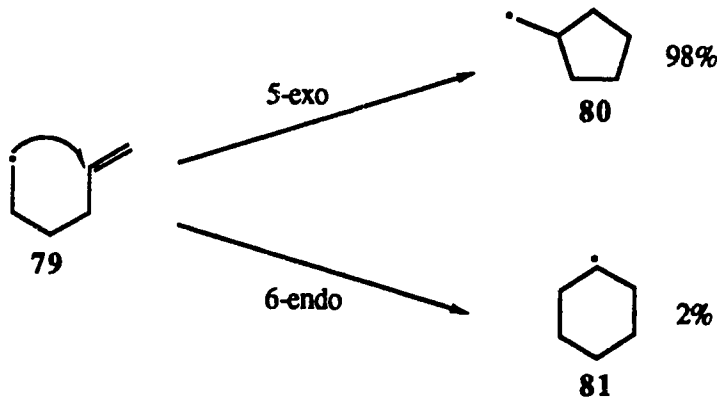
77 **78**

D.3. Radical Cyclization Routes to α-Methylene γ-Butyrolactones

The formation of a carbon-carbon bond in the construction of the α-methylene γ-butyrolactone unit can also be brought about by means of free radical chemistry. This approach has recently become the subject of a great deal of interest among synthetic organic chemists. The appeal of the approach is due in part to the mild conditions under which free radical reactions take place and to the convenience of avoiding the use of protecting groups that are often required in ionic chemistry.

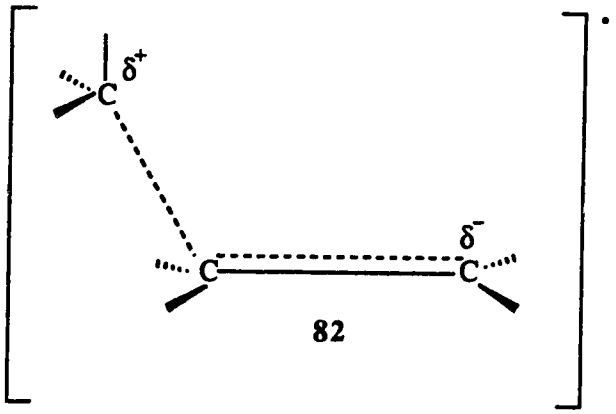
The use of radical cyclization to elaborate the α-methylene γ-butyrolactone unit depends primarily on the design of efficient routes to the radical precursors, a subject which will be dealt with later in this section. Before proceeding with synthetic details, a brief summary of the basic principles involved in free radical cyclization will be given.[87]

The basic reaction is ring closure of the 5-hexenyl radical **79** (eq. 16), which was first generated in solution in 1963.[88] This reaction has since been studied in detail and is widely accepted as a mechanistic probe to detect 5-hexenyl radical species.[89] Ring closure of **79** leads almost exclusively to cyclopentylmethyl radical **80** via the 5-*exo* mode. The preferred formation of a less stable primary radical, rather than a secondary radical resulting from 6-endo closure, is due to an efficient overlap between the



eq. 16

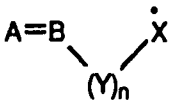
semi-occupied 2p (SOMO) orbital of the radical and the π* orbital of the olefin in the transition structure **82**.[90] Consequently, the transition structure must have three participating atoms at the vertices of an obtuse triangle orthogonal to the nodal plane of the π-system. Inspection of



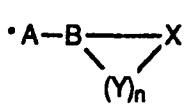
82

models and calculations[90] reveal that such a disposition of centers can be much more readily accommodated in the transition state for 1,5-closure of **79** (leading to **80**) than for 1,6-closure (leading to **81**). Both processes, however, are allowed by Baldwin's rules.[91] A consequence of this stereoelectronic control is that less stable primary radical

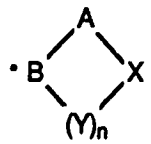
80 is formed faster than the thermodynamically more stable secondary radical **81**. Beckwith has proposed the following statements about the regiochemistry of cyclization: The *exo*-ring closure (**79** → **80**) will be kinetically favoured over the *endo*-ring closure (**79** → **81**) for those radicals where Y (see **83**) is part of a chain of up to 5 atoms (n ≤3), A=B is any double (or triple) bond and X represents a C, O or N center. When the chain is short (n = 1,2) the transition state for the *endo* process is very highly strained; however, when the chain is long the system will be more flexible and so the difference in strain energy between the transition state leading to **84** and **85** will be small. Consequently, in those cases the *degree* of preference for *exo* over *endo* closure will be less pronounced.



83



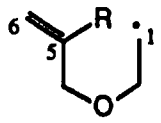
84



85

The rate of closure and the regioselectivity are altered by any structural feature which affects the ability of the unsaturated radical to accommodate the triangular transition structure. A case in point is provided by the 3-oxa-5-hexenyl systems (**86a** and **86b**) undergo, which ring closure much faster than their hexenyl analogues and display a

greater preference for the 5-*exo* mode. This has been attributed[89c] to the fact that the minimum C(1)-C(5) distance



86a, R = H
86b, R = CH_3

in radical **86a** is less than it is in the 5-hexenyl system, while the C(1)-C(6) distance is greater.[89c] Similar conclusions can be made regarding chains which contain a nitrogen atom.

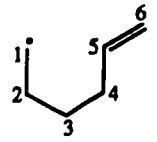
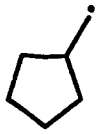
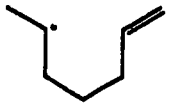
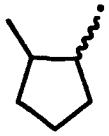
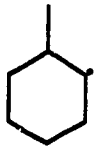
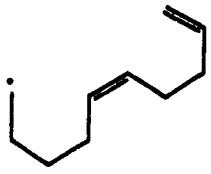
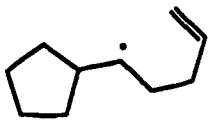
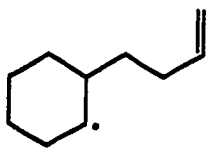
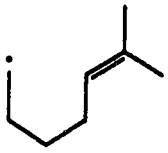
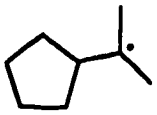
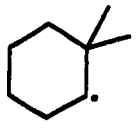
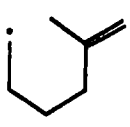
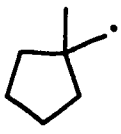
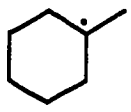
The preference for *exo* over *endo* closure may be inverted sterically or by inducing reversibility. For the 5-hexenyl radical, alkyl substituents at the 1- or 6-position have little effect on rate and/or regiochemistry; however, substitution at the 5-position can cause preference for *endo* closure.[92] Table **1**[89e] provides examples and relative rate data for the effects of substitution. Substituents at the 2-, 3-, or 4- positions are also found to enhance the rate of *exo* closure. It can be seen, for example, that closure of radical **87** (eq. 17) has a rate constant almost ten times larger than that of its unsubstituted analogue.

The Thorpe-Ingold or gem-dialkyl effect[93] has been invoked to explain this observation in the following way: In the ground state, the presence of two methyl substituents in

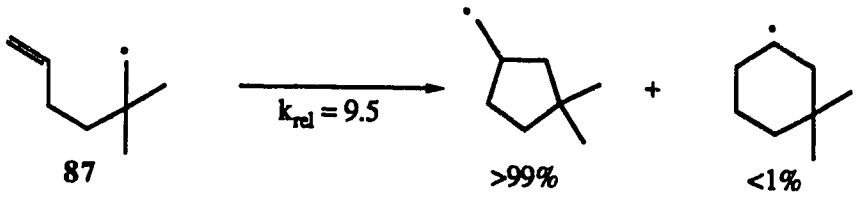
87 causes more *gauche* interactions than those present in the unsubstituted case. However, there is a smaller difference

TABLE 1[89e]

Relative rate values for $k_{1,5}$ and $k_{1,6}$ at 20°C

Starting Radical	1,5-exo	1,6-endo	$k_{1,5}$	$k_{1,6}$
			1.0	0.02
			1.4	0.02
			1.4	0.007
			2.4	0.011
			0.022	0.04

in the number of *gauche* interactions between the two cases in the cyclic transition state. The rate of ring closure in the substituted case is therefore enhanced since the free energy of the reactant ground state is raised relative to that of



87 >99% <1% eq. 17

the cyclic transition state in comparison to the unsubstituted one. Therefore, the $\Delta H^{\ddagger}$ for ring closure is effectively lower when there are substituents at C(2), C(3) or C(4) of the chain.[94] The effect is less pronounced in the case of monosubstitution.

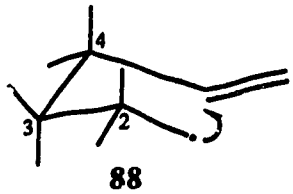
The observed stereoselectivity in radical closures of 5-hexenyl and similar systems has been summarized in the following two guidelines published by Beckwith:[90]

(1) 1- or 3- substituted radicals preferentially give *cis*-disubstituted cyclopentyl products.

(2) 2- or 4- substituted radicals give mainly *trans*-disubstituted cyclopentyl products.

The explanation for this behavior is illustrated in structure **88**, which represents one conformation of the 5-hexenyl radical before closure. It can be seen that the conformation resembles the chair form of cyclohexane. At

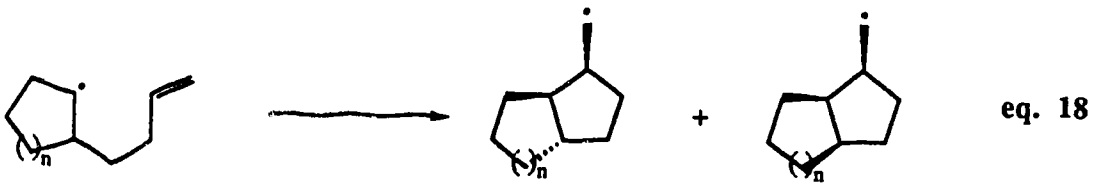
C(2), C(3), and C(4) axial and equatorial positions are clearly distinguishable and so the most favored conformation



88

will be that in which the substituents are equatorial. An equatorial substituent at C(3) will then necessarily lead to a *cis* product while one at either C(2) or C(4) will produce a *trans* compound.

The guidelines discussed above cannot be fully applied to the formation of bicyclic products, but in these cases the experimental results can usually be rationalized by using the same steric and stereoelectronic arguments on which the guidelines are based. For example, in the ring closure of butenyl cycloalkyl radicals **89a** and **89b** (eq. 18), which may be regarded formally as 1,2 disubstituted hexenyl systems, the *anticipated* major products antecipated from the above guidelines are **90a** and **90b**, where the newly-formed radical



89a; n = 1
89b; n = 2

90a
90b

91a
91b

eq. 18

is *cis* to the formal 1-substituent and *trans* to the formal 2-substituent. The actual major products are, however, the all *cis* compounds **91a** and **91b**. This observation conflicts with the guidelines but, from inspection of models, Beckwith[90] suggests that overlap of the semi-occupied orbital (SOMO) and the π^* orbital is more readily attained when **89b** reacts through the conformation containing the substituent in a pseudo-axial position.

Use of these general principles for prediction of the observed regio- and stereochemistry in *intra*molecular radical cyclizations is extremely valuable for synthetic applications.

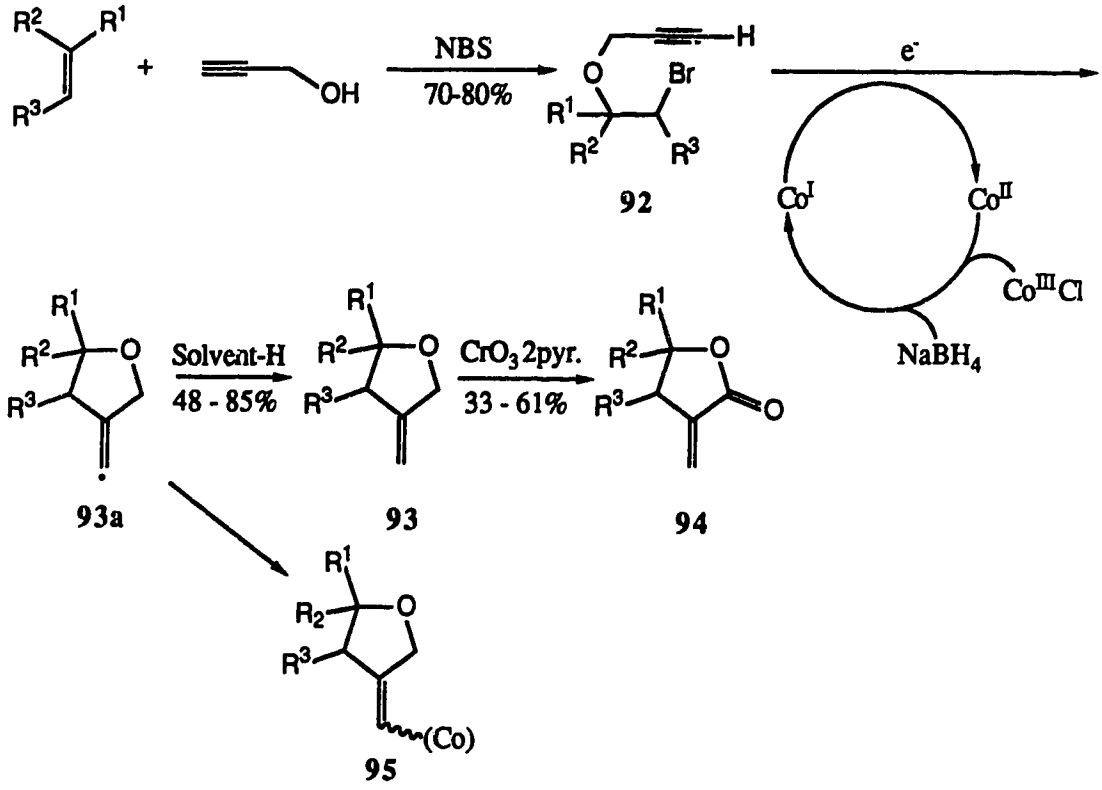
D.3.1. Radical Closure of Acetylenic Ethers and Acetals

In previous sections of this introduction, α-methylene γ-butyrolactones were mostly elaborated by ionic means. Here, I will provide a few examples which have so far been developed for the construction of the α-methylene γ-butyrolactone unit using free radical technology.

In 1982, Tada and co-workers[95] showed (Scheme 35) that radicals generated from 2-[(2-propynyl)oxy]ethyl bromides **92** undergo radical cyclization onto the triple bond in a regio- and stereoselective manner to afford cyclic ethers **93**, which were further oxidized to the corresponding α-methylene γ-butyrolactones **94**.

The radical precursors **92** are readily assembled by treatment of the corresponding olefins with 2-propynol and *N*-bromosuccinimide. The cyclic ethers are then assembled by homolysis of the C-Br bond in a single-electron transfer process[96] (SET) via oxidation of cobaloxime(I) to cobaloxime(II) by the bromides **92**. The cobaloxime(I) is

SCHEME 35

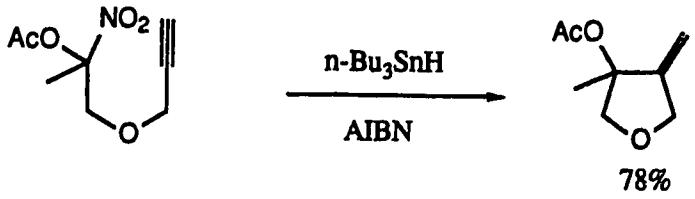


generated in situ by reduction of a catalytic amount of chlorocobaloxime(III)[97] with sodium borohydride. Thus, the formation of **95** can be avoided due to the low concentration

couple with radical **93a**.

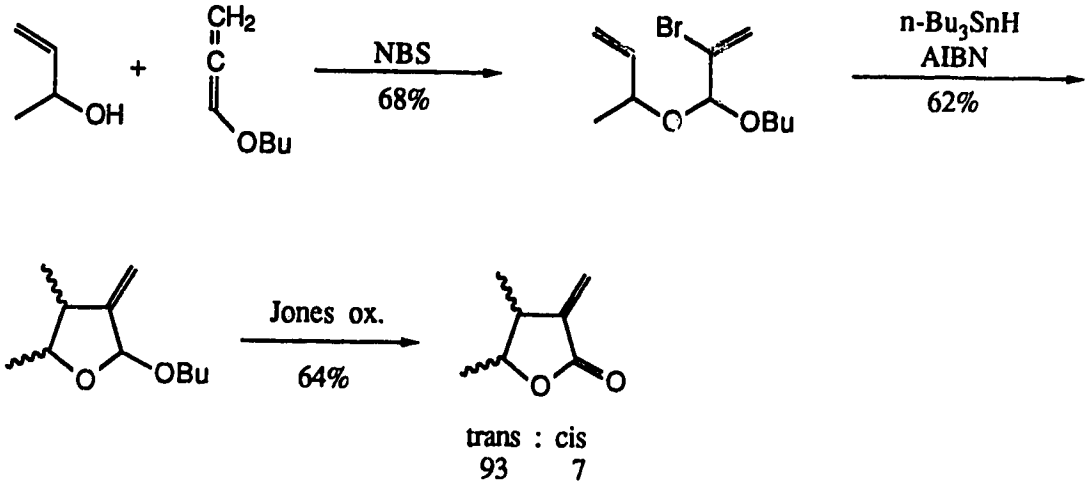
Ono and co-workers[98] used a nitro compound to obtain a cyclic ether in reasonable yield (eq. 19).

Ueno[99] has employed vinyl bromoacetals as precursors to α-methylene γ-butyrolactones. He prepared the starting materials using a similar method to that described above (Scheme 35). However, Ueno used an alkoxy allene rather than an olefin (Scheme 36).



eq. 19

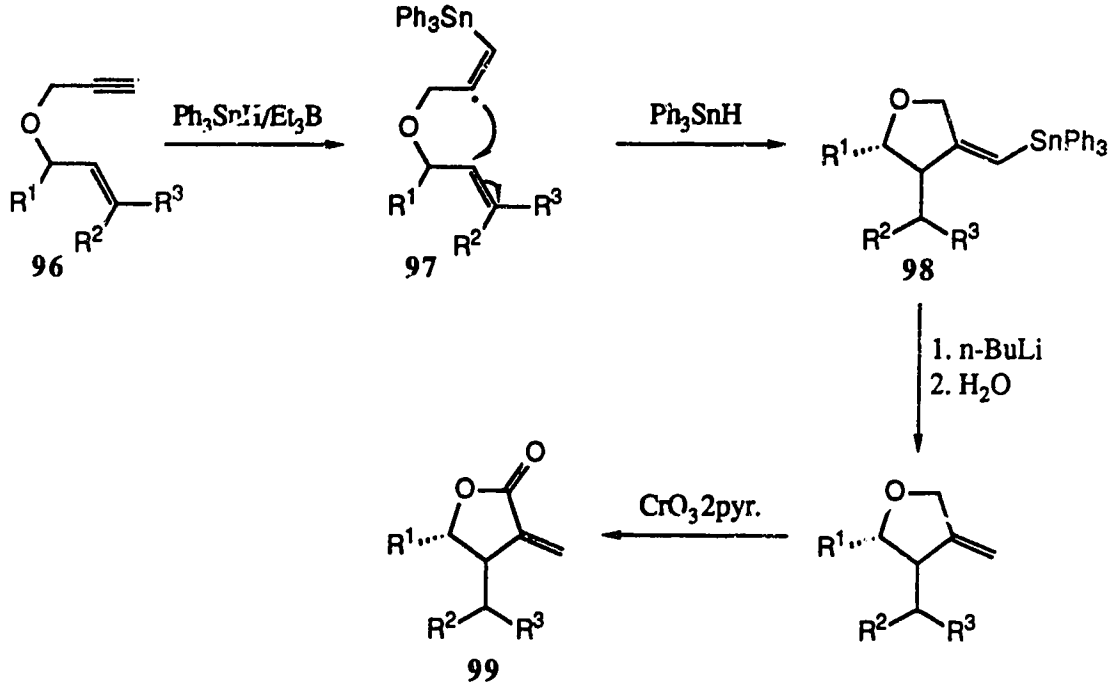
SCHEME 36



In 1987, Oshima[100] *et al.* reported an interesting route to make the same ring system. Their approach (Scheme 37) is

based on the easy and regioselective addition of triphenyltin hydride to acetylenes induced by triethylborane.[101] Thus, triethylborane-induced addition of triphenyltin hydride to a suitably constituted acetylenic olefin **96** generates a vinyl radical **97** which undergoes cyclization[102] to **98**.

SCHEME 37

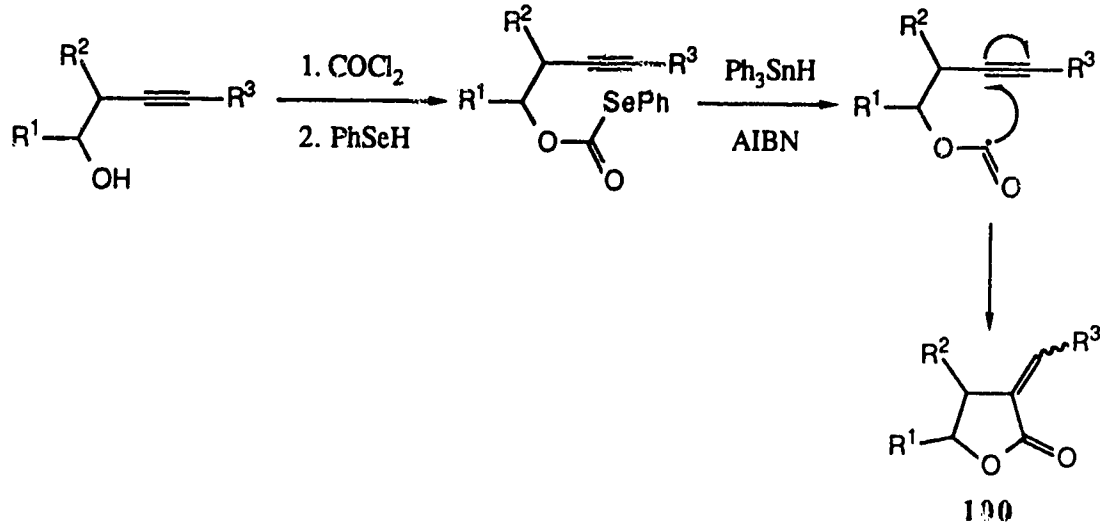


Starting materials			Products yields %	
R_1	R_2	R_3	**98**	**99**
a; Me	Me	Me	84	57
b; Ph	Me	Me	70	39
c; n-Bu	H	n-Pr	83	41
d; Me	n-Bu	H	75	59
e;	$-(CH_2)_3-$	H	71	31

Destannylation[103] followed by oxidation affords α-methylene γ-butyrolactones **99** in fair yields, as shown in Scheme 37. It is worth noting that the cyclized products **98** consist of only the (*Z*)-*trans*-isomer independently of the stereochemistry of the double bond in the starting enynes (**96c** and **96d**). In contrast, cyclization of **96e** gave exclusively the (*Z*)-*cis*-fused compound **98e**.

D.3.2. Intramolecular Addition of Alkoxycarbonyl Radicals to Acetylenes

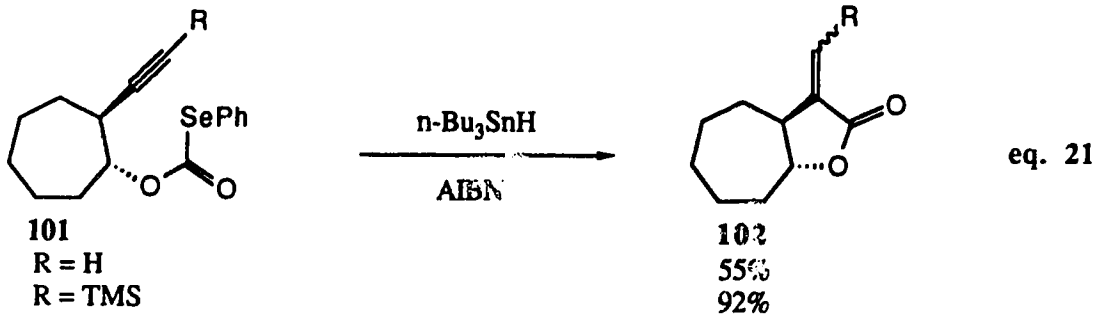
Bachi and Bosch[104] have recently described a new method for the preparation of α-alkylidene γ-lactones **100**. Their method is based on intramolecular addition of alkoxycarbonyl free radicals to acetylenes as displayed in eq. 20.



100

eq. 20

A variety of α alkylidene γ-lactones **100** in which R^3 represents a phenyl, alkyl or trimethylsilyl group were obtained in very high yields.[105] However, an extension of this method to prepare *trans*-fused α-methylene γ-lactones, e.g. **102** (R = H), resulted in low to moderate yields. Thus, radical cyclization of **101** (R = H) afforded **102** (R = H) in 55%. In contrast, the trimethylsilyl derivative **101** (R = TMS) gave **102** (R = TMS) in 92% by a similar procedure (eq. 21). It must be pointed out that desilylation of **102**

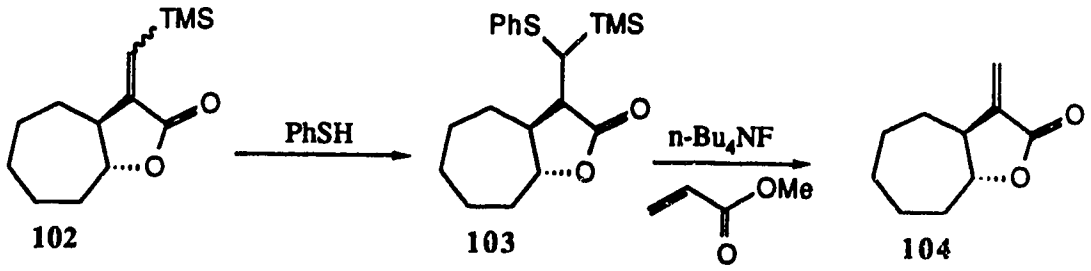


101
R = H
R = TMS

102
55%
92%

eq. 21

(R = TMS) was not accomplished using standard methods, i.e., tetrabutylammonium fluoride, trifluoroacetic acid, or hydriodic acid. To circumvent the difficulties encountered in removing the silicon group, Bachi first converted **102** (R = TMS) into phenylthio(trimethylsilyl)methyl lactone **103** (eq. 22), and subsequent treatment with anhydrous tetrabutylammonium fluoride and a large excess of methyl acrylate then afforded the α-methylene γ-lactone **104** in high yield.



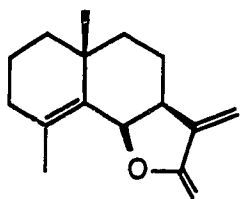
102 103 104

eq. 22

It is clear that such an important class of heterocycles as the α-methylene γ-butyrolactones mobilizes the whole arsenal of synthetic methods which are at our disposal and the use of free radicals in this particular area is becoming a valuable synthetic tool. There still remains, however, the need for more work in the development of new methodologies for setting up the starting materials for use in radical cyclization as well as further applications of the radical chemistry in total synthesis of α-methylene γ-lactones.

D.4. Synthesis of Frullanolide (±)-105

(±)-Frullanolide (±)-**105**, an allergenically active α-methylene γ-lactone sesquiterpene was first isolated by Ourisson and co-workers.[106] The dextrorotatory enantiomer of this lactone was isolated from *Frullania tamarisci* and its antipode from *Frullania dilatata*.

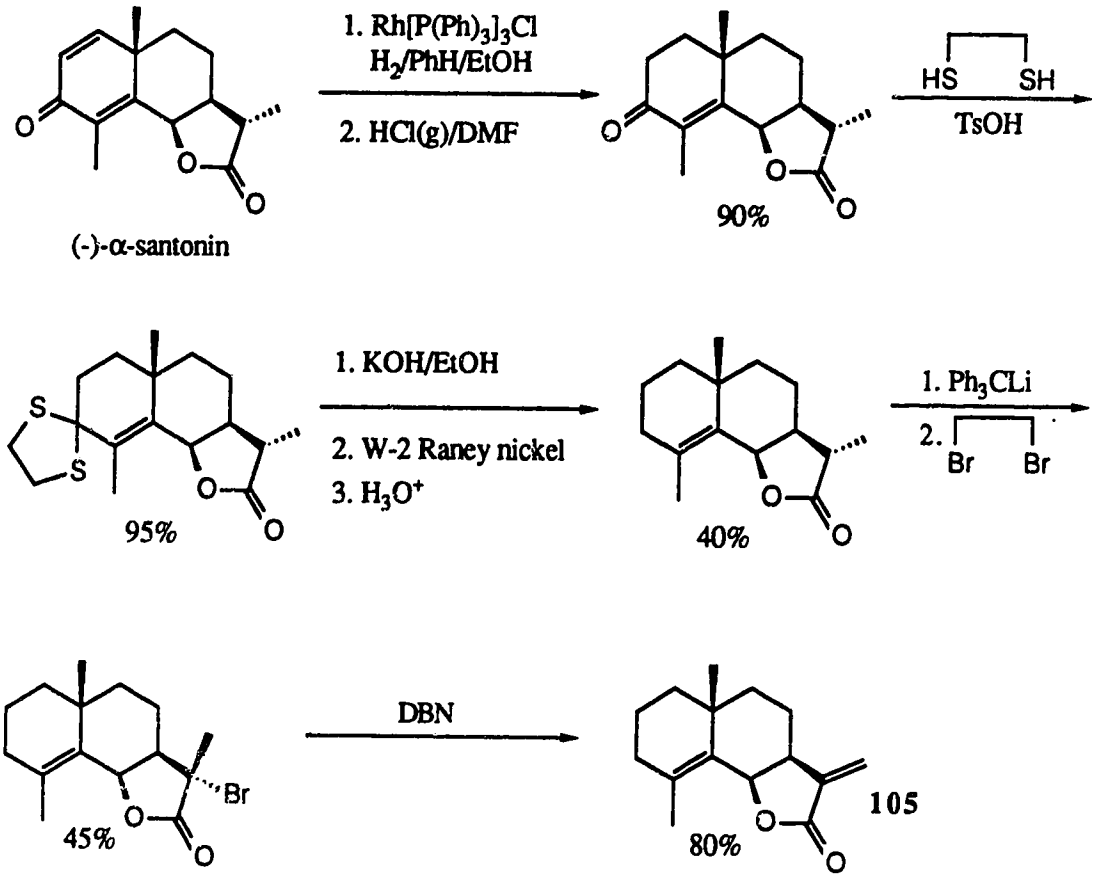


(±)-105

An application of methodologies which have been discussed above will be presented for the synthesis of frullanolide **105**.

In 1972, Ourisson et al.[107] using (-)-α-santonin as starting material synthesized (-)-frullanolide (-)-**105** (Scheme 38). Basically, the key step of this synthesis is

SCHEME 38

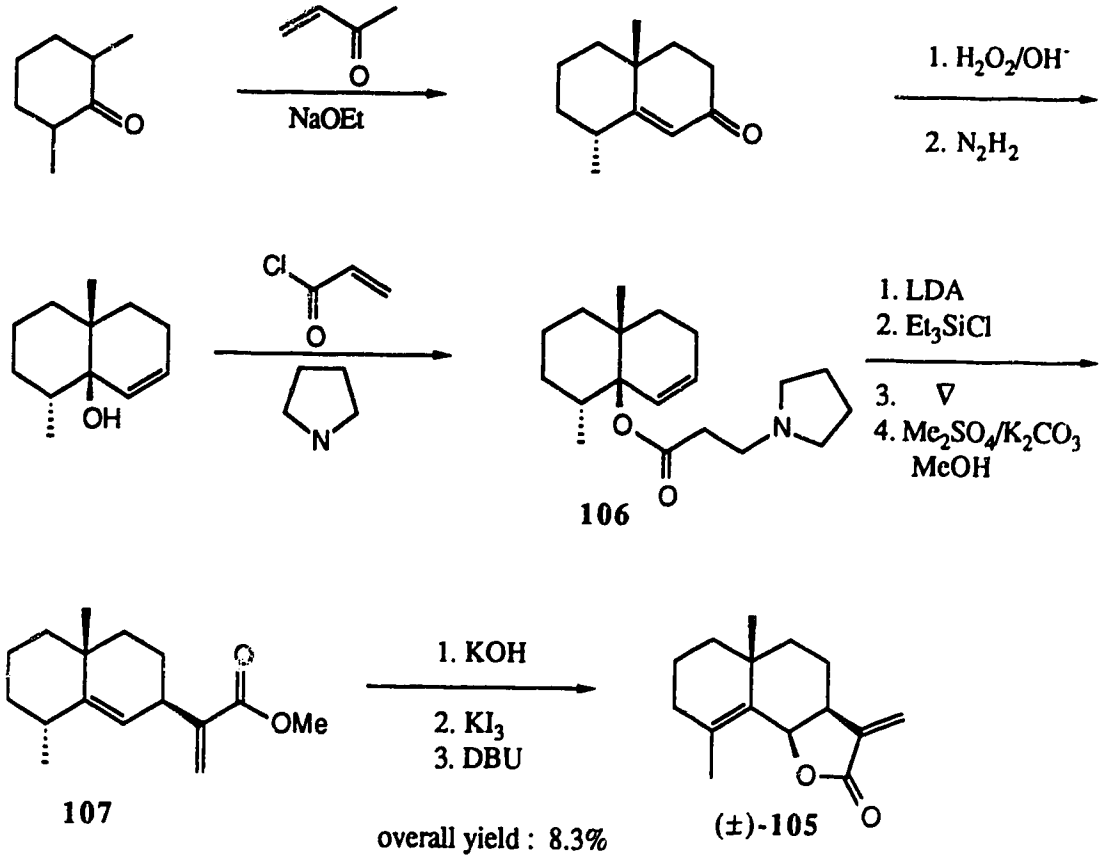


the conversion of an α-methyl lactone to an α-methylene lactone by stereoselective introduction of bromine α to the

lactone carbonyl followed by dehydrobromination, as shown in Scheme 38.

Some years later, in 1977, Still and Schneider[42] devised a concise route for the synthesis of racemic frullanolide (±)-**105**. Their approach involves the synthesis of α-methylene γ,δ-unsaturated acid **107** (Scheme 39), which is the substrate for subsequent iodolactonization, followed by dehydroiodination, to furnish the desired lactone (±)-**105**.

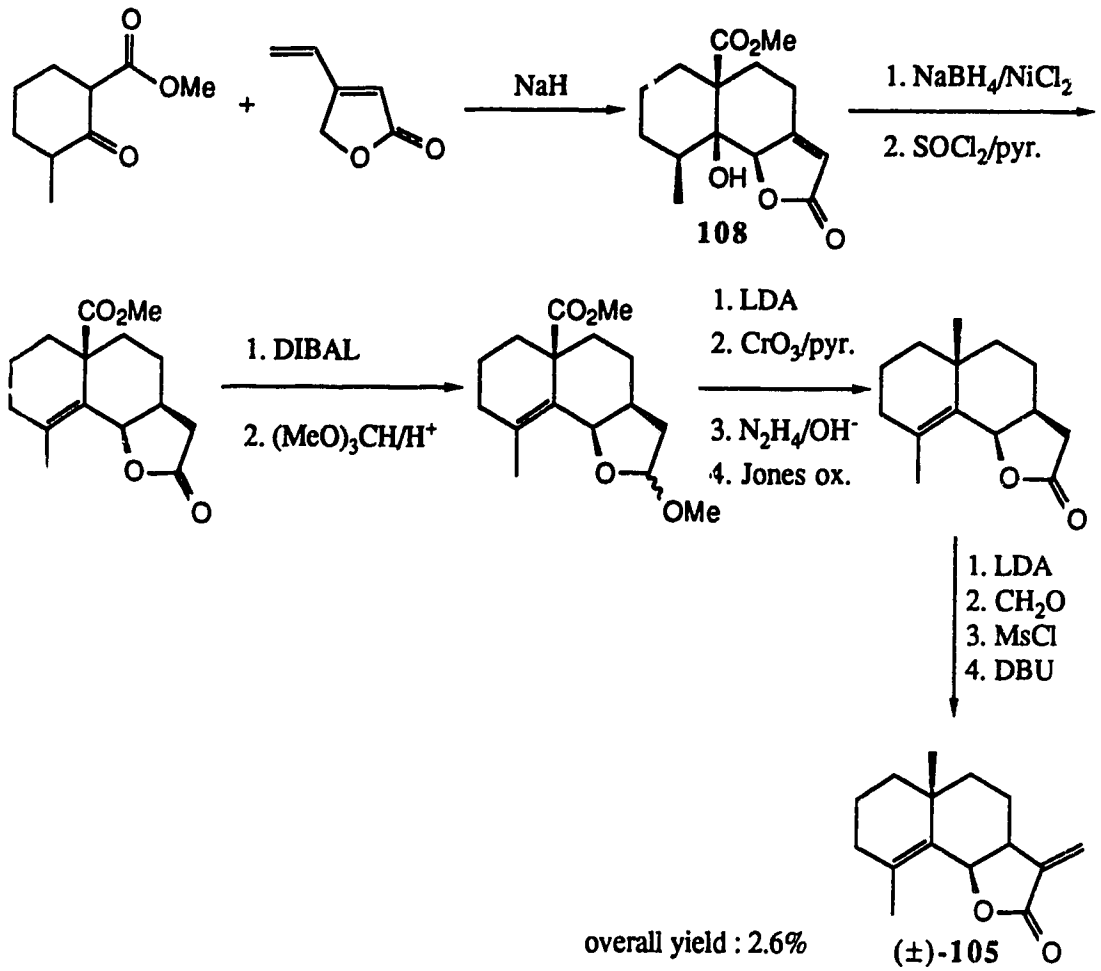
SCHEME 39



The unsaturated acid **107** was assembled via Ireland-Claisen rearrangement of allylic acrylate equivalent **106**. The overall yield was about 8.3%.

Another synthesis of (±)-frullanolide (±)-**105** was developed by Yoshikoshi and co-workers[108] (Scheme 40), and the

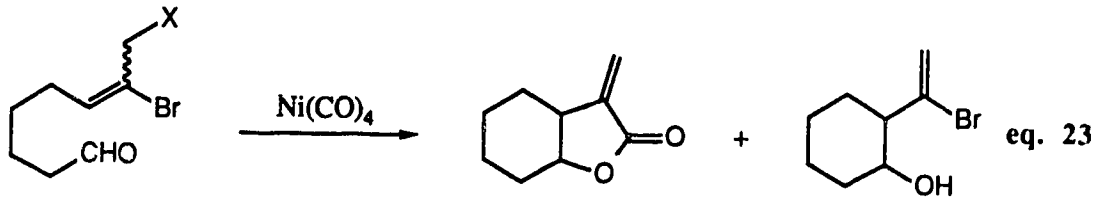
SCHEME 40



α-methylene γ-butyrolactone moiety was assembled via α-methylenation of a preformed γ-lactone ring. However, the key

step is the stereoselective reduction of **108** with sodium borohydride and nickel(II) chloride.

In 1981, Semmelhack and Brickner[68] synthesized racemic frullanolide (±)-**105** based on nickel-promoted cyclization-carbonylation methodology. This method, where nickel tetracarbonyl brings about two different carbon-carbon coupling steps, is sensitive to stereochemical features. For example, the nickel-promoted cyclization/carbonylation reaction of **109** (X = Br) (eq. 23) with *E*-geometry affords a mixture of **110** and **111** with the *cis:trans* ratio of 1:2 in both products. With the *Z*-isomer **109** (X = Br) the ratio is 1:1 for **110** and 2:3 for **111**. A sample of **109** (X = OSO_2Me)



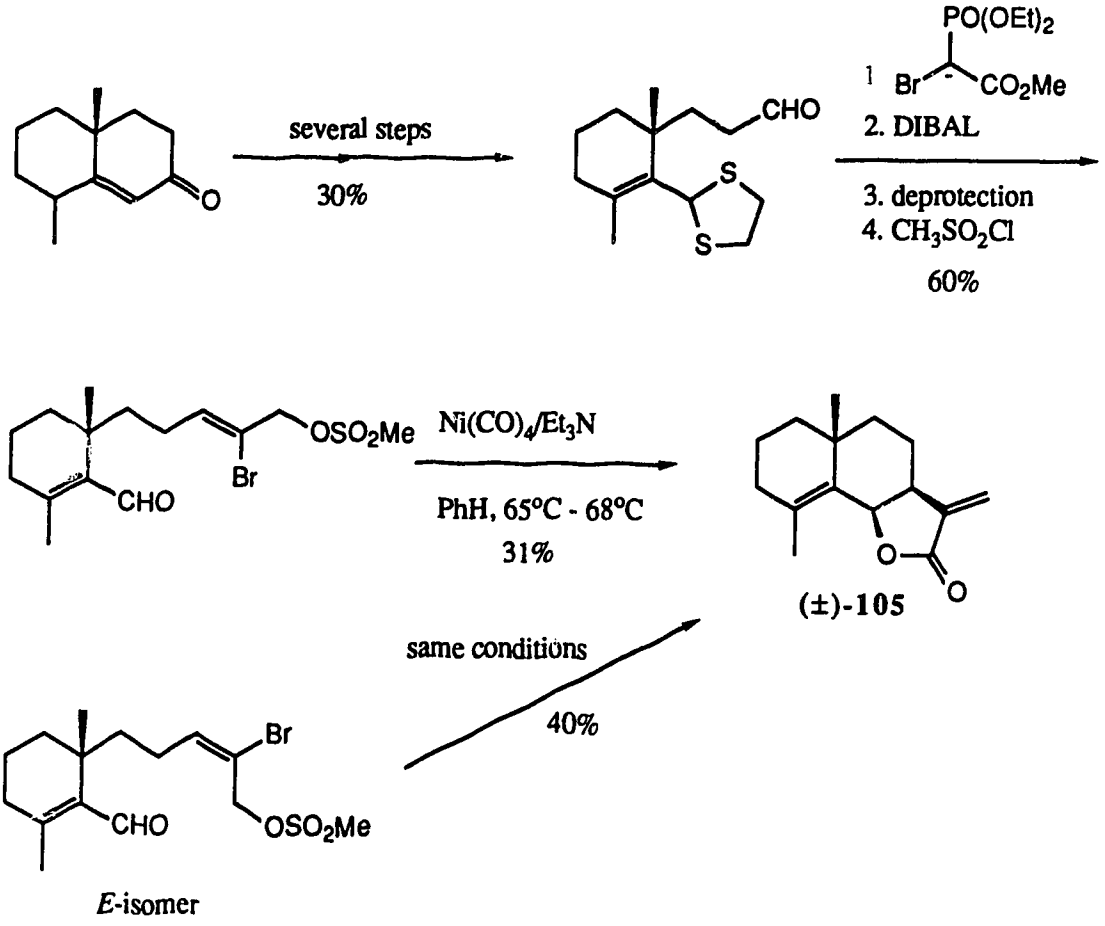
eq. 23

109		**110**	**111**
geometry	X	cis : trans	cis : trans
E	Br	1 : 2	1 : 2
Z	Br	1 : 1	2 : 3
E	$-OSO_2Me$	1 : 2	-

with *E*-geometry gave **110** with a 1:2 ratio in favor of the *trans* isomer. There is no significant dependence of yield on double bond geometry, but clearly the process is only moderately selective, tending toward the *trans* product. On the other hand, in a more complicated example (Scheme 41)

there was high selectivity for cis ring fusion and a syn orientation of the lactone ring with respect to the angular methyl group.

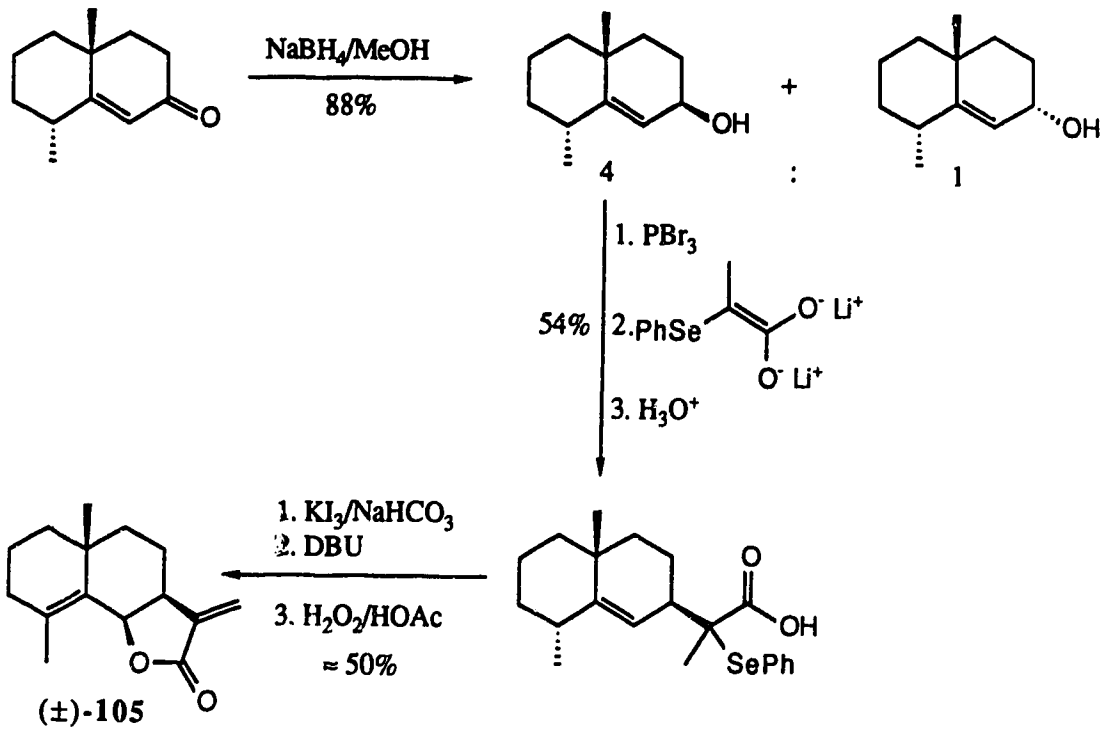
SCHEME 41



Petragnani and co-workers[109] also synthesized (±)-frullanolide (±)-**105** in their exploration of the utility of selenium-containing reagents. They used 2-(phenylseleno)propanoic acid as a masked acrylate equivalent for construction

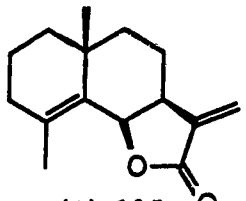
of the α-methylene γ-butyrolactone moiety. The approach is shown in Scheme 42.

SCHEME 42



II. RESULTS AND DISCUSSION

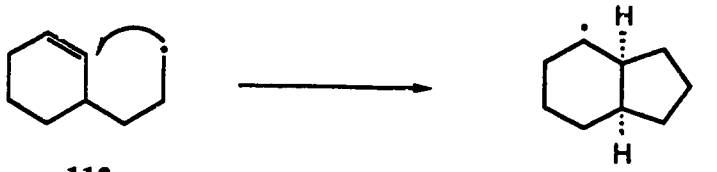
Synthesis of (±)Frullanolide: This section of the thesis describes a synthesis of the sesquiterpene α-methylene γ-lactone, frullanolide [(±)-**105**]. This substance occurs in



(±)-**105**

a number of plants of the *Frullania* genus,[106] and has the property of producing an allergic response on contact. The compound occurs naturally in both enantiomeric [(+) and (-)] forms,[106] and a number of syntheses of the racemic material have been described[42,68,108,109] as well as one synthesis of the (-)-isomer.[107] Our own interest in making the substance was based in part on the opportunity that such an exercise would provide for exploring certain features of the radical ring closure and, in the light of those features, for developing a general method to attach a five-membered ring to either face of an existing cyclic structure.

The particular aspects of radical cyclization that we wished to explore can be understood by reference to equations 24 and 25. Many examples of radical cyclization that conform to the pattern represented by the transformation of **112** into **113** are known, and cases have been examined in which the

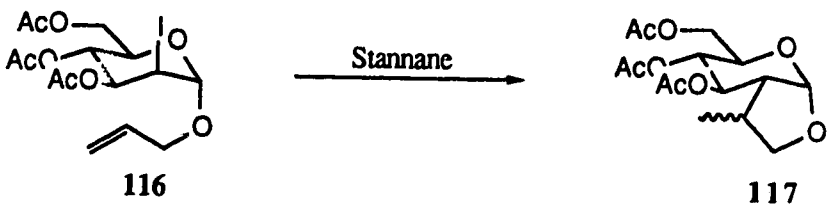


112 113 eq. 24

114 115 eq. 25

pendant chain was in an equatorial or in an axial conformation.[110]

An alternative way of making bicyclic compounds is shown in equation 25 (**114** → **115**). Here, in principle, the pendant chain can again be equatorial or axial, but at the outset of this work it was not clear whether the cyclization would be successful in both of these situations. A few examples are *now* known of analogous closures wherein the pendant chain is in either of the two conformations. In the carbohydrate series it was found[111] that species such as **116** undergo cyclization (60% yield) to provide **117** as a 1:1 mixture of

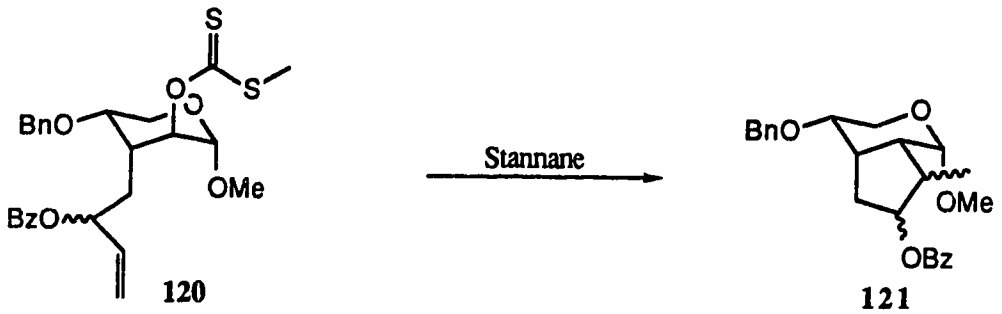


116 117

isomers. Although the olefinic pendant in **116** is formally axial, the ring system is not in a locked conformation. The all equatorial analogue **118** gave **119** in quantitative yield.

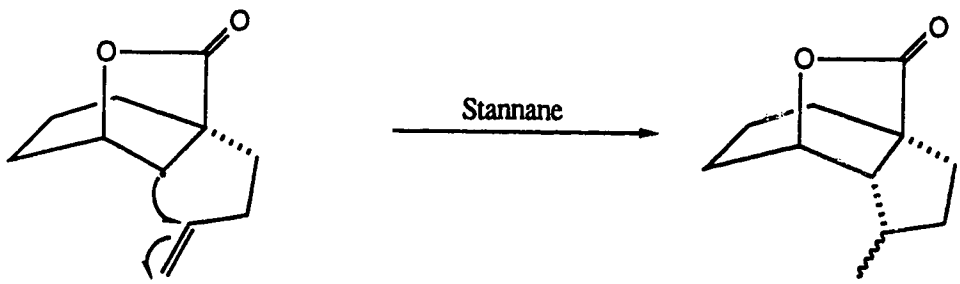
118 **119**

Compound **120**, whose conformation (axial or equatorial olefinic pendant) is not clear, undergoes cyclization to **121**.



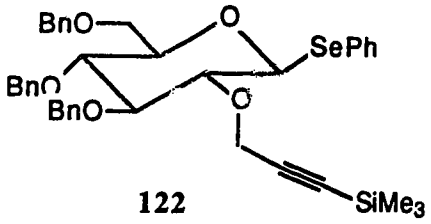
120 **121**

Hart has reported a number of cases[112] in which a radical, as in equation 26, closes onto an olefinic pendant

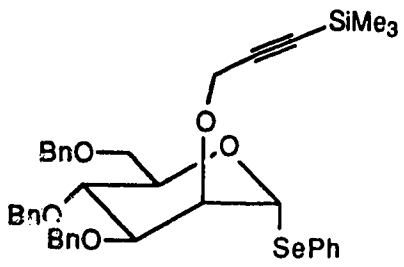


eq. 26

After our work (see below) was submitted for publication, De Mesmaeker submitted his own findings[113] that the substrates **122** and **123**, with the acetylenic unit presumably in an equatorial and axial conformation, respectively, undergo efficient radical closure.



122



123

Finally, a detailed examination has been reported of closures onto axial and equatorial pendants, in which some attempt was made to lock the conformations of the parent six-membered rings to which the pendants are attached.[114] Radicals **124** and **126** underwent cyclization in poor yields. The emphasis in this study was on the influence of pendant conformation (axial or equatorial) on the isomer ratio in the products (**125** and **127**).

124 **125**

As stated above, it was not clear, when we began this work, whether closure onto axial and equatorial pendants would be equally successful. Examination of Dreiding models suggested[115] that closure with the pendant in an axial conformation would be energetically easier. Diagrams 1 and 2 show the approach vectors of the cyclohexyl radical to the olefinic pendant and, at least from these pictures, which

DIAGRAM 1

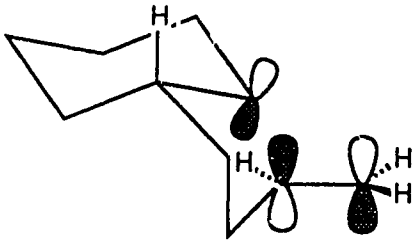
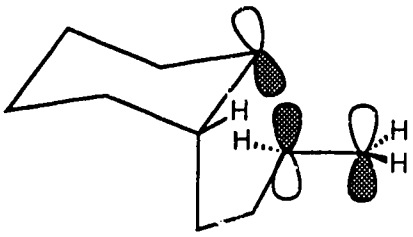


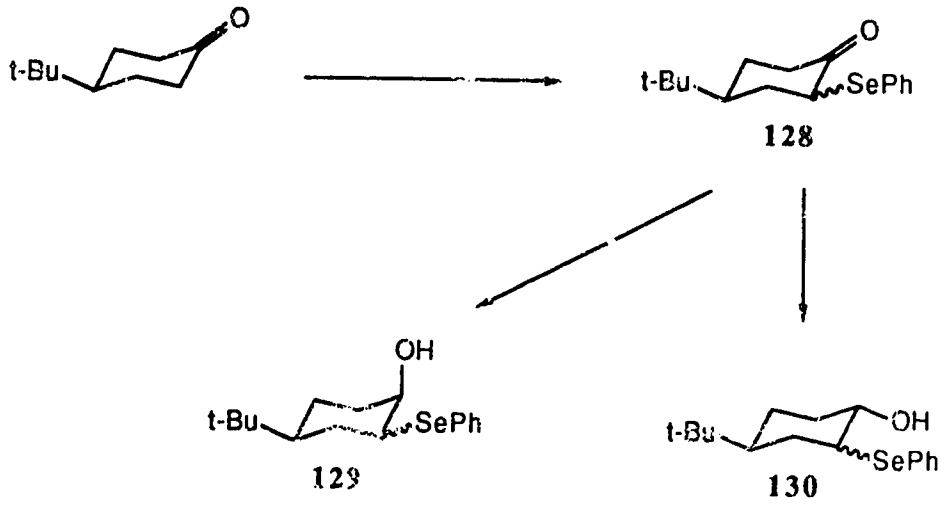
DIAGRAM 2



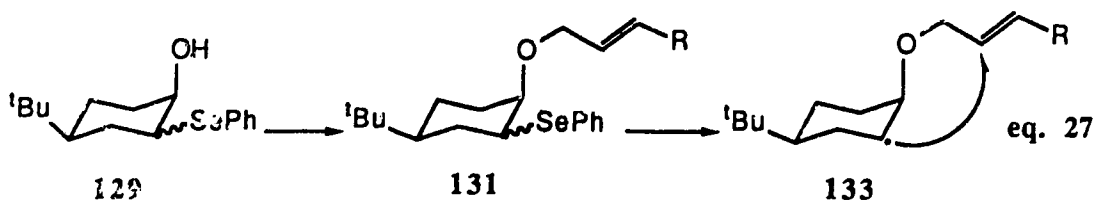
represent the Dreiding models, it would appear that the situation shown in diagram 2 is more favorable. In order to find out if the ring closure would be equally successful, irrespective of the conformation of the side chain, we decided to carry out a model study with compounds derived from 4-*tert*-butylcyclohexanone. The plan (Scheme 43) was to convert 4-*tert*-butylcyclohexanone into the corresponding α-(phenylseleno) ketone (**128**),[116] and to obtain from that

s[illegible]uce the axial and equatorial alcohols **129** and **130**, respectively. We would then attach to the hydroxyl a

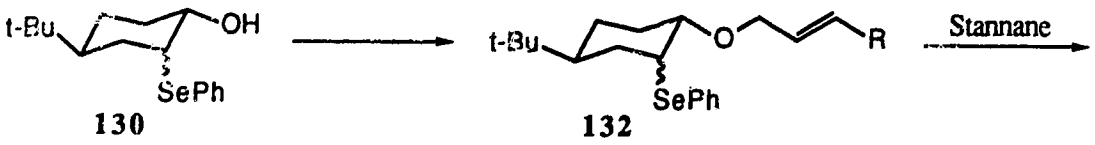
SCHEME 43



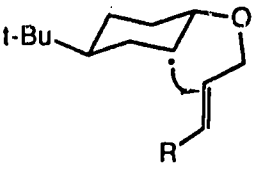
suitable pendant containing a carbon-carbon double bond, as shown schematically in equations 27 and 28. Treatment of each of these substances (i.e., **131** and **132**) with a stannane would serve to generate the required radicals **133** and **134**, respectively, and we hoped to establish whether each of these radicals would cyclize with equal facility. The outcome of these experiments might be subject, of course, to some ambiguity, because we could not guarantee that the six-membered ring carrying the *tert*-butyl group would rigorously maintain a chair conformation,[117] but the experiments appeared simple and worth doing as an entry to the problem.



129 131 133



130 132



134 eq. 28

On the basis of these ideas, then, 4-*tert*-butylcyclohexanone was selenenylated in the standard way[118] and ketones **128** were obtained in good yield. The ^{1}H and ^{13}C NMR spectra of the material showed that it was a mixture of axial and equatorial isomers. The compound is quite sensitive, and we were not able to separate the isomers. This did not appear to matter at the time as the stereochemistry at the selenium-bearing carbon was not crucial to our plans, provided we could control the stereochemistry at the hydroxyl-bearing carbon.

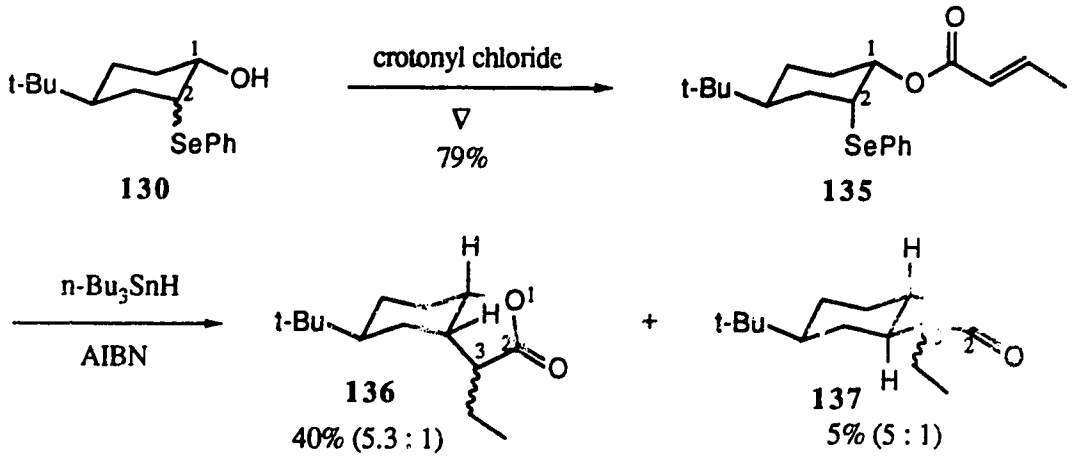
Reduction of α-(phenylseleno) ketones to the corresponding alcohols is known to present some difficulties[119] because of the tendency for the selenium unit to be lost. In the present case, conversion of the carbonyl

into a hydroxyl (i.e., **128** → **129** or **128** → **130**) was attempted with borane-methyl sulfide complex[120] and also with L-Selectride. Only the experiments with the borane were satisfactory, and even then the yield was modest. A white crystalline solid was obtained in 48% yield, but the melting point was broad, and spectroscopic measurements showed that a small amount of another substance (presumably a stereoisomer) was present. However, reduction with tributyltin hydride gave (92%) a single alcohol identified by its ^{13}C NMR spectrum as *trans*-4-*tert*-butylcyclohexanol.[121a] Consequently, the major hydroxy selenide from the borane-methyl sulfide reduction must have the structure shown in **130**. This material (together with the accompanying minor isomers) was then acylated with crotonyl chloride. Standard methods for acylation did not work but, when the two components were heated as a neat mixture, it was possible to isolate **135** in high yield and as a single compound of sharp melting point. Examination of the ^{1}H NMR coupling constants allowed us to establish the stereochemistry shown in **135**, and so the parent alcohol **130** must have been largely material of corresponding stereochemistry at C-2.

Treatment of selenide ester **135** with tributyltin hydride gave lactone **136** (*ca.* 40%) as a 5.3:1 mixture of two isomers, epimeric at C-3 (Scheme 44). This result represents good presumptive evidence that a pendant chain disposed in an equatorial fashion can be used as a radical acceptor for

cyclization. For completeness, we attempted to prepare corresponding material with an axial

SCHEME 44

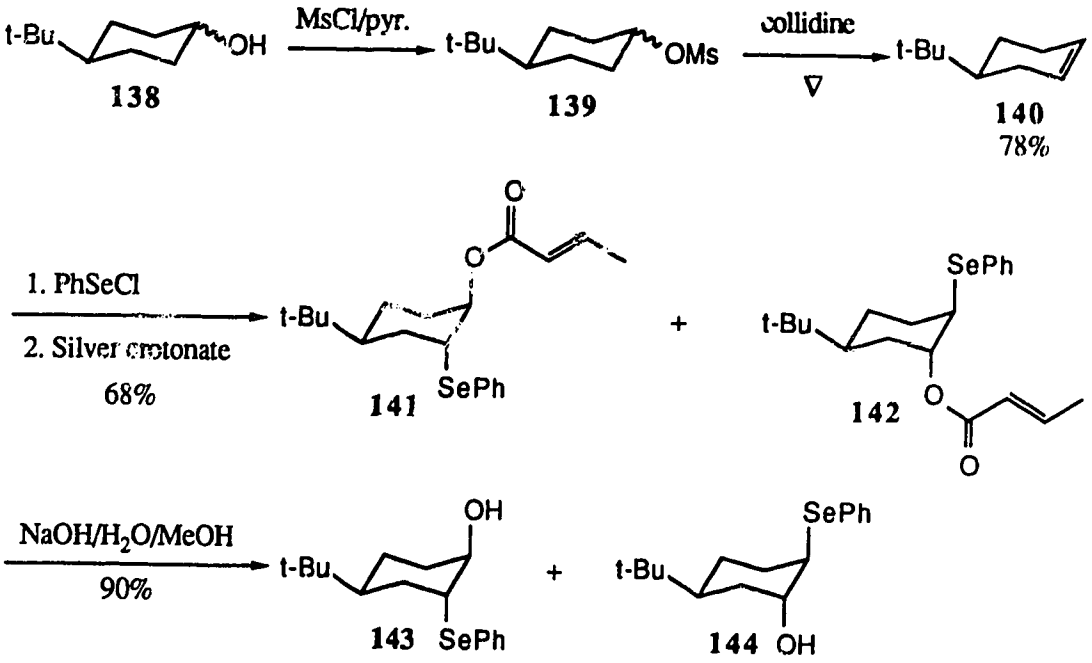


pendant but, surprisingly, this proved difficult. From the cyclization of **135** we were able to isolate a small amount (*ca.* 5.1%) of an isomer, to which we assign the trans ring-fused stereochemistry **137**, as a 5:1 mixture of isomers. The assignment of the ring fusion stereochemistry was most conveniently made on the basis of the characteristic chemical shifts[122] for cis and trans ring-fused γ-lactones.

A mixture of the commercially available alcohols **138** was mesylated (Scheme 45, **138** → **139**) and converted into the olefin **140**. Treatment with benzeneselenenyl chloride in the presence of silver crotonate[122] then gave a mixture of esters, assumed, on mechanistic grounds, to be **141** and **142**, which was directly saponified to the corresponding alcohols (**143**

and **144**, respectively). Neither the esters nor the alcohols could be separated by chromatography, and the subject was not

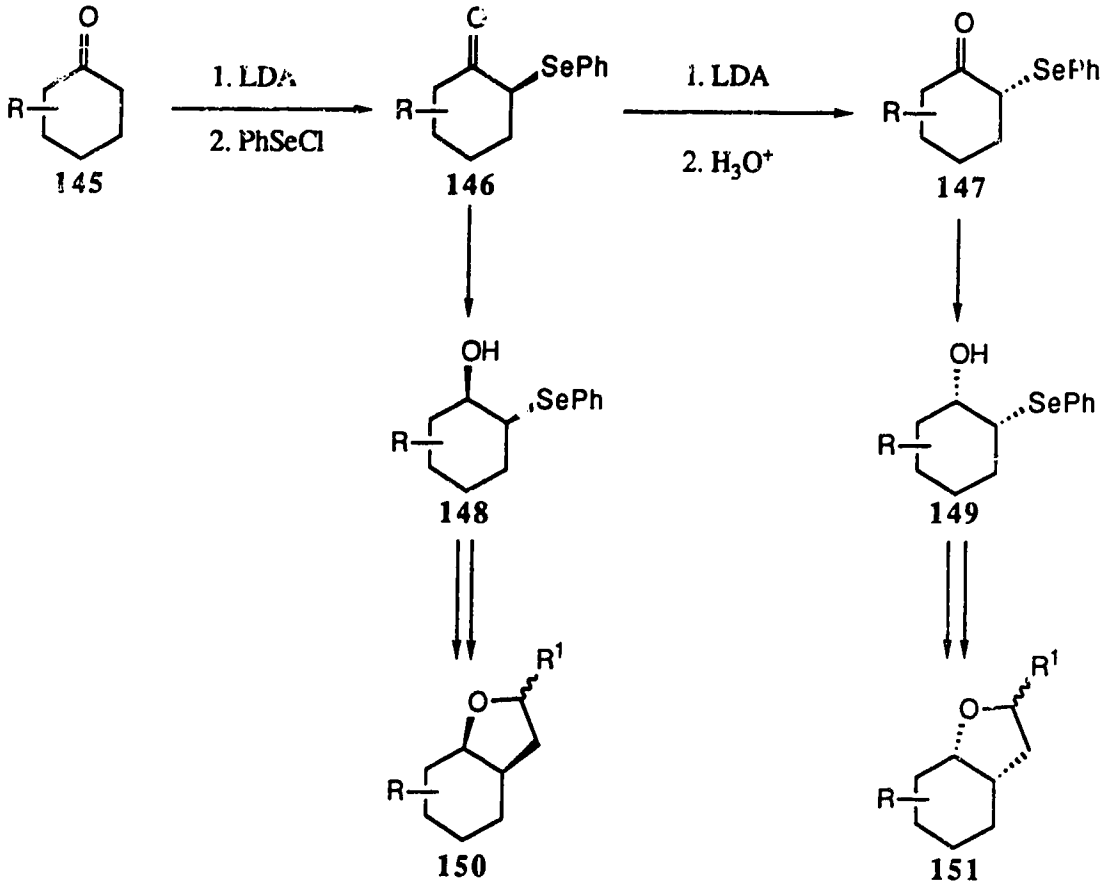
SCHEME 45



examined further; we had some evidence that radical cyclization could be successful with an equatorial pendant. It was appropriate, therefore, to pursue our plan to develop a methodology for constructing a ring on either face of an existing cyclic structure; in one case radical closure would occur onto an equatorial unsaturated pendant and, in the other case, the cyclization would involve the corresponding axial pendant.

The present basic strategy for generating a ring on either face of another ring is summarized in Scheme 46. In the first stage, a ketone **145**, containing one or more

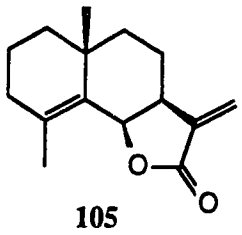
SCHEME 46



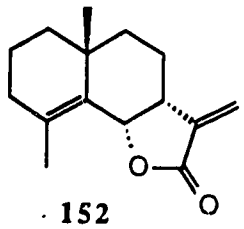
stereogenic centers, would be selenenylated (**145** → **146**). It is assumed (and will later be illustrated) that selenenylation gives exclusively, or predominantly, one isomer (**146**) in which the phenylseleno group controls the stereochemistry of carbonyl reduction (by a suitably bulky reagent) so as to produce the *cis* vicinal hydroxy selenide **148**. In these

circumstances [in which a single selenide **146** is formed by quenching of the parent enolate (see **145** → **146**)] it was hoped that the selenide **146** could be isomerized by deprotonation and reprotonation. Those operations should give the isomeric keto selenide **147**. As before, reduction would occur from the face opposite to the bulky phenylseleno group so as to generate **149**. The two alcohols **148** and **149** would then be elaborated into the isomeric bicyclic structures **150** and **151**.

It was decided to test the above proposal by a synthesis of racemic frullanolide (**105**) and its diastereoisomer (**152**), although, in the event, we did not pursue the synthesis of **152** beyond the stage of proving that we could annulate a ring on the α face of the octahydronaphthalene skeleton, as in **152**.



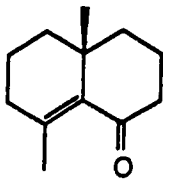
105



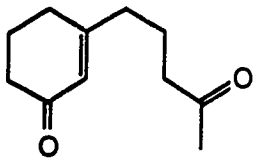
152

A suitable starting material for elaboration into frullanolide appeared to be the α,β-unsaturated ketone **153**. This substance is reported in the chemical literature[123] but, unfortunately, no experimental details have been published and the full paper mentioned in the communication has never

appeared. We made this ketone in several steps from the monocyclic diketone **154**. This compound, likewise, is

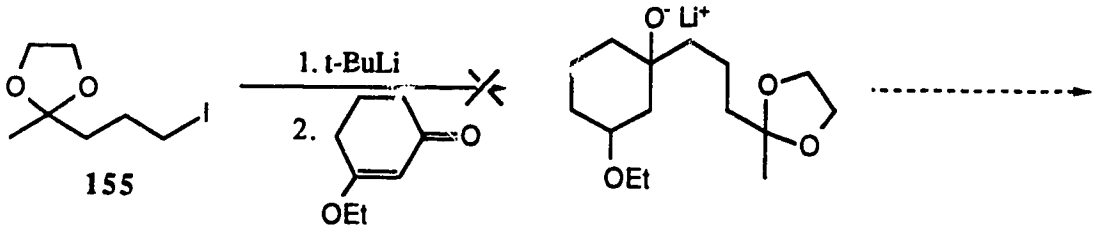


153

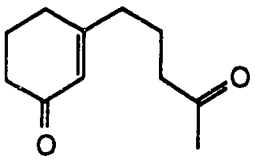


154

reported in the literature, but again without experimental details.[123] Our first attempt (eq. 29) to prepare it involved treating iodo ketal **155**, itself derived from the corresponding chloro ketal by a Finkelstein reaction, with *tert*-butyllithium and then with 3-ethoxy-2-cyclohexenone.



155



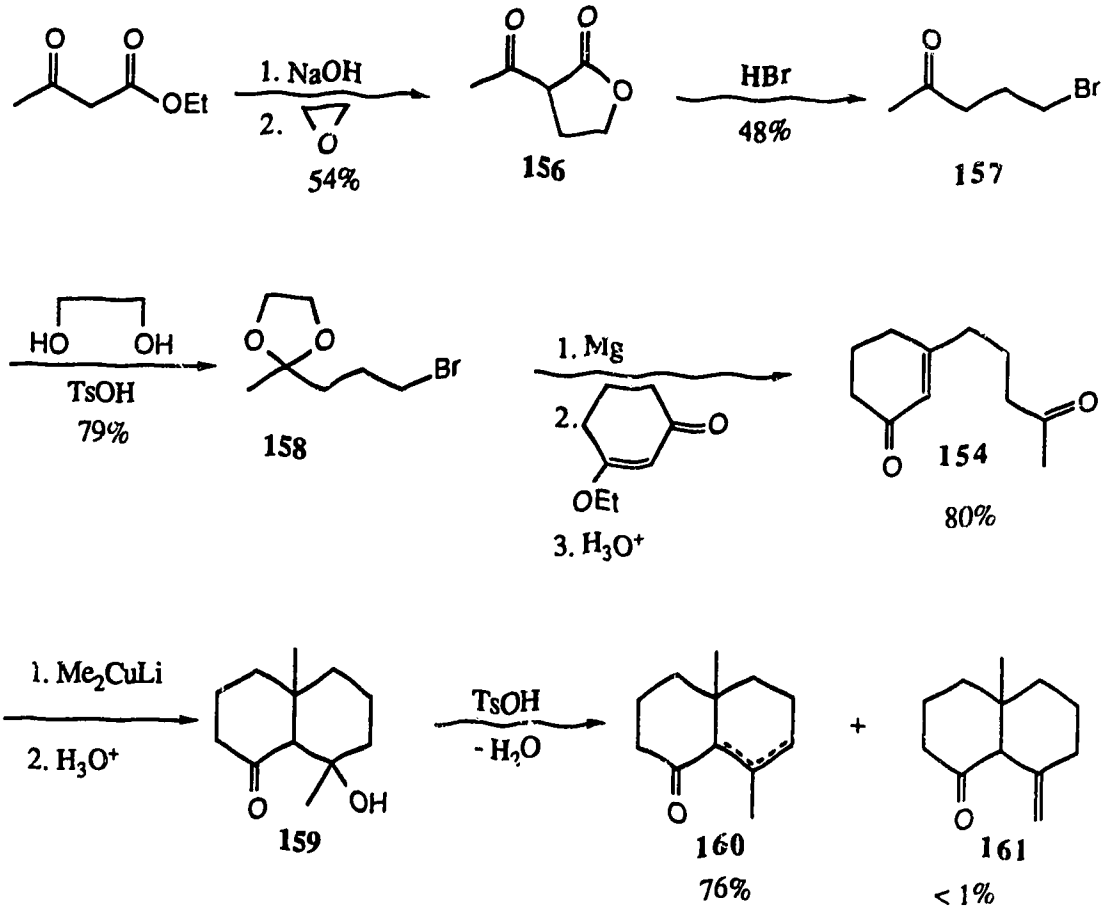
154

eq. 29

We must have encountered some problem in the halogen-metal exchange, because none of the desired product was isolated after mild acid hydrolysis of the reaction mixture. The cause of this problem was not established because we quickly

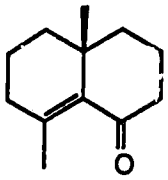
found that use of a Grignard reagent smoothly gave the desired product (see Scheme 47). Ethyl acetoacetate was condensed with ethylene oxide, and the resulting keto lactone **156** was converted in acceptable yield (54%) into bromo ketone **157**. Ketalization then gave the corresponding bromo ketal **158**.

SCHEME 47

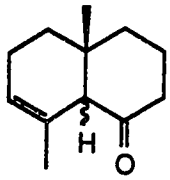


This substance readily formed a Grignard reagent which reacted with 3-ethoxy-2-cyclohexenone in the required manner.

Mild acid hydrolysis of the crude product served to release the diketone **154**. Addition of lithium dimethylcuprate then gave directly the bicyclic tertiary alcohol **159**. Although we isolated this alcohol on one occasion, we did not determine its stereochemistry; we usually treated the crude material directly with *p*-toluenesulfonic acid in refluxing benzene. This operation caused elimination of the tertiary hydroxyl and provided a mixture of olefins **160** probably containing a trace of **161**. ^{1}H NMR measurements showed that the two major isomers had structures **153** (54% yield) and **162** (22% yield). Compound **162** was a single isomer (^{13}C NMR), but we did not establish its stereochemistry.



153

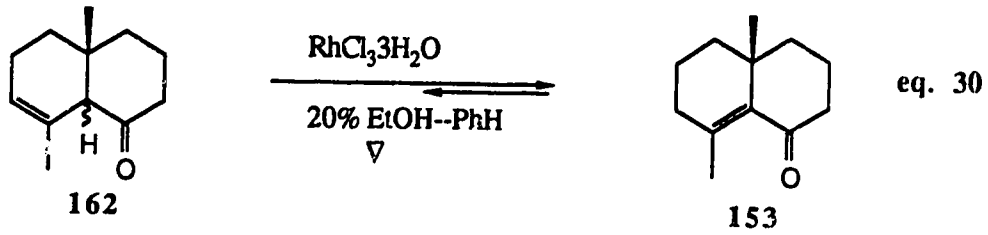


162

In one of the cuprate addition experiments we inadvertently worked up the reaction by adding dilute hydrochloric acid to the mixture instead of pouring the mixture into the acid. In this one case we isolated diketone **163** and found that the action of *p*-toluenesulfonic acid then led to the olefin mixture **160**.

Of the components of **160** only structure **153** is suitable for our purposes and so we made a careful study of the isomerization of **162** into **153**. We examined the conventional

reagent, rhodium trichloride trihydrate, and found that the result was sensitive to the nature of the solvent. The experiments were easy to monitor because **153** and **162** are separable by thin layer chromatography. In both refluxing benzene or refluxing ethanol no isomerization occurs. However, a mixture of the two solvents was very suitable. In a 1:1 mixture the isomerization was slow but in a 1:4 mixture of ethanol and benzene, respectively, reaction was complete in 28 hours and the equilibrium mixture of isomers contained **153** and **162** in a ratio of 2:1 in favour of the desired compound, **153** (eq. 30). The non-conjugated enone could easily be separated and recycled.

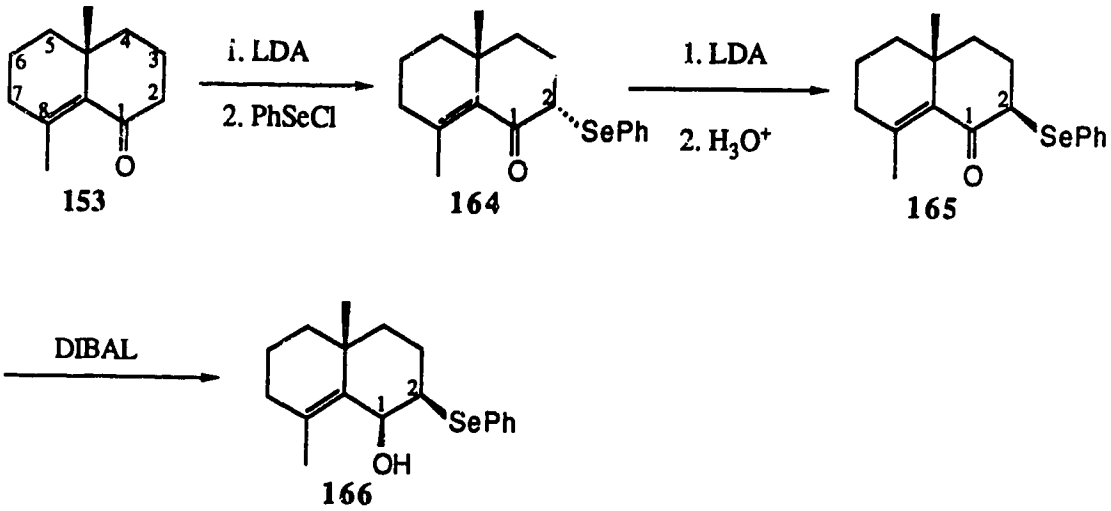


162 **153** eq. 30

With α,β-unsaturated enone **153** in hand, we then examined the phenylselenylation. Kinetic deprotonation by addition to a slight excess of LDA gave the desired enolate, and this was

In practice it is not necessary to separate the two compounds. In order to direct the subsequent carbonyl reduction, keto selenide **164**, containing a small amount of **165**, was epimerized by kinetic deprotonation (addition to excess of LDA) and reprotonation (from the less hindered side) by quenching at -78°C with aqueous ammonium chloride. This procedure gave a mixture of the β-selenide **165** and the α-selenide **164** (Scheme 48). The former was now the major component and was isolated in 71% yield, and the latter was isolated in 12% yield.

SCHEME 48



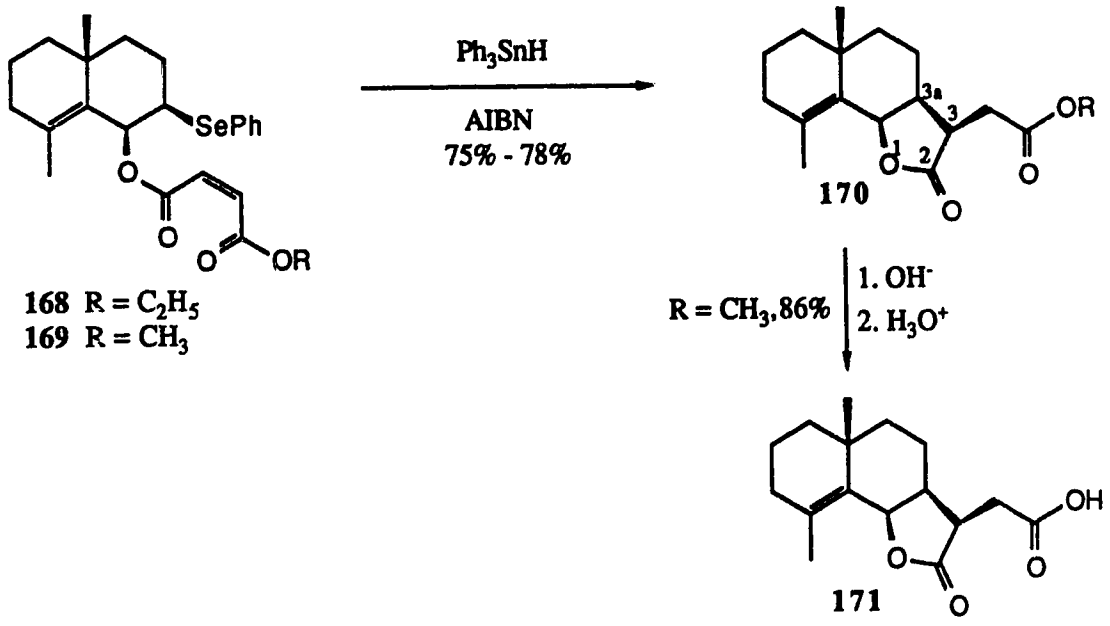
seleno group and generally gave mixtures of the deselenated ketone and the corresponding alcohol. However, diisobutylaluminum hydride, when used in toluene at -78 °C, gave the desired β-alcohol **166**. A number of other solvents (benzene, ether, dichloromethane) were also tried, but the result was best (70%) with toluene.

The fact that selenide **165** and alcohol **166** have the indicated stereochemistry is crucial for the synthesis, and the assignments were made in the following way. In the case of the ^{1}H NMR spectrum of the seleno ketone, the methine proton at C-2 was split into a doublet of doublets in which one coupling is large (12.5 Hz) and the other small (7.5 Hz). These values are appropriate for an axial hydrogen at C-2 (as in structure **165**). The ^{1}H NMR spectrum of alcohol **166** also established the indicated stereochemistry in an unambiguous manner. The methine proton at C-1 appeared as a broad singlet, as expected for a small coupling with the adjacent methine proton. The latter appeared as a doublet of doublets

the anticipated product (**167**) could, in principle, be elaborated into frullanolide. Unfortunately, the alcohol, which is evidently very hindered, did not react. This experiment was tried only at room temperature because, in the meantime, we had discovered how to perform an equivalent acylation. The alcohol **166** was treated with ethyl hydrogen

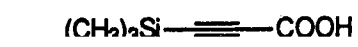
yield of a single γ-lactone with structure **170** (Scheme 49). The stereochemistry at C-3 is assigned tentatively from the magnitude (13 Hz) of the coupling constant between C(3)-H and C(3a)-H. Inspection of Dreiding models suggests that the alternative stereochemistry should lead to a zero coupling

SCHEME 49



We next attempted to convert acid **171** into frullanolide by Kochi degradation[125] but, under the standard conditions, the ^1H NMR spectrum of the total reaction mixture showed no olefinic protons as would be expected for the required α-methylene lactone. Consequently, we did not examine this unpromising route any further.

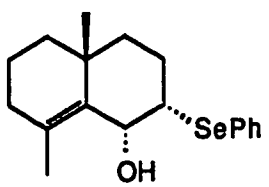
We turned our attention again to propiolic acid as an acylating agent, but this time we used the silylated derivative **172**. This is another of the compounds we have met

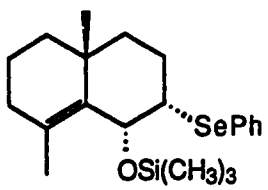


that is reported in the literature without, as far as we can tell, any experimental procedure. We prepared it from propargyl alcohol by *O*-protection (tetrahydropyran) and silylation, followed by mild acid hydrolysis and Jones oxidation.[126] However, our attempts to acylate hydroxy selenide **166** with acid **172** were no more successful than those with propiolic acid itself. We examined the use of DMAP and DCC[124] and another set of standard conditions—coupling in the presence of 2-chloro-*N*-methyl-pyridinium iodide[127] In both cases the starting hydroxy selenide was unchanged or was converted into a complex mixture.

Finally, we took the hydroxy selenide **173**, whose synthesis will be described later, and attempted to carry out a Mitsunobu inversion[128] at the hydroxyl-bearing carbon with acid **172**. A new product was isolated in about 50% yield, but it turned out to be merely the *O*-silyl ether **174**, the silyl group having been transferred from the acid **172**.

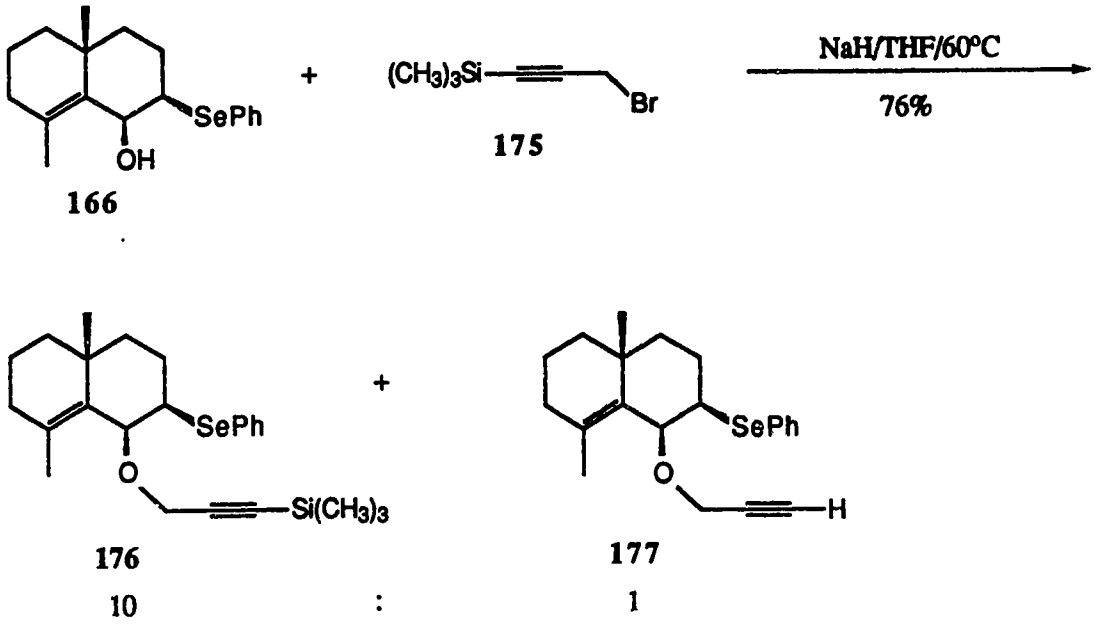
In the light of the above experience we decided to try *alkylation* of the hydroxyl as opposed to *acylation* and in the first experiment we succeeded in attaching the desired pendant to the hydroxyl group.





Treatment (Scheme 50) of hydroxy selenide **166** with sodium hydride and two equivalents of the bromo acetylene **175**

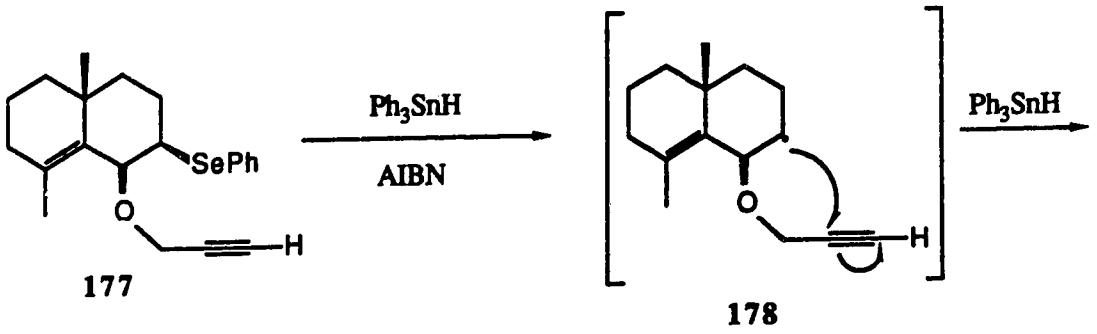
SCHEME 50



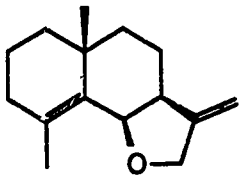
gave a 2:3 mixture of *O*-alkylated products **176** and **177**, respectively. When an excess of the acetylene **175** was used the yield of **176** rose to 69% and the amount of **177** was quite low (7%). Some starting material (11%) was recovered. [Compound **177** could be obtained directly by using propargyl bromide in the alkylation, but material made in this way was not easily purified.]

We were now ready to try the radical cyclization and we examined first the desilylated compound **177**. Treatment with triphenyltin hydride and AIBN under standard conditions used

not isolate the desired heterocycle **179** that would be expected to arise by closure of radical **178** (eq. 32).



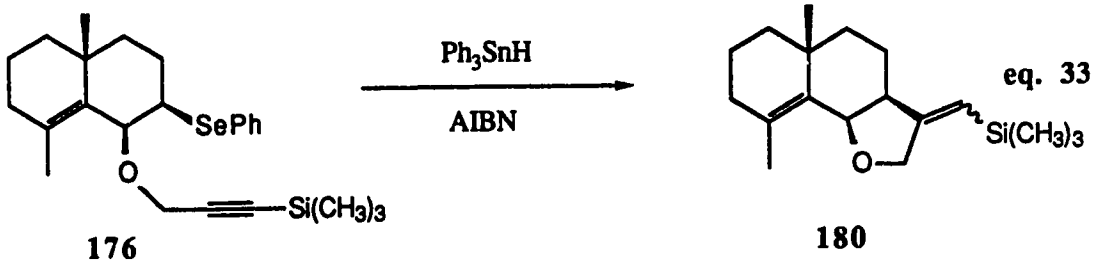
177 **178**



179

eq. 32

This result was disappointing because a number of related closures are known[95,98,100,122,129] and we would have pursued the matter further if we had not in the meantime discovered how to assemble an equivalent heterocycle. Application of exactly the same radical cyclization conditions to the silylated acetylene **176** (eq. 33) proceeded in the desired manner and in nearly quantitative yield. The product **180** was



176 **180**

eq. 33

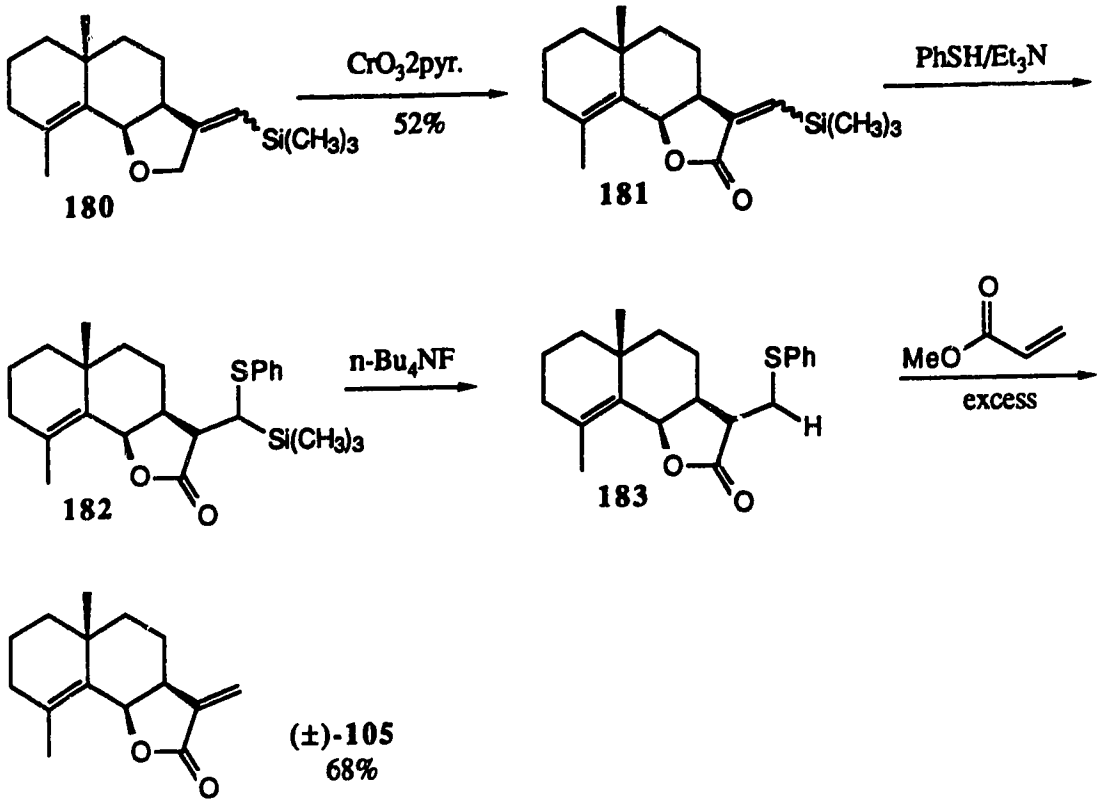
obtained as an approximately 1:1 mixture of geometrical isomers. The material was slightly contaminated by tin residues but these turned out to be easily separated in the next step.

Initially we tried to remove the silicon unit in one operation by treating **180** (see eq. 33) with *p*-toluenesulfinic acid in aqueous acetonitrile.[130] A clean product could not be isolated and so other acids were tried. Hydriodic acid in benzene produced a complex mixture and hydrochloric acid in dichloromethane failed to attack the silane. For these reasons a less direct route had to be found.

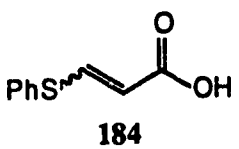
Oxidation of the vinyl silanes with chromium trioxide-pyridine complex[95] in dichloromethane gave the lactones **181** (Scheme 51) in 47% yield for the two steps from **176**. Finally, we applied a standard[104] method for removing silicon from α,β-unsaturated lactones. This involves treatment with thiophenol in the presence of triethylamine to afford the adduct **182**. This material was then used directly for desilylation with fluoride ion, and transfer of thiophenol to methyl acrylate, as shown in **182** → **183** → **105**. Although three steps are required to remove the silicon unit, the overall yield was acceptable (68%) and the frullanolide obtained was a pure and sharp-melting solid [mp 93-93.5°C (lit.[109] mp 93-93.5°C).]

At this stage we looked briefly at a modified approach to introduce the acrylate substructure of the final product.

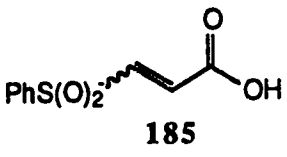
SCHEME 51



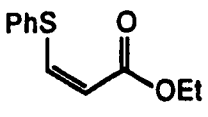
and **185**. Both of these are known compounds and the literature procedure[131] involves merely addition of thiophenol to ethyl propiolate followed by oxidation.



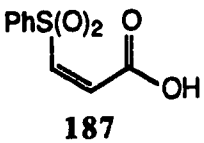
184



185



186

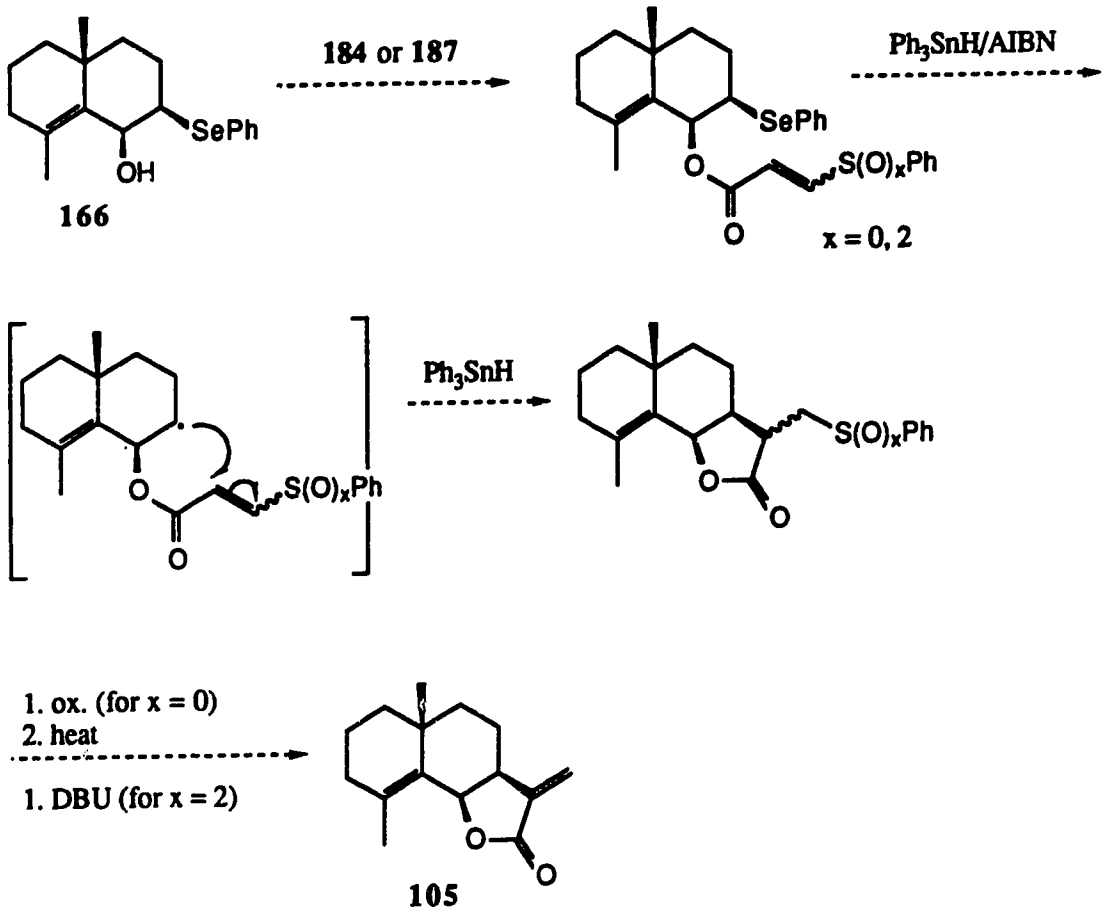


187

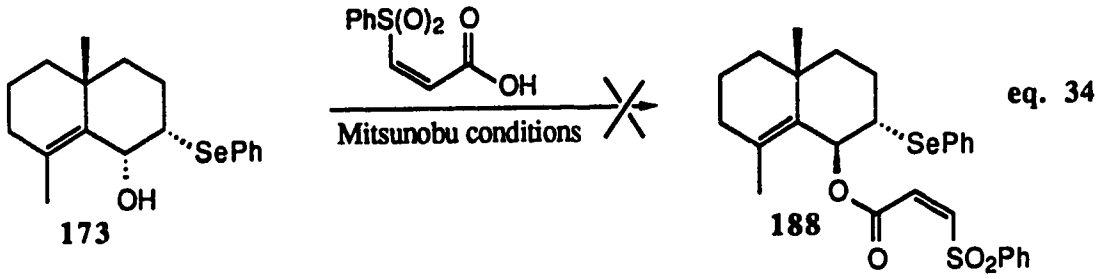
The initial step, thiophenol addition to ethyl propiolate, gives a mixture containing mainly the *Z* isomer **186** if the reaction is run in ethanol.[131b] However, use of THF provides a 1:1.5 mixture in favor of the *E* geometry. Hydrolysis of material prepared in THF affords acid of similar isomeric composition to the starting material, and, as the isomeric composition is not important for our purposes, we did not hydrolyze the ester prepared in ethanol (and therefore of mainly *Z* geometry). In order to make the sulfone **187** we found it more convenient to add thiophenol directly to propiolic acid[131a] and to treat the resulting (*Z*)-β-(phenylthio)acrylic acid with hydrogen peroxide in acetic acid in the presence of a catalytic amount of concentrated sulfuric acid.[131a] This procedure gave the sulfone **187** in 74% yield. Surprisingly, oxidation with sodium metaperiodate or with an oxaziridine[132] was unsuccessful.

With the sulfur-containing materials in hand we attempted to convert hydroxy selenide **166** into frullanolide along the lines of Scheme 52. However, several attempts to acylate **166** with **184** (as a mixture of geometrical isomers) or with **187** (as the *Z* isomer) using standard procedures mediated by DCC/DMAP[124] or by 2-chloro-*N*-methylpyridinium iodide[127] were unsuccessful. An attempt was also made to use hydroxy selenide **173** (see below), which, in principle, should be amenable to Mitsunobu reaction[128] with **187** to give the

SCHEME 52



desired derivative **188** (see eq. 34) by inversion at the hydroxyl-bearing carbon. Alcohol **173** was, however, inert to the standard Mitsunobu conditions.



eq. 34

An alternative method of using acids **184** and **185** was via their acid chlorides and so we prepared compound **189**,[133] but this failed to react with hydroxy selenide **166**.

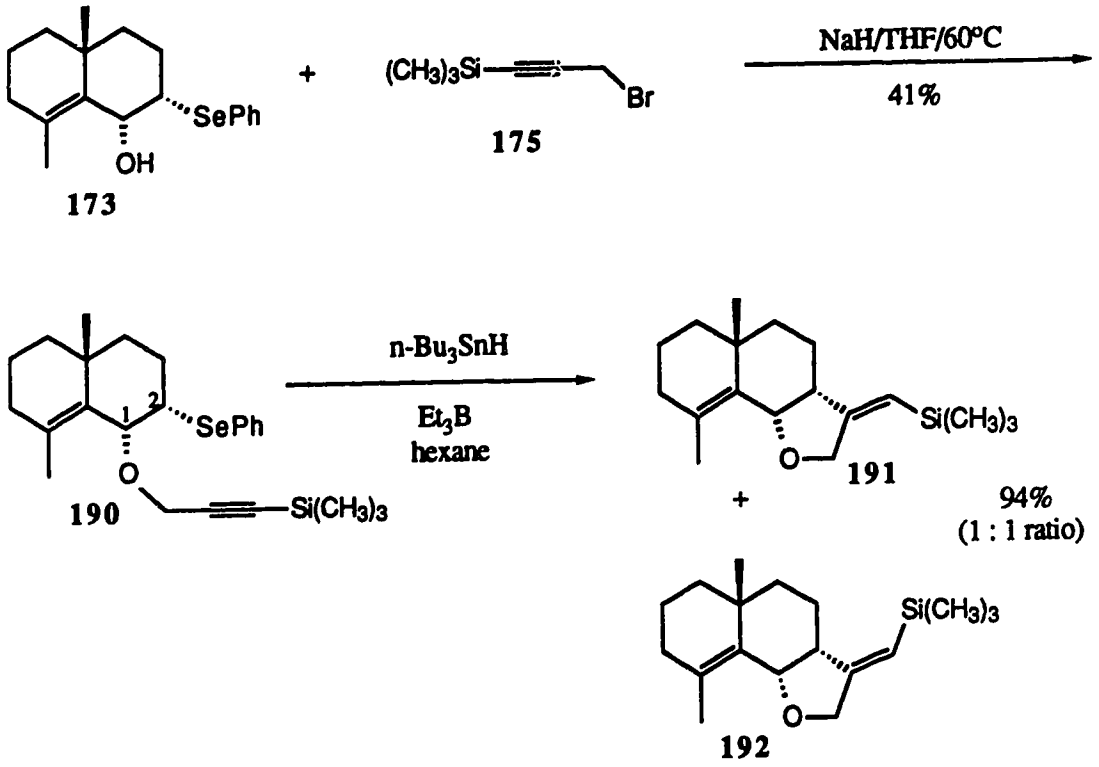
189

Clearly, it was not worthwhile to pursue the acylation studies, and so we turned to the other part of this project, that is, the demonstration that a ring could be formed on either face of our bicyclic system.

Based on the results we had obtained in the frullanolide series, we took the α-phenylseleno ketone **164** (see Scheme 48), which is the main product of the initial selenenylation in the frullanolide synthesis, and reduced it with diisobutylaluminum hydride. Alcohol **173** (Scheme 53) was produced in 70% yield and was, of course, differentiable by spectroscopic means from the isomeric alcohol **166** that had been taken on to the natural product. Alkylation as before, using bromo acetylene **175**, served to attach the unsaturated pendant (**173** → **190**) in 41% yield. [The *O*-silylated ether **174** (38% yield) was formed as a byproduct, which was reconverted (91% yield) into alcohol **173**. The corrected yield of **190** was, therefore, 75%.] Treatment of **190** with tributyltin hydride in the usual way[101] gave **191** and **192** in 90% yield, based on recovered starting material (Scheme 53). If no correction is made

for recovery of starting material then the yield was 75% [A second run was done and gave in 94% yield a mixture of both isomers in a 1:1 ratio (^{1}H NMR).] It is clear, therefore,

SCHEME 53



that our method does indeed provide access to a five-membered ring, fused, at will, on either face of the original bicyclic system. The isomers **191** and **192** could be resolved chromatographically and NOE experiments showed that the major product of the radical cyclization 39.5% (or 48% based on recovered starting material) had the *E* geometry shown in **192**. We did not take this material on to the corresponding α-methylene

lactone as that operation was now perceived as being superfluous to the main objective of the project.

III. Conclusion

The above experiments have led to a total synthesis[146] of (±)-frullanolide by methodology that allows attachment of a five-membered ring to either face of a cyclic structure.

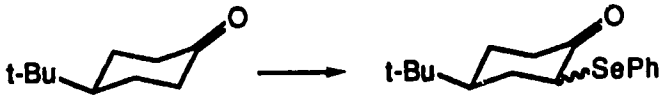
IV. Experimental

General Procedures: Unless stated to the contrary, the following particulars apply: When a solution was added over a specified time, the time refers to the main volume of the solution and not to the solvent used as a rinse; the latter was usually added at a fast dropwise rate. Reactions involving water-and air-sensitive reagents were done under argon, purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[134] and then through a similar column of Drierite. Glassware was dried in a oven for at least 3 h (130°C), cooled in a desiccator, assembled quickly, and sealed with rubber septa (when applicable). An inlet needle for argon was passed through a septum on the apparatus which was then kept under a static pressure of argon. Stirring was effected by using a dry Teflon-coated magnetic stirring bar. Solvents were distilled before use for chromatography or extractions. Where required, solvents and reagents were dried with suitable drying agents and distilled under argon. Dry tetrahydrofuran and benzene were distilled from sodium-benzophenone ketyl; triethylamine was distilled from calcium hydride. Commercial solutions (Aldrich) of *n*-butyllithium in hexanes were titrated before use by the diphenylacetic acid method.[135] Azobisisobutyronitrile (AIBN) from Eastman was

compounds were isolated by simple evaporation of their solutions, the residues were kept under vacuum (<0.1 mm) until of constant weight. Melting points were measured with a Kofler block melting point apparatus. Commercial silica (Merck 60F-254) thin layer chromatography (TLC) plates were used. Silica gel for flash column chromatography was Merck type 60 (230-400 mesh). TLC plates were examined under UV radiation (254 nm), treated with iodine vapor, and charred on a hot plate after being sprayed with a solution of phosphomolybidic acid.[136] Combustion elemental analyses were performed in the microanalytical laboratories of the University of Alberta. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR model. Liquids were run as neat films on potassium bromide plates, and solids were run as solutions in the specified solvent in 0.5-mm potassium bromide cells. Proton NMR spectra were recorded on Bruker WP-80 (at 80 MHz), Bruker WH-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker WH-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on Bruker WH-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker WH-400 (at 100.6 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. The following abbreviations are used in the text: br, broad; s,

Mass spectra were recorded on an A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 EV.

4-*tert*-Butyl-2-(phenylseleno)cyclohexanone (128):



A solution of phenylselenenyl chloride (1.92 g, 10 mmol) in dry ether (20 mL) was added dropwise over 1 h to a stirred and cooled (-78°C) solution of the trimethylsilyl enol ether of 4-*tert*-butylcyclohexanone[118] (2.26 g, 10 mmol) in ether (10 mL). After the addition was complete, the reaction mixture was allowed to warm to room temperature. The mixture was washed with 10% aqueous sodium bicarbonate (2 x 50 mL) and then water (2 x 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm) with 4% acetone--hexane gave an isomeric mixture of **128**[116] as a yellow oil (2.3 g, 74%): IR (film) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (s, 3.6 H), 0.92 (s, 5.4 H), 1.38--1.54 (m, 1 H), 1.73 (tt, J = 12.2, 3.0 Hz, 1 H), 2.00 (dt, J = 14.0, 4.5 Hz, 1 H), 2.05--2.13 (m, 1 H), 2.25--2.44 (m, 2 H), 2.60 (ddd, J = 14.0, 4.5, 3.0 Hz, 0.4 H), 3.14 (dt, J = 14.0, 6.0 Hz, 0.6 H), 3.84 (dt, J = 4.5, 2.25 Hz, 0.6 H), 4.08 (ddd, J = 14.0, 6.0, 1.0 Hz, 0.4 H), 7.20--7.32 (m, 3

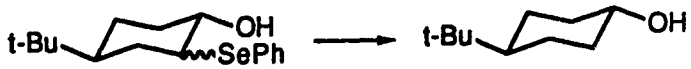
27.64 (minor), 32.14 (minor), 33.17 (minor), 33.97, 36.71, 40.15 (minor), 40.62, 41.16 (minor), 42.77, 47.82 (minor), 50.01 (minor), 50.33, 52,43, 127.64 (minor), 128.04, 128.26, 128.89 (minor), 129.12, 129.24 (minor), 134.16, 134.17 (minor), 207.50 (minor), 207.91; exact mass, *m/z* calcd for $C_{16}H_{22}OSe$ 310.0836, found 310.0836.

[1*R*-(1α,2α,4β)]- and [1*S*-(1α,2α,4β)]- and [1*R*-(1α,2β,4β)]- and [1*S*-(1α,2β,4β)]-4-*tert*-butyl-2-(phenylseleno)cyclohexanol (130).

A procedure described in the literature[120] was followed. Borane-methyl sulfide (2.0 M solution in THF, 8 mL, 16 mmol) was added dropwise over 10 min to a stirred solution of (phenylseleno)ketones **128** (3.5 g, 11.33 mmol). Stirring was continued for a further 18 h at room temperature, and then water (25 mL) was added. The mixture was stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 60 mL). The combined organic extracts were washed with water (2 x 100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm) with 10% ethyl acetate--hexane afforded an isomeric mixture of (phenylseleno)alcohols **130**

cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ 0.81 (s, 1.8 H), 0.86 (s, 7.2 H), 1.00--1.14 (m, 1 H), 1.24--1.38 (m, 2 H), 1.58--1.70 [series of m (including a doublet at 2.27, J = 10.5 Hz), 2 H], 2.87--2.98 (m, 0.2 H), 3.28 (ddt, J = 10.5, 4.5, 1.5 Hz, 0.2 H), 3.56 (tt, J = 11.0, 4.0 Hz, 0.8 H), 3.78 (dt, J = 6.0, 4.0 Hz, 0.8 H), 7.21--7.35 (m, 3 H), 7.57--7.66 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 25.40, 27.60 (minor), 27.64, 32.13, 32.44 (minor), 33.38, 33.68, 34.82 (minor), 43.02, 48.87 (minor), 54.25 (minor), 57.80, 71.62, 72.72 (minor), 127.32, 128.08 (minor), 129.05 (minor), 129.15, 130.87, 133.85, 135.80 (minor); exact mass, *m/z* calcd for $C_{16}H_{24}OSe$ 312.0992, found 312.0990.

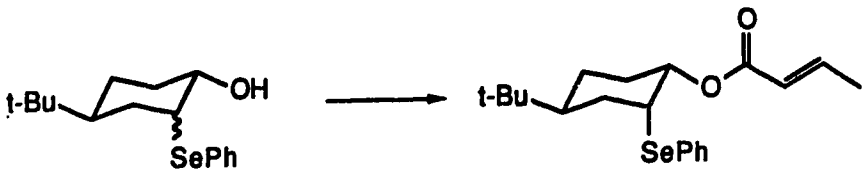
Reduction of Phenylseleno alcohols (130) with tributyltin hydride. Formation of *trans*-4-*tert*-butylcyclohexanol.



A solution of phenylseleno alcohols **130** (100 mg, 0.32 mmol), tributyltin hydride (0.114 mL, 0.425 mmol), and AIBN (2 mg) in toluene (7 mL) was heated at reflux for 3 h. The solvent was removed and flash chromatography of the residue over silica gel (1 x 17 cm) with 20% ethyl acetate--hexane yielded *trans*-4-*tert*-butylcyclohexanol (46.1 mg, 92%) as a white solid: mp 82°C (lit[121b] mp 83°C); IR ($CHCl_3$) 3670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (s, 9 H), 0.93--1.11 (m, 3 H), 1.13--

1.29 (m, 2 H), 1.65 (s, 1 H), 1.71--1.82 (m, 2 H), 1.95--2.06 (m, 2 H), 3.51 (tt, J = 11.0, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 25.61, 27.65, 32.29, 36.04, 47.19, 71.20.

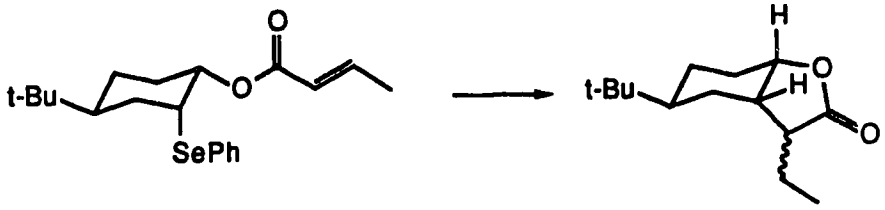
(*E*)-[1*R*-(1α,2α,4β)]- and [1*S*-(1α,2α,4β)]-[4-*tert*-Butyl-2-(phenylseleno)cyclohexyl]-2-butenoate (135).



A mixture of phenylseleno alcohols **130** (624 mg, 2 mmol) and crotonyl chloride (0.30 mL, 3.1 mmol) was heated at 100°C for 25 min under argon. The reaction mixture was taken up in ether (60 mL), washed with 10% aqueous sodium bicarbonate (2 x 40 mL), and then with water (2 x 40 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm) with 5% ethyl acetate--hexane afforded the phenylseleno ester **135** (602.3 mg, 79%) as a white solid: mp 55-56°C; IR (film) 1710, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (s, 9 H), 1.10--1.24 (m, 1 H), 1.42 (tt, J = 12.5, 3.0 Hz, 1 H), 1.64 (dt, J = 12.5, 3.0 Hz, 1 H), 1.79 (dd, J = 7.0, 1.9 Hz, 3 H), 1.81--1.95 (m, 3 H), 2.09 (dq, J = 14.0, 1.5 Hz, 1 H), 4.03 (dq, J = 4.0, 1.5 Hz, 1 H), 4.87 (dt, J = 11.0, 4.0 Hz, 1 H), 5.64 (dq, J = 15.5, 1.9 Hz, 1 H), 6.77 (dq, J = 15.5, 7.0 Hz, 1 H), 7.16--7.24 (m, 3 H), 7.50--7.60 (m, 2 H); ^{13}C NMR (CDCl3, 75,47 MHz) δ 17.95, 25.47, 27.50,

28.24, 32.12, 32.20, 42.30, 48.61, 74.39, 122.65, 127.08, 128.87, 130.09, 134.42, 144.60, 165.84; exact mass, *m/z* calcd for $C_{20}H_{28}O_2Se$ 380.1254, found 380.1248

[3*R*-(3α,3aβ,5β,7aβ)- and [3*S*-(3α,3aα,5α,7aα)-3a,4,5,6,7,7a-hexahydro-5-tert-butyl-3-ethyl-2 (3*H*)-benzofuranone (136).



Tributyltin hydride (0.24 mL, 0.90 mmol) in benzene (10 mL) and AIBN (6 mg, 0.042 mmol) in the same solvent (10 mL) were added simultaneously over 12 h by double syringe pump to a stirred and refluxing solution of phenylseleno ester **135** (313.0 mg, 0.82 mmol) in benzene (50 mL). Refluxing was continued for a further 6 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm) with 10% ethyl acetate--hexane yielded a mixture of isomeric benzofuranones **136** and **137** (82.3 mg, 45%). The isomer mixture had: IR (film) 1760 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ 0.7--2.7 (series of m, 23 H), 4.63 (isomer **136**, q, J = 5.0 Hz, 0.14 H), 4.41 (isomer **136**, dt, J = 11.0, 6.0 Hz, 0.75 H), 3.92 (isomer **137**, dt, J = 11.0, 2.0 Hz, 0.02 H), 3.66 (isomer **137**, dt, J = 11.0, 2.0 Hz, 0.09 H); ^{13}C NMR

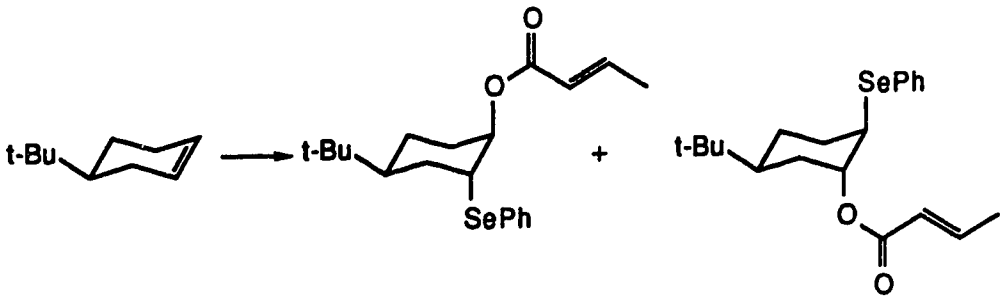
(CDCl3, 75,47 MHz) δ (isomer **136**): 10.85, 12.34 (minor), 18.84 (minor), 20.12 (minor), 21.22, 23.43, 25.40 (minor), 25.87, 26.75 (minor), 27.32, 28.13 (minor), 29.63, 32.07, 33.16 (minor), 35.12 (minor), 38.79 (minor), 39.68, 39.71 (minor), 41.39, 41.56, 76.89, 77.59 (minor), 178.79, 178.99 (minor); δ (isomer **137**): 11.33, 20.87, 24.87, 27.62, 28.59, 29.76, 32.45, 47.37, 47.68, 48.97, 82.57.

4-*tert*-Butylcyclohexene (140).[137]

Methanesulphonyl chloride (20 g, 0.175 mol) was added dropwise over 20 min to a stirred and cooled (-10°C) solution of *cis* and *trans* 4-*tert*-butylcyclohexanols **138** (15.6 g, 0.10 mol) in pyridine (40 mL). Stirring was continued for a further 18 h at 0°C. The mixture was cooled to -15°C, and cold water (200 mL) was then added. The crystals were filtered off, washed with water (2 x 100 mL), and dried under high vacuum to afforded the methanesulphonates **139** (23.40 g). The material was dissolved in collidine (40 mL) and heated at reflux with vigorous stirring for a period of 3 h, cooled and poured into a mixture of ice-cold hydrochloric acid (300 mL, 2 N). The product was taken up in pentane (3 x 100 mL) and the combined extracts were washed with water (3 x 100 mL), dried ($MgSO_4$), and evaporated. Vacuum distillation of the residue using a Vigreaux column (30 cm) afforded 4-*tert*-

butylcyclohexene (**140**) (10.69 g, 78%, > 98% pure by VPC) as a colorless liquid [bp 68-69°C (22 mm)], [lit[137] 85%, bp 54-55°C (10 mm)]. The material had: IR (film) 3010, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 9 H), 1.07--1.38 (series of m, 2 H), 1.72--1.87 (m, 2 H), 1.95--2.15 (m, 3 H), 5.70 (s, 2 H).

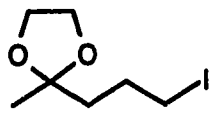
(*E*)-[1*R*-(1α,2β,4α)]- and (*E*)-[1*S*-(1α,2β,4α)]-[4-*tert*-butyl-2-(phenylseleno)cyclohexyl]-2-butenoate (141) and (*E*)-[1*R*-(1α,2β,5β)]- and (*E*)-[1*S*-(1α,2β,5β)]-[5-*tert*-butyl-2-(phenylseleno)cyclohexyl]-2-butenoate (142).



A solution of 4-*tert*-butylcyclohexene (1.87 g, 13.7 mmol) in dry dichloromethane (8 mL) was added dropwise over 10 min to a stirred solution of phenylselenenyl chloride (2.30 g, 12 mmol) in the same solvent (20 mL). After the color had been discharged, dry acetonitrile (60 mL) was added followed by silver (*E*)-2-butenoate[122] (2.62 g, 13.56 mmol). The mixture was kept in the dark overnight in a sonic bath at room temperature. Suction filtration through a pad of Celite (2 x 4 cm) using ether (3 x 50 mL) for washings, and concentration

under reduced pressure gave an orange oil. Flash chromatography over silica gel (5 x 20 cm) with 5% ethyl acetate--hexane yielded **141** and **142** (3.13 g, 68%) as an inseparable mixture of isomers. The mixture had: IR (film) 1710, 1650 cm^{-1}; 1H NMR ($CDCl_3$, 400 MHz) δ 7.50--7.65 (m, 2 H), 7.20--7.30 (m, 3 H), 6.88--7.00 (m, 1 H), 5.82 (d, J = 16.0 Hz, 1 H), 5.28 (br s, 0.5 H), 5.14 (br s, 0.5 H), 3.68 (br s, 0.5 H), 3.59 (br s, 0.5 H), 2.18--2.01 (m, 1 H), 2.00--1.92 (m, 1 H), 1.90--1.70 [m (including two singlets at 1.87 and 1.85), 4 H], 1.69--1.55 (m, 1 H), 1.44--1.20 (m, 3 H), 0.86 (s, 9 H). This mixture of isomers was saponified (NaOH, H_2O, MeOH) yielding a mixture of seleno alcohols (90%) **143** and **144**, which again could not be separated.

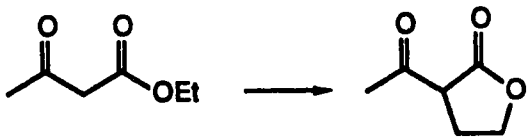
2-(3-Iodopropyl)-2-methyl-1,3-dioxolane (155).[138]



A mixture of 2-(3-chloropropyl)-2-methyl-1,3-dioxolane[139] (1.65 g, 0.01 mol), sodium iodide (3.0 g, 0.02 mol), and acetone (20 mL) was heated at reflux under argon for 2 h. The mixture was cooled and evaporated. The dark red residue was taken up in ether (2 x 100 mL) and the solution was washed with water (2 x 100 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm) with 10% ethyl acetate--hexane afforded (^1H

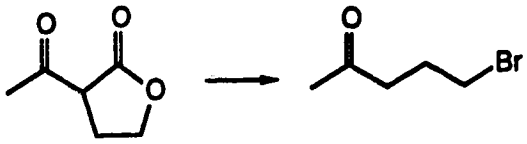
NMR) the iodoketal **155** as a dark red oil (1.65 g, 64%). The material was used immediately without full characterization.

α-Acetyl-γ-butyrolactone (156).[140]



Ice-cold ethylene oxide (44 g, 1.0 mol) and then ethyl acetoacetate (145.7 g, 1.12 mol), also at 0°C, were added rapidly to a stirred and cooled (0 to -5°C) solution of sodium hydroxide (44.8 g, 1.12 mol) in a mixture of water (300 mL) and ethanol (100 mL). The mixture was kept at 0 to -5°C for 48 h and was then neutralized at this temperature with glacial acetic acid (300 g). The product was extracted with dichloromethane (4 x 100 mL) and the organic layer was washed with water (3 x 200 mL), dried ($MgSO_4$), and evaporated. Distillation of the residue afforded α-acetyl-γ-butyrolactone **156** (69 g, 54%) as a colorless liquid [bp 78-80°C (0.7 mm)], [lit.[140] bp 107-108°C (5 mm), 60%]. The compound had ^1H NMR ($CDCl_3$, 200 MHz), δ 4.42--4.28 (m, 2 H), 3.80 (dd, J = 1.70, 1.50 Hz, 1 H), 2.82--2.60 (m, 1 H), 2.58--2.23 [m (including a singlet at 2.42), 4 H].

5-Bromo-2-pentanone (157).[138]

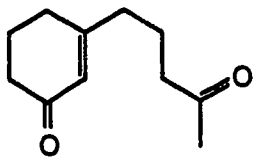


A mixture of hydrobromic acid (48% w/v, 20.3 mL), water 17.5 mL), and α-acetyl-γ-butyrolactone **156** (12.8 g, 0.1 mol) were placed in a 100 mL distilling flask containing a boiling chip and fitted with a condenser and a receiver that was immersed in an ice-water bath. The still pot temperature was raised at such a rate that the reaction mixture did not foam into the condenser. After about 30 mL of distillate had been collected, water (15 mL) was added to the distilling flask and another portion (10 mL) of distillate was collected. The organic layer of the distillate was separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic extracts were mixed with the original organic layer of the distillate, dried ($MgSO_4$), and evaporated. Distillation of the residue afforded 5-bromo-2-pentanone **157** [8.02 g, 48%, bp.82-84°C (18 mm)], [lit.[138] bp 77°C (14 mm), 78%]. The material had: ^1H NMR ($CDCl_3$, 200 MHz), δ 2.14 (quintet, J = 6.0 Hz, 2 H), 2.18 (s, 3 H), 2.68 (t, J = 6.0 Hz, 2 H), 3.48 (t, J = 6.0 Hz, 2 H).

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane (158).[138]

A stirred mixture of 5-bromo-2-pentanone **157** (4.0 g, 24.24 mmol), 1,2-ethanediol (1.5 mL), *p*-toluenesulfonic acid (92 mg), 3Å molecular sieves (15 g), and benzene (25 mL) was heated at reflux under argon for 4.3 h. The mixture was cooled and washed with saturated aqueous sodium bicarbonate (25 mL) and the organic layer was separated, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm) with 8% ethyl acetate--hexane afforded 2-(3-bromopropyl)-2-methyl-1,3-dioxolane (4.0 g, 79%) as a light yellow, homogeneous (TLC, silica, 8% ethyl acetate--hexane) liquid: ^1H NMR ($CDCl_3$, 200 MHz), δ 1.30 (s, 3 H), 1.72--2.06 (m, 4 H), 3.42 (t, J = 6.0 Hz, 2 H), 3.92 (m, 4 H).

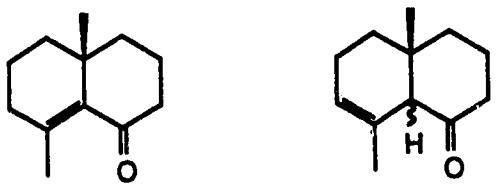
3-(4-Oxopentyl)-2-cyclohexen-1-one (154).[123]



A solution of Grignard reagent (15 mL) [prepared from magnesium turnings (486 mg, 19.99 mmol) and 2-(3-bromopropyl)-2-methyl-1,3-dioxolane[138] **158** (4.18 g, 19.19 mmol) in

dry THF (17.5 mL)]^{141} was added under argon over about 20 min to a stirred and cooled (-60°C) solution of 3-ethoxy-2-cyclohexenone (1.40 g, 10 mmol) in dry THF (30 mL). The reaction mixture was kept at -60°C for 1 h, and at -30°C for 1 h, and then the cold-bath was removed. When the mixture had attained room temperature the solvent was evaporated and the crude product was stirred and warmed (40-50°C) with hydrochloric acid (40 mL, 0.5 N) for 2 h. The mixture was cooled and extracted with ether (5 x 100 mL) and the combined extracts were washed with water (3 x 200 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm) with 30% ethyl acetate--hexane yielded 3-(4-oxopentyl)-2-cyclohexen-1-one **154** (1.45 g, 80%) as a pale yellow, homogeneous (TLC, silica, 30% ethyl acetate--hexane) oil: IR (KBr, $CHCl_3$) 1705, 1660, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.79 (quintet, J = 7.5 Hz, 2 H), 2.00 (quintet, J = 6.5 Hz, 2 H), 2.15 (s, 3 H), 2.23 (t, J = 7.5 Hz, 2 H), 2.31 (t, J = 6.5 Hz, 2 H), 2.35 (t, J = 6.5 Hz, 2 H), 2.48 (t, J = 7.5 Hz, 2 H), 5.86 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 20.43, 22.42, 29.24, 29.76, 36.92, 37.07, 42.30, 125.64, 165.29, 199.38, 207.66; exact mass, *m/z* calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1151. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.9; O, 17.75. Found: C, 73.07; H, 8.83.

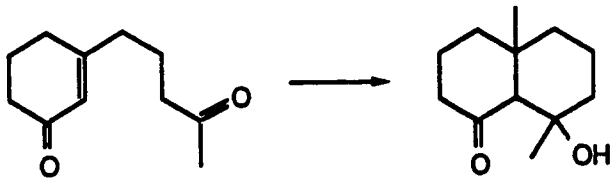
3,4,4a,5,6,7-Hexahydro-4a,8-dimethyl-1(2*H*)-naphthalenone (153) and 3,4,4a,5,6,8a-Hexahydro-4a,8-dimethyl-1(2*H*)-naphthalenone (162).



Methyllithium (1.4 M in ether, 47.3 mL, 66.16 mmol) was added dropwise over *ca* 10 min to a stirred and cooled (-78°C) suspension of copper(I) iodide[142] (6.3 g, 33.08 mmol) in dry ether (136 mL). The cooling-bath was exchanged for one at -15°C and, after 15 min, the original cooling-bath (-78°C) was replaced. A solution of diketone **154** (4.91 g, 27.28 mmol) in dry ether (73 mL) was added dropwise with stirring over *ca* 20 min. The mixture was stirred at -78°C for a further 1.5 h, and then at ice-bath temperature for 1 h, and it was then poured into ice-cold hydrochloric acid (400 mL, 1 N) and stirred for 15 min. The mixture was adjusted to pH 8 with concentrated ammonium hydroxide and the organic layer was separated. The aqueous phase was extracted with ether (2 x 100 mL) and the combined extracts were washed with water (2 x 100 mL), dried (Na_2SO_4) and evaporated. A solution of the residue in benzene (400 mL) containing *p*-toluenesulfonic acid monohydrate (10 g) and 3Å molecular sieves was stirred and refluxed for 4 h under argon. The mixture was filtered,

mL) and water (2 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (repeated three times) of the residue over silica gel (5 x 20 cm) using 3% ethyl acetate--hexane afforded **153** (2.60 g, 54%), **162** (1.08 g, 22%) and a third isomer (60 mg, 1%). Compound **153** was a white solid and had: mp 45-47°C; FT-IR ($CHCl_3$ cast) 1689, 1627 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 3 H), 1.36--1.50 (m, 1 H), 1.53--1.70 (m, 5 H), 1.74 (s, 3 H), 1.80--2.13 (m, 4 H), 2.31 (ddd, J = 15, 12.5, 7.5 Hz, 1 H), 2.44--2.54 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.26, 20.60, 21.18, 25.32, 33.17, 37.64, 38.31, 40.21, 43.33, 138.70, 139.20, 206.35; exact mass, *m/z* calcd for $C_{12}H_{18}O$ 178.1358, found 178.1360. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18; O, 8.98. Found: C, 80.94; H, 10.19. Compound **162** was a pale yellow oil and had: FT-IR ($CHCl_3$ cast) 1711, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (s, 3 H), 1.13--1.24 (quintet, J = 6.5 Hz, 1 H), 1.40--1.55 (sextet, J = 6.5 Hz, 2 H), 1.61 (br s, J = 1.0 Hz, 3 H), 1.74--1.92 (m, 2 H), 1.96--2.23 (m, 2 H), 2.28 (t, J = 6.5 Hz, 2 H), 2.55 (br s, 1 H), 5.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 22.30, 22.49, 22.73, 26.57, 31.78, 34.35, 40.34, 62.02, 122.49, 129.92, 213.26; exact mass, *m/z* calcd for $C_{12}H_{18}O$ 178.1358, found 178.1357. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18; O, 8.98. Found: C, 80.94; H, 10.14.

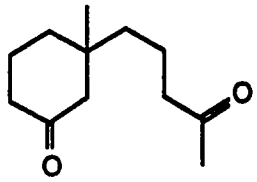
3,4,4a,5,6,7,8,8a-Octahydro-8-hydroxy-4a,8-dimethyl-1(2*H*)-naphthalenone (159).[123]



Methyllithium (1.4 M in ether, 5.14 mL, 7.20 mmol) was added dropwise over *ca* 2 min to a stirred and cooled (-78°C) suspension of copper(I) iodide[142] (712.5 mg, 3.60 mmol) in dry ether (15 mL). The cooling-bath was exchanged for one at -15°C and, after 10 min, the original cooling-bath (-78°C) was replaced. A solution of diketone **154** (540 mg, 3.0 mmol) in dry ether (8 mL) was added dropwise with stirring over *ca* 5 min. The mixture was stirred at -78°C for a further 1.5 h, and then at ice-bath temperature for 1 h, and it was then poured into ice-cold hydrochloric acid (40 mL, 1 N) and stirred for 15 min. The mixture was adjusted to pH 8 with concentrated ammonium hydroxide and the organic layer was separated. The aqueous phase was extracted with ether (2 x 50 mL) and the combined extracts were washed with water (2 x 50 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm) with 15% ethyl acetate--hexane afforded **159** (362.5 mg, 51%): IR (film) 3450, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 3 H), 1.20--1.60 [series of m (including a singlet at 1.28), 8 H], 1.64--1.74 (m, 1 H), 1.80--2.00 (m, 4 H), 2.22--2.36 [quintet (including

a broad singlet at 2.26), J = 8.5 Hz, 2 H], 2.44--2.58 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.01, 20.56, 28.73, 30.53, 33.98, 37.88, 39.35, 40.86, 66.50, 75.56, 214.57, (two signals are coincident in this spectrum); exact mass, *m/z* calcd, for $C_{12}H_{20}O_2$ 196.39, found 196.39.

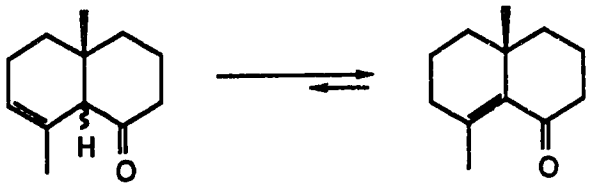
3-Methyl-3-(4-oxopentyl)cyclohexanone (163).[123]



Methyllithium (1.48 M in ether, 3.24 mL, 4.80 mmol) was added dropwise over *ca* 2 min to a stirred and cooled (-15°C) suspension of copper(I) iodide[142] (475 mg, 2.40 mmol) in dry ether (10 mL). The cooling-bath was exchanged for one at -78°C and a cooled (0°C) solution of diketone **154** (360 mg, 2.0 mmol) in dry ether (5 mL) was added dropwise with stirring over *ca* 3 min. The mixture was stirred at -78°C for a further 1.5 h, and then at ice-bath temperature for 1 h, and methanol (1 mL) was added, followed by ice-cold hydrochloric acid (27 mL, 1 N). The mixture was stirred for 20 min. The organic layer was separated and the aqueous phase was extracted with ether (4 x 30 mL). The combined extracts were washed with water (3 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm) with 30% ethyl acetate--hexane afforded **163** (221 mg,

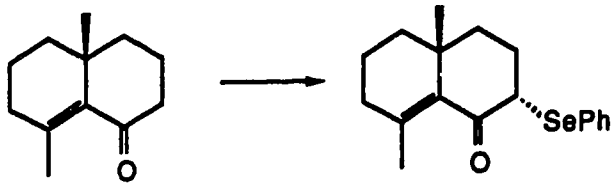
56%): IR (film) 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 3 H), 1.17--1.27 (m, 2 H), 1.46--1.72 (series of m, 4 H), 1.80--1.92 (q, J = 6.5 Hz, 2 H), 2.07--2.23 [m (including a singlet at 2.13), 5 H], 2.23--2.32 (t, J = 7 Hz, 2 H), 2.36--2.46 (t, J = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 17.62, 22.09, 25.05, 29.98, 35.54, 38.58, 40.78, 40.99, 43.94, 53.75, 208.61, 212.07.

Isomerization of 3,4,4a,5,6,8a-Hexahydro-4a,8-dimethyl-1(2*H*)-naphthalenone (162) to 3,4,4a,5,6,7-Hexahydro-4a,8-dimethyl-1(2*H*)-naphthalenone (153).



A solution of the β,γ-enone **162** (80 mg, 0.449 mmol) in 20% ethanol--benzene (8 mL), containing a catalytic amount of rhodium trichloride trihydrate (*ca* 2 mg) was refluxed for 28 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm) with 5% ethyl acetate--hexane afforded a mixture (79 mg, 0.443 mmol, 99%) of the α,β-enone **153** and the β,γ-enone **162** in a ratio (^1H NMR) of 2:1. This procedure was used to recycle compound **162** from previous experiments and the desired isomer **153** was isolated by flash chromatography over silica gel using 3% ethyl acetate--hexane.

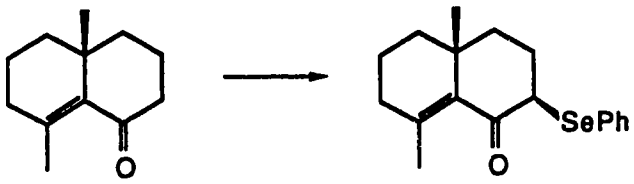
(2*R*,*trans*)- and (2*S*,*trans*)-3,4,4a,5,6,7-Hexahydro-4a,8-dimethyl-2-(phenylseleno)-1(2*H*)-naphthalenone (164).



A solution of the α,β-enone **153** (178.14 mg, 1 mmol) in dry THF (2 mL) was added dropwise over 30 min to a stirred and cooled (-78°C) solution of LDA [prepared from diisopropylamine (1.65 mmol) and *n*-butyllithium (1.3 mmol) in THF (4 mL)]. Stirring was continued for a further 1.5 h at -78°C and phenylselenenyl chloride (1.8 mmol) in THF (1 mL) was added in one portion. The cooling-bath was exchanged for one at -30°C and, after 2 h, the reaction was quenched with glacial acetic acid (112 μL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 18 cm) with 4% ethyl acetate--hexane afforded the α-(phenylseleno) ketone **164** (273 mg, 82%) and the β-epimer **165** (46 mg, 14%). The α-epimer **164** was a pale yellow solid: mp 70-73°C; FT-IR ($CHCl_3$ cast) 1673, 1625, 1575, 1475, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.0 (s, 3 H), 1.51--1.70 (m, 5 H), 1.73 (s, 3 H), 1.81 (dt, J = 14, 4 Hz, 1 H), 2.55 (ddt, J = 14, 4.5, 4 Hz, 1 H), 3.91 (dt, J = 4.5, 1.5 Hz, 1 H), 7.26 (m, 3 H), 7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.30 (t), 21.30 (q), 25.34 (q), 27.70 (t), 33.13 (t), 36.98 (t), 37.69

(s), 38.23 (t), 53.06 (d), 127.85 (d), 129.15 (d), 129.46 (s), 133.93 (d), 136.47 (s), 142.30 (s), 200.56 (s); exact mass, *m/z* calcd for $C_{18}H_{22}OSe$ 334.0836, found 334.0835. Anal. Calcd for $C_{18}H_{22}OSe$: C, 64.86; H, 6.65; O, 4.80; Se, 23.69. Found: C, 64.70; H, 6.69; O, 5.07.

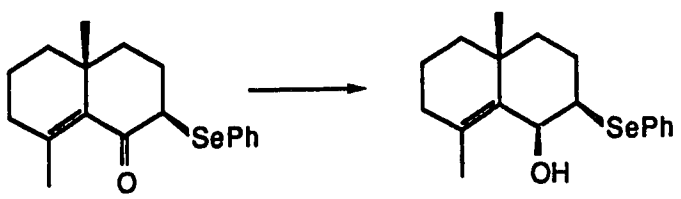
(2*R*,*cis*)- and (2*S*,*cis*)-3,4,4a,5,6,7-Hexahydro-4a,8-dimethyl-2-(phenylseleno)-1(2*H*)-naphthalenone (165)..



A solution of the α,β-enone **153** (248 mg, 1.39 mmol) in THF (2 mL plus 0.5 mL as a rinse) was injected over 5 min into a stirred solution of LDA [made from diisopropylamine (0.24 mL, 1.7 mmol) and *n*-butyllithium (1.59 M in hexanes, 1.05 mL, 1.65 mmol) in dry THF (10 mL)] at -78°C. Stirring was continued for 15 min and phenylselenenyl chloride (350 mg, 1.83 mmol) in THF (1 mL) was then injected in one portion. The mixture was stirred for 20 min at -78°C, and transferred by cannula over 20 min to a stirred and cooled (-78°C) solution of LDA, prepared on the same scale as described above. Stirring was continued at -78°C for 30 min and the reaction was quenched by addition of saturated aqueous ammonium chloride (10 mL). The mixture was allowed to warm

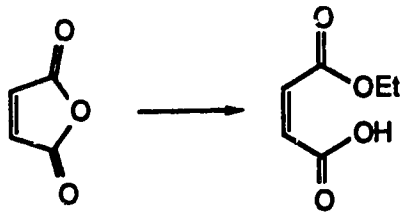
to room temperature and was then extracted with ether (3 x 30 mL). The extracts were washed with brine (50 mL) and water (3 x 50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm) with 4% ethyl acetate--hexane yielded the β-isomer **165** (330 mg, 71%) as a homogeneous (TLC, silica, 5% ethyl acetate--hexane) orange oil, and the α-isomer **164** (54 mg, 12%) as a homogeneous (TLC, silica, 5% ethyl acetate--hexane) oil. The β-isomer **165** had: FT-IR ($CHCl_3$ cast) 1678, 1625, 1580, 1476, 1455, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 3 H), 1.30--1.48 (m, 1 H), 1.52--1.60 (m, 5 H), 1.60 (s, 3 H), 2.00--2.20 (m, 4 H), 4.18 (dd, J = 12.5, 7.5 Hz, 1 H), 7.28 (m, 3 H), 7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.26, 21.20, 25.40, 30.15, 32.98, 38.07, 38.19, 41.18, 55.49, 127.74, 128.12, 128.95, 135.62, 138.53, 139.46, 202.36; exact mass, *m/z* calcd for $C_{18}H_{22}OSe$ 334.0836, found 334.0833. Anal. Calcd for $C_{18}H_{22}OSe$: C, 64.86; H, 6.65; O, 4.80; Se, 23.69. Found: C, 64.94; H, 6.74; O, 4.92.

[1*R*-(1α,2α,4aα)]- and [1*S*-(1α,2α,4aα)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-naphthalenol (166).



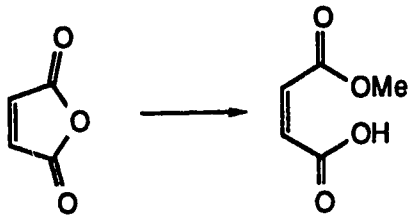
Diisobutylaluminum hydride (1.0 M solution in hexane, 4.66 mL, 4.66 mmol) was added dropwise over 35 min to a stirred and cooled (-78°C) solution of phenylseleno ketone **165** (775 mg, 2.33 mmol) in toluene (28 mL). Stirring was continued for a further 3 h at -78°C and then methanol (5 mL) was added followed by aqueous acetic acid (50% v/v, 2 mL), and the mixture was allowed to warm to room temperature. The solvents were evaporated, the residue was extracted with 10% ethyl acetate--hexane (3 x 20 mL), and the combined organic extracts were washed with water (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm) with 5% ethyl acetate--hexane afforded phenylseleno alcohol **166** (546 mg, 70%) as a homogeneous (TLC, silica, 5% ethyl acetate--hexane), pale yellow oil: FT-IR ($CDCl_3$ cast) 3470, 1625, 1595, 1477, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18--1.33 (m, 5 H), 1.37--1.46 (dt, J = 13, 3.5 Hz), 1 H), 1.50--1.84 (series of m, 7 H), 1.88--2.10 (m, 2 H), 2.22 (dq, J = 13, 3.5 Hz, 1 H), 2.23 (br s, 1 H), 3.33 (ddd, J = 13, 4, 3 Hz, 1 H), 4.71 (br s, 1 H), 7.28 (m, 3 H), 7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.55, 19.03, 24.01, 26.98, 33.47, 40.98, 43.01, 51.95, 67.56, 127.53, 128.91, 129.12, 132.79, 134.22, 134.25; exact mass, *m/z* calcd for $C_{18}H_{24}OSe$ 336.0993, found 336.1000. Anal. Calcd for $C_{18}H_{24}OSe$: C, 64.47; H, 7.26; O, 4.80; Se, 23.69. Found: C, 64.48; H, 7.14.

Ethyl hydrogen maleate.[143]



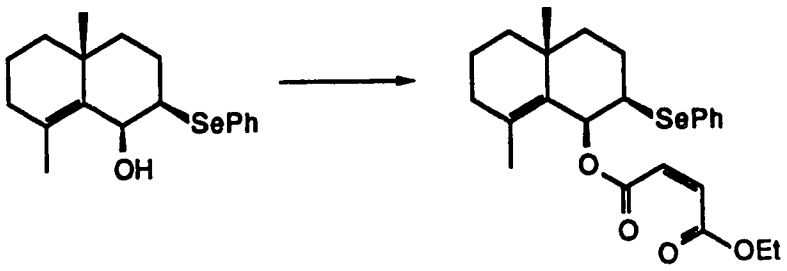
A solution of maleic anhydride (9.80 g, 0.10 mol) in dry ethanol (25 mL) was heated at reflux for 2 h. The excess of ethanol was removed (water pump) and vacuum distillation of the crude product afforded ethyl hydrogen maleate (13.7 g, 95%) as a colorless liquid: bp 117-118°C (2.4 mm); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.38 (t, J = 7.0 Hz, 3 H), 4.38 (q, J = 7.0 Hz, 2 H), 6.45 (s, 2 H), 12.20 (br s, 1 H).

Methyl hydrogen maleate.[143]



A solution of maleic anhydride (3.70 g, 0.038 mol) in dry methanol (15 mL) was heated at reflux for 1 h. The excess of methanol was evaporated and vacuum distillation of the crude product gave methyl hydrogen maleate (4.16 g, 84%) as a colorless liquid: bp 125-126°C (4.5 mm); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 3.81 (s, 3H), 6.50 (s, 2 H), 12.25 (s, 1 H).

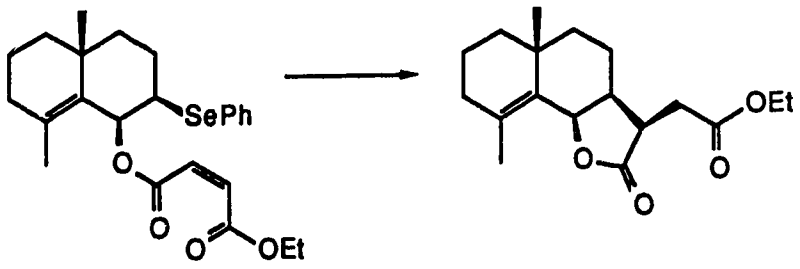
Ethyl [1*R*-(1α,2α,4aα)]- and [1*S*-(1α,2α,4aα)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-naphthalenyl maleate (168).



Solutions of ethyl hydrogen maleate (254.4 mg, 1.62 mmol), DMAP (144 mg, 1.08 mmol), and then DCC (485 mg, 2.16 mmol), each in dichloromethane (5 mL), were added to a stirred and cooled (0°C) solution of phenylseleno alcohol **166** (120 mg, 0.36 mmol) in dry dichloromethane (20 mL). Stirring was continued for 10 min and the mixture was allowed to warm to room temperature. After 12 h (TLC control, silica, 10% ethyl acetate--hexane), the mixture was filtered through a pad of silica gel (2 x 3 cm) using 2% triethylamine--dichloromethane (50 mL). The solvent was evaporated, the residue was taken up in hexane (30 mL), filtered, and evaporated to afford phenylseleno ester **168** (134 mg, 80%). The compound, which contained trace impurities (TLC), had: FT-IR ($CHCl_3$ cast) 1720, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 3 H), 1.20--1.32 (m, 2 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.41--1.68 (series of m, 4 H), 1.75 (s, 3H), 1.90--2.02 (m 3 H), 2.28

(dq, J = 13.5, 3.5 Hz, 1 H), 3.22 (ddd, J = 13.5, 4.5, 2.5 Hz, 1H), 4.28 (q, J = 7.0 Hz, 2 H), 6.13 (d, J = 2.5 Hz, 1 H), 6.85 (d, J = 3.5 Hz, 2 H), 7.23--7.30 (m, 3 H), 7.54--7.59 (m 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.17, 18.44, 19.63, 25.73, 26.75, 33.60, 33.75, 41.34, 42.71, 48.14, 61.30, 73.36, 127.64, 129.04, 129.19, 131.35, 133.42, 134.09, 134.66, 135.58, 163.79, 165.14.

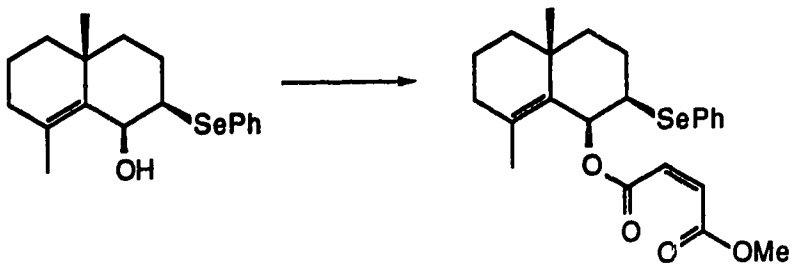
Ethyl [3*R*-(3α,3aβ,5aα,9bβ)]- and [3*S*-(3α,3aβ,5aα,9bβ)]-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-5a,9-dimethyl-2-oxonaphtho[1-2b]furan-3-ylacetate (170, R = Ethyl).



Triphenyltin hydride (13.9 mg, 0.0396 mmol) in benzene (2 mL) and AIBN (0.5 mg, 0.0033 mmol) in benzene (2 mL) were added simultaneously over 6 h by syringe pump to a stirred and refluxing solution of phenylseleno ester **168** (18.0 mg, 0.039 mmol) in the same solvent (2 mL). Refluxing was continued for a further 6 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (0.7 x 10 cm) with 10% ethyl acetate--hexane gave the cyclized product **170** (R = ethyl) (8.9 mg, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$,

200 MHz) δ 1.16--1.40 (m, including a singlet at 1.20 and a triplet at 1.38 (J = 7.0 Hz), 8 H), 1.42--1.88 [series of m (including a singlet at 1.60), 8 H], 2.00--2.15 (m, 3 H), 2.66 (dd, J = 5.5, 2.0 Hz, 2 H), 3.15 (dt, J = 13.0, 5.5 Hz, 1 H), 3.60 (dd, J = 13.0, 7.5 Hz, 1 H), 4.18 (q, J = 7.0 Hz, 2 H), 4.49 (ddd, J = 11.0, 7.5, 6.0 Hz, 1 H); exact mass, *m/z* calcd for $C_{18}H_{26}O_4$ 306.1831, found 306.1835.

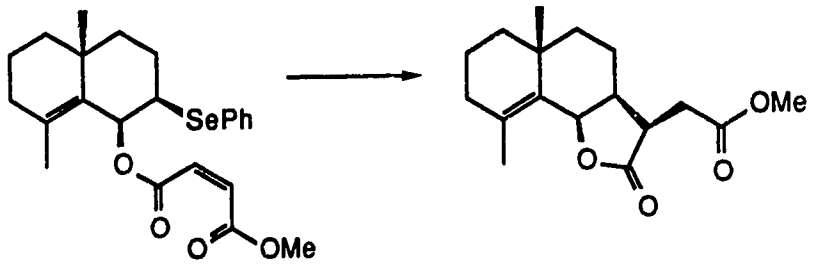
Methyl [1*R*-(1α,2α,4aα)]- and [1*S*-(1α,2α,4aα)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-naphthalenyl maleate (169).



Solutions of methyl hydrogen maleate (70.2 mg, 0.54 mmol), DMAP (44 mg, 0.36 mmol), and then DCC (148.3 mg, 0.72 mmol), each in dichloromethane (2 mL) were added to a stirred and cooled (0°C) solution of phenylseleno alcohol **166** (60.5 mg, 0.36 mmol) in dry dichloromethane (9 mL). Stirring was continued for 10 min and the mixture was then allowed to warm to room temperature. After 6 h (TLC control, silica, 10% ethyl acetate--hexane), the solvent was removed and the residue taken up in hexane (100 mL), washed with hydrochloric

acid (0.30 N, 2 x 75 mL), and water (2 x 50 mL), and evaporated. The residue was filtered through a pad of Florisil (2 x 5 cm) with 10% ethyl acetate--hexane (30 mL), and removal of the solvents afforded the phenylseleno ester **169** (65.0 mg, 81%). The compound, which contained trace impurities (TLC), was used directly in the next step. The material had: FT-IR ($CHCl_3$ cast) 1725, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.13 (s, 3 H), 1.20--1.74 (series of m, 6 H), 1.76 (s, 3 H), 1.86--2.10 (m, 3 H), 2.30 (dq, J = 13.5, 3.5 Hz, 1 H), 3.25 (dq, J = 13.5, 4.5, 2.5 Hz, 1 H), 3.85 (s, 3 H), 6.15 (d, J = 2.5 Hz, 1 H), 6.90 (d, J = 2.0 Hz, 2 H),7.23--7.36 (m, 3 H), 7.51--7.66 (m, 2 H).

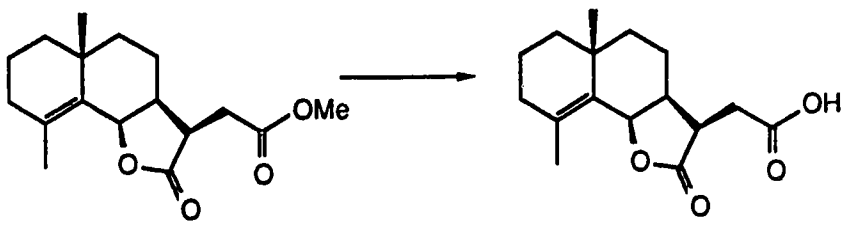
Methyl [3*R*-(3α,3aβ,5aα,9bβ)]- and [3*S*-(3α,3aβ,5aα,9bβ)]-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-5a,9-dimethyl-2-oxonaphtho[1-2b]furan-3-ylacetate (170, R = Methyl).



Triphenyltin hydride (27.8 mg, 0.0792 mmol) in benzene (2 mL)

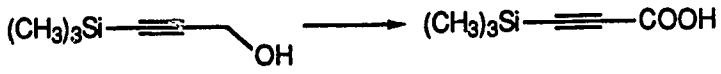
mmol) in the same solvent (5 mL). Refluxing was continued for a further 6 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1 x 18 cm) with 20% ethyl acetate--hexane gave the cyclized product **170** (R = methyl) (9.0 mg, 78%) as a colorless oil: FT-IR (CH_2Cl_2 cast) 1775, 1741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (s, 3 H), 1.19--1.37 (m, 2 H), 1.40--1.88 [series of m (including a singlet at 1.59), 8 H], 1.96--2.12(m, 3 H), 2.65 (dq, J = 8.0, 5.5 Hz, 2 H), 3.15 (dt, J = 13.0, 5.5 Hz, 1 H), 3.57 (dd, J = 13.0, 7.8 Hz, 1 H), 3.69 (s, 3 H), 4.47 (ddd, J = 11.2, 7.8, 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.31, 19.89, 24.97, 26.50, 32.60, 33.21, 33.63, 37.03, 41.04, 41.53, 51.90, 78.90, 129.96, 132.85, 171.63, 177.23, (two signals are coincident in this spectrum); exact mass, *m/z* calcd for $C_{17}H_{24}O_4$ 292.1675, found 292.1670.

[3*R*-(3α,3aβ,5aα,9bβ)]- and [3*S*-(3α,3aβ,5aα,9bβ)]-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-5a,9-dimethyl-2-oxonaphtho[1-2b]furan-3-ylacetic acid (171).



water--dioxane (7 mL) was stirred at room temperature for 1 h (TLC control, silica gel, 20% ethyl acetate--hexane). The reaction mixture was washed with dichloromethane (1 x 15 mL), and the aqueous phase was separated, acidified with hydrochloric acid (2 N), and extracted with dichloromethane (2 x 15 mL). The combined organic extracts were washed with water (2 x 15 mL), dried ($MgSO_4$), and evaporated to give the acid-lactone **171** (26.6 mg, 86%): FT-IR ($CHCl_3$ cast) 3600--2400, 1773, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (s, 3 H), 1.20 --1.35 (m, 2 H), 1.43--1.87 [series of m (including a singlet at 1.63), 8 H], 1.99--2.11 (m, 3 H), 2.69 (dq, J = 8.0, 5.5 Hz, 2 H), 3.14 (dt, J = 13.0, 5.5 Hz, 1 H), 3.58 (dd, J = 13.0, 7.8 Hz, 1 H), 4.49 (ddd, J = 11.2, 7.8, 6.0 Hz, 1 H), 9.53 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.17, 19.92, 24.22, 26.45, 32.41, 33.06, 33.52, 36.90, 40.94, 41.27, 41.34, 79.03, 129.63, 133.06, 176.70, 177.26; exact mass, *m/z* calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1518.

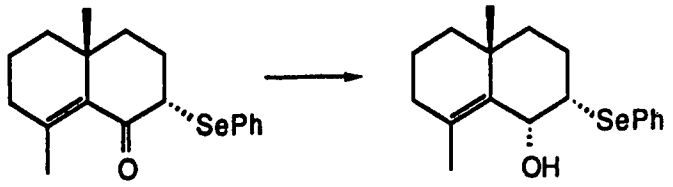
3-(Trimethylsilyl)-2-propynoic acid (172).[126]



A solution of chromium trioxide (9.4 M) in sulfuric acid (5.5 M) was added dropwise to a stirred solution of 3-hydroxy-1-(trimethylsilyl)-1-propyne[144] (2.56 g, 20.0 mmol) in acetone

isopropanol was added until the color of the mixture changed to green. The solution was neutralized with saturated aqueous sodium bicarbonate and filtered, and the solid was washed with acetone (10 mL). The combined extracts were evaporated and vacuum distillation afforded 3-(trimethylsilyl)-2-propynoic acid **172** (2,20 g, 86%) [bp 62°C (0.20 mm)] as a colorless liquid: IR (film) 3500--2500, 2180, 1685 (broad) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.13 (s, 9 H), 10.45 (br s, 1 H).

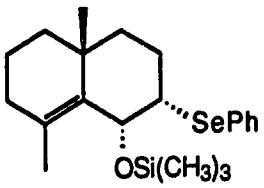
[1*R*-(1α,2α,4aβ)]- and [1*S*-(1α,2α,4aβ)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-naphthalenol (173).



Diisobutylaluminum hydride (1.0 M solution in hexane, 2.65 mL, 2.65 mmol) was added dropwise over 20 min to a stirred and cooled (-78°C) solution of phenylseleno ketone **164** (493 mg, 1.48 mmol) in toluene (17 mL). Stirring was continued for a further 1 h at -78°C and then methanol (3 mL) was added, followed by aqueous acetic acid (50% v/v, 1 mL), and the mixture was allowed to warm to room temperature. The solvents were evaporated and the residue was extracted with

extracts were washed with water (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm) with 5% ethyl acetate--hexane afforded phenylseleno alcohol **173** (350 mg, 70%) as a homogeneous (TLC, silica, 5% ethyl acetate--hexane), pale yellow oil: FT-IR ($CHCl_3$ cast) 3470, 1650, 1580, 1477, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 3 H), 1.24--1.45 (m, 3 H), 1.54--1.74 (m, 3 H), 1.76 (s, 3 H), 1.78--2.15 (m, 3 H), 2.18 (m, 1 H), 2.48 (d, J = 4.5 Hz, 1 H), 3.76 (dt, J = 7.5, 3.0 Hz, 1 H), 4.53 (br dd, J = 4.5, 3 Hz, 1 H), 7.28 (m, 3 H), 7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.36, 19.49, 25.20, 25.95, 33.26, 33.90, 35.58, 39.75, 50.82, 69.05, 127.52, 129.12, 129.48, 131.75, 134.23, 135.04; exact mass, *m/z* calcd for $C_{18}H_{24}OSe$ 336.0993, found 336.1000. Anal. Calcd for $C_{18}H_{24}OSe$: C, 64.47; H, 7.26; O, 4.80; Se, 23.69. Found: C, 64.72; H, 6.94.

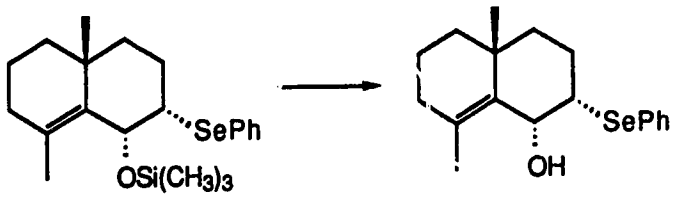
[1*R*-(1α,2α,4aβ)]- and [1*S*-(1α,2α,4aβ)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-(trimethylsilyloxy)naphthalene (174).



A solution of diethyl azodicarboxylate (DEAD) (154.0 mg, 0.884 mmol) in THF (2 mL) was added over 20 min by means of a

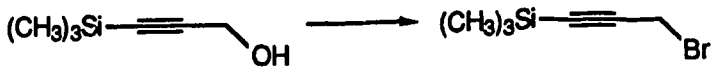
phenylseleno alcohol **173** (148.0 mg, 0.442 mmol), triphenylphosphine (232.0 mg, 0.884 mmol), and 3-(trimethylsilyl)-2-propynoic acid **172** (126.0 mg, 0.884 mmol) in THF (3 mL). The ice bath was removed and stirring was continued for a further 22 h at room temperature (TLC control, silica gel, 5% ethyl acetate--hexane). The solvent was evaporated and flash chromatography of the residue over silica gel (3 x 18 cm) with hexane gave the *O*-silyl protected phenylseleno alcohol **174** (114.0 mg, 56%) as a colorless oil: IR (film) 3080, 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 9 H), 1.12 (s, 3 H), 1.26--1.41 (m, 2 H), 1.44--1.62 (series of m, 3 H), 1.69 (dt, J = 13.5, 4.5 Hz, 1 H), 1.83--2.09 [series of m (including a singlet at 1.94), 6 H], 2.17 (tt, J = 13.5, 4.3 Hz, 1 H), 3.61 (q, J = 3.5 Hz, 1 H), 4.75 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ -0.19, 18.97, 20.98, 25.54, 28.26, 35.53, 36.83, 37.88, 41.07, 56.38, 74.04, 126.65, 128.71, 129.60, 131.61, 133.37, 134.21. The compound was further characterized by desilylation (see below).

Desilylation of [1*R*-(1α,2α,4aβ)]- and [1*S*-(1α,2α,4aβ)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-(trimethylsilyloxy)naphthalene (174).



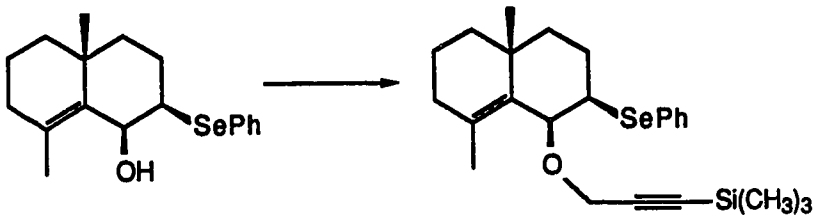
control, silica gel, 5% ethyl acetate--hexane, and reaction mixture was filtered through a pad of silica gel (2 x 3 cm) with 5% ethyl acetate--hexane (4 x 5 mL). The solvents were evaporated and flash chromatography of the residue over silica gel (2 x 18 cm) with 5% ethyl acetate--hexane yielded the phenylseleno alcohol **173** (59.3 mg, 91%), identical (^{1}H NMR) with the sample made by DIBAL reduction of phenylseleno ketone **164**.

3-Bromo-1-(trimethylsilyl)-1-propyne (175).[144]



A solution of phosphorus tribromide (4.32 g, 16.0 mmol) in ether (5 mL) was added dropwise over 5 min to a solution of 3-hydroxy-1-(trimethylsilyl)-1-propyne[144] (5.0 g, 39.0 mmol) and dry pyridine (0.08 mL, 1.0 mmol) in dry ether (20 mL). The mixture was heated at reflux for 2 h and then poured onto ice. The organic layer was separated, washed with water (2 x 10 mL), 5% aqueous sodium bicarbonate (2 x 10 mL), and water (2 x 10 mL), dried ($MgSO_4$), and evaporated. Vacuum distillation of the crude material gave **175** (6.10 g, 81%) [bp 104-105°C (90 mm)] as a colorless liquid [lit[144] bp 71-73°C

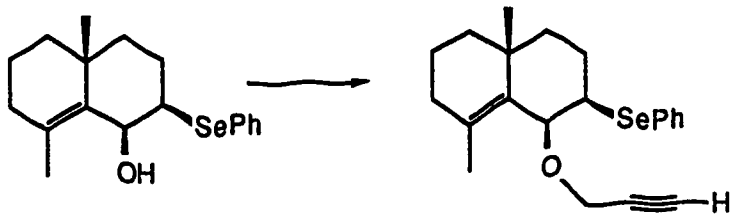
[[3-(trimethylsilyl)-2-propynyl]oxy]naphthalene (176).



Sodium hydride (60% dispersion in oil, 59.2 mg, 1.48 mmol) was added in one portion to a stirred solution of phenylseleno alcohol **166** (330 mg, 0.985 mmol) in THF (15 mL). Stirring at room temperature was continued for 20 min and then 3-bromo-1-trimethylsilyl-1-propyne[144] (565 mg, 2.955 mmol) in THF (5 mL) was added rapidly. The mixture was heated at 60-62°C for 21 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm) with hexane was carried out twice and afforded the desilylated product **177** (26 mg, 7%), starting material **166** (36 mg, 11%), and the phenylseleno ether **176** (304 mg, 69%). The latter was a pale yellow, homogeneous (TLC, silica, hexane) solid: mp 93-94°C; FT-IR ($CDCl_3$ cast) 3060, 2180, 1640, 1580, 1480, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.20 (s, 9 H), 1.22 (s, 3 H), 1.25--1.38 (dt, J = 13,

Hz, 1 H), 7.27 (m, 3 H), 7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ -0.09, 18.69, 19.59, 25.91, 26.09, 33.73, 33.94, 41.49, 43.34, 49.11, 54.82, 74.97, 90.54, 103.09, 126.82, 128.88, 131.11, 131.41, 133.72, 134.95; exact mass, *m/z* calcd for $C_{24}H_{34}OSeSi$ 446.1544, found 446.1545. Anal. Calcd for $C_{24}H_{34}OSeSi$: C, 64.69; H, 7.69; O, 3.59; Se, 17.72; Si, 6.30. Found: C, 64.04; H, 7.74.

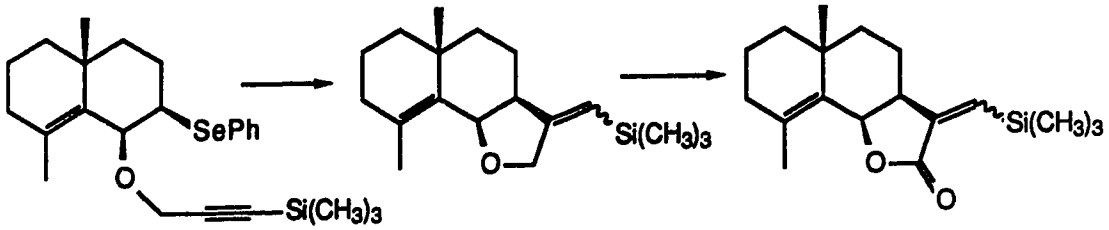
[1*R*-(1α,2α,4aα)]- and [1*S*-(1α,2α,4aα)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-(2-propynyloxy)naphthalene (177).



Sodium hydride (60% dispersion in oil, 26 mg, 0.66 mmol) was added in one portion to a stirred solution of phenylseleno alcohol **166** (100 mg, 0.3 mmol) in THF (4 mL). Stirring at room temperature was continued for 15 min and then 3-bromo-1-trimethylsilyl-1-propyne[144] (115 mg, 0.60 mmol) in THF (1 mL)

was added rapidly. The reaction mixture was refluxed for 25 h. The reaction was monitored by TLC (silica, 5% ethyl acetate--hexane) and was found to produce mainly the desilylated product **177**. The mixture was cooled and tetrabutylammonium fluoride (1.0 M in THF, 1.0 mL) was added. After 15 min at room temperature, the solvent was evaporated and flash chromatography of the residue over silica gel (1 x 18 cm) with 2% ethyl acetate--hexane afforded phenylseleno ether **177** (80.4 mg, 72%; 82% based on recovered starting material) as a colorless, homogeneous (TLC, silica, 2% ethyl acetate--hexane), oil: FT-IR ($CHCl_3$ cast) 3060, 2928, 1640, 1580, 1477, 1436 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 1.03 (dq, J = 13, 3.5 Hz, 2 H), 1.14 (s, 3 H), 1.25 (dt, J = 13, 3.5 Hz, 1 H), 1.37 (dt, J= 13, 3.5 Hz, 2 H), 1.40--1.51 (m, 1 H), 1.53 (s, 3 H), 1.62--1.79 (m, 2 H), 1.90 (dq, J = 13.5, 3.5 Hz, 1 H), 2.01 (t, J = 2.5 Hz, 1 H), 2.54 (dq, J = 13.5, 3.5 Hz, 1 H), 3.23 (ddd, J = 13, 4.3, 3.2 Hz, 1 H), 3.75 and 3.94 (d of AB system, J = 15.5, 2.5 Hz, 2 H), 5.00 (d, J = 3.2 Hz, 1 H), 6.95 (m, 3 H), 7.60 (m, 2 H); ^{13}C NMR (C_6H_6, 75.47 MHz) δ 18.92, 19.51, 25.99, 26.81, 33.82, 33.95, 41.66, 43.41, 49.53, 54.28, 73.98, 75.73, 81.08, 126.95, 129.13, 131.74, 132.03, 134.11, 134.76; exact mass, *m/z* for $C_{21}H_{26}OSe$ 374.1186, found 374.1150. Anal. Calcd for $C_{21}H_{26}OSe$: C, 67.55; H, 7.02; O, 4.29; Se, 21.15. Found: C, 67.43; H, 7.02; O, 4.59.

(*Z*)- and (*E*)-[3a*R*-(3aα,5aβ,9bα)]- and (*Z*)- and (*E*)-[3a*S*-(3aα,5aβ,9bα)]-3a,4,5,5a,6,7,8,9b-Octahydro-5a,9-dimethyl-3-[(trimethylsilyl)methylene]naphtho-[1,2-b]furan-2(3*H*)one (181).



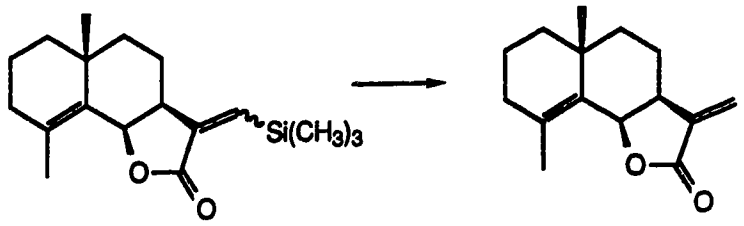
Triphenyltin hydride (132 mg, 0.377 mmol) in benzene (5 mL) and AIBN (2 mg, 0.0125 mmol) in the same solvent (5 mL) were added simultaneously over 8 h by double syringe pump to a stirred, refluxing solution of **176** (140 mg, 0.314 mmol) in benzene (25 mL). Refluxing was continued for a further 6 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm) with 2% ethyl acetate--hexane yielded a mixture of two products **180** (111 mg), which was dissolved in dichloromethane (5 mL) and added over about 5 min to a stirred slurry of pyridine (0.64 mL, 7.89 mmol) and chromium trioxide (640 mg, 6.4 mmol) in dichloromethane (6.5 mL).[95] After 10 min (TLC control, silica, 5% ethyl acetate--hexane), the mixture was filtered through a pad of silica gel (2 x 3 cm), using dichloromethane (20 mL). The solvent was evaporated and flash chromatography of the residue over silica gel (1 x 18 cm) with 2% ethyl

acetate--hexane afforded the (*E*) and (*Z*) isomers of the silyl lactone **181**.

The (*E*) isomer (42 mg, 44%) was a colorless oil and had: FT-IR ($CDCl_3$ cast) 1758, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.20 (s, 9 H), 1.08 (s, 3 H), 1.22--1.39 (m, 2 H), 1.41--1.53 (m, 2 H), 1.57--1.70 (m, 3 H), 1.76 (s, 3 H), 1.77--1.89 (m, 1 H), 2.06--2.13 (m, 2 H), 2.93--3.01 (m, 1 H), 5.19 (d, J = 5.5 Hz, 1 H), 6.79 (d, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -0.73, 18.16, 19.39, 24.59, 25.68, 32.67, 33.25, 38.30, 39.28,41.18, 75.61, 128.57, 137.02, 138.38,147.63, 171.03; exact mass, *m/z* calcd for $C_{18}H_{28}O_2Si$ 304.1858, found 304.1851.

The (*Z*) isomer (8.0 mg, 8%) was a white solid and had: mp 90-94°C; FT-IR ($CDCl_3$ cast) 1760, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.21 (s, 9 H), 1.08 (s, 3 H), 1.17--1.52 (m, 4 H), 1.58--1.69 (m, 3 H), 1.75 (s, 3 H), 1.77--1.90 (m, 1 H), 2.04--2.13 (m, 2 H), 2.73--2.85 (m, 1 H), 5.27 (d, J = 6.0 Hz, 1 H), 6.32 (d, J = 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ -0.65, 18.29, 19.46, 25.33, 25.92, 32.80, 33.28, 38.20, 39.32, 44.83, 75.61, 129.00, 138.13, 141.62, 148.87, 170.46; exact mass, *m/z* calcd for $C_{18}H_{28}O_2Si$ 304.1858, found 304.1873. Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27; O, 10.51; Si, 9.22 Found: C, 70.22; H, 9.29.

[3aR-(3aα,5aβ,9bα)]- and [3aS-(3aα,5aβ,9bα)]-3a,4,5,5a,6,7,8,9b-Octahydro-5a,9-dimethyl-3-methylene-naphtho[1,2-b]furan-2(3H)-one: (±)-Frullanolide (105).



A solution of the (*E*)- and (*Z*)-silyl lactones **181** (29.0 mg, 0.095 mmol), thiophenol (97.7 μL, 0.95 mmol), and triethylamine (132.4 μL, 0.95 mmol) in THF (4 mL) was stirred for 51 h at room temperature.[104] Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 18 cm) with 5% ethyl acetate--hexane afforded a mixture of isomers of thiophenol adduct **182** (32.8 mg, 0.08 mmol), which was dissolved in dry THF (4 mL). Tetrabutylammonium fluoride on silica gel (Fluka, 1.16 mmol of F^-/g) (138 mg, 0.16 mmol) and methyl acrylate (72 μL, 0.8 mmol) were added to this solution and the mixture was stirred for 1 h.[104] Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm) with 5% ethyl acetate--hexane afforded (±)-frullanolide **105** (15.0 mg, 68%) as a white solid: mp 93-93.5°C [lit.[109] mp 93-93.5°C]; FT-IR ($CDCl_3$ cast) 1760, 1660, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 3 H), 1.22--1.52 (m, 4 H), 1.59--1.74 (m, 2 H), 1.76 (s, 3

H), 1.78--1.89 (m, 1 H), 2.08--2.13 (m, 2 H), 2.91--2.99 (m, 1 H), 5.26 (d, J = 6 Hz, 1 H), 5.57 (d, J = 1 Hz, 1 H), 6.16 (d, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 18.26, 19.43, 25.90, 32.76, 33.24, 37.97, 39.24, 41.34, 75.97, 120.13, 128.65, 138.57, 142.41, 171.00; exact mass, *m/z* calcd. for $C_{15}H_{20}O_2$ 232.1463, found: 232.1457. Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.78. Found: C, 77.29; H, 8.46.

(*Z*)-3-(Phenylthio)-2-propenoic acid [(*Z*)-184].[131a]

Propiolic acid (3.08 mL, 0.05 mol) was added in one portion to a solution of thiophenol (5.12 mL, 0.05 mol) in aqueous potassium hydroxide (30 mL, 4 N) and the mixture was heated at 100°C for 2 h. After cooling, the mixture was acidified with sulfuric acid (3 N) and the resulting solid was filtered off, washed with water (3 x 100 mL), and dried under high vacuum. Recrystallization from benzene afforded (*Z*)-3-(phenylthio)-2-propenoic acid **184** (5.50 g, 62%) as white crystals: mp 106-107°C [lit.[131b] mp 107-108°C, 50%]; ^1H NMR ($CDCl_3$, 80 MHz) δ 6.00 (d, J = 10 Hz, 1 H), 7.09--7.88 (m, 6 H), 12.23 (br s, 1 H).

(*Z*)-3-(Phenylsulfonyl)-2-propenoic acid (187).[131a]

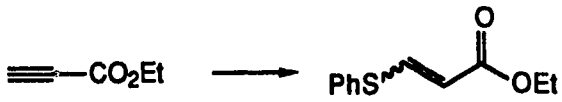
(*Z*)-3-(Phenylthio)-2-propenoic acid [(*Z*)-**184**] (1.00 g, 5.55 mmol) was added in one portion to a solution of hydrogen peroxide (4 mL, 30%), glacial acetic acid (12 mL), and sulfuric acid (1 drop). The mixture was heated at 100°C for 3 h. The solvents were then removed (water pump) and the resulting solid was crystallized from ether to yield (*Z*)-3-(phenylsulfonyl)-2-propenoic acid **187** (0.873 g, 74%) as white crystals: mp 160-163°C [lit.[131a] mp 164-165°C, 80%].

Ethyl (*Z*)-3-(Phenylthio)-2-propenoate (186).[145]

A solution of ethyl propiolate (1.01 mL, 10 mmol), thiophenol (1.28 mL, 12.5 mmol), and triethylamine (1.0 mL, 7.2 mmol) in ethanol (10 mL) was stirred for 1.3 h at room temperature. The reaction mixture was taken up in 10% ethyl acetate--hexane (150 mL) and washed with aqueous sodium hydroxide (4 x [illegible] and dried (Na_2SO_4). The

J = 7.0 Hz, 3 H), 4.29 (q, J = 7.0 Hz, 2 H), 5.95 (d, J = 10 Hz, 1 H), 7.09--8.00 (m, 6 H).

Ethyl (*Z*) and (*E*)-3-(Phenylthio)-2-propenoate [(*Z*)-186 and (*E*)-186].



A solution of ethyl propiolate (1.01 mL, 10 mmol), thiophenol (1.03 mL, 10.0 mmol), and triethylamine (1.0 mL, 7.2 mmol) in THF (10 mL) was stirred for 0.5 h at room temperature. The reaction mixture was taken up in 10% ethyl acetate--hexane (150 mL) and washed with aqueous sodium hydroxide (4 x 50 mL, 3.0 M), and water (3 x 50 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) with 30% ethyl acetate--hexane gave a mixture of geometrical isomers [40*E*:60*Z*, (^{1}H NMR)] (2.0 g, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.10--1.55 (two sets of overlapping t, J = 7.0 Hz, 3 H), 4.00--4.55 (two sets of overlapping q, J = 7.0 Hz, 2 H), 5.71 (d, J= 15 Hz, 0.4 H), 5.93 (d, J = 10 Hz, 0.6 H), 7.09--7.69 (m, 5.6 H), 7.80 (d, J = 15 Hz, 0.4 H).

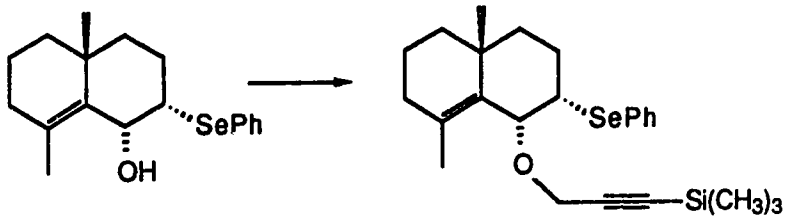
Hydrolysis of Ethyl (*Z*)- and (*E*)-3-(Phenylthio)-2-propenoate [(*Z*)-186 and (*E*)-186]. [Preparation of 184.]

Ethyl (*Z*)- and (*E*)-3-(phenylthio)-2-propenoate [(*Z*)-**186** and (*E*)-**186**] (2.0 g, 9.6 mmol) was added in one portion to a stirred solution of potassium hydroxide (0.976 g, 17.4 mmol) in 27% ethanol--water (22 mL) and stirring was continued at room temperature for 18 h (TLC control, silica, 30% ethyl acetate--hexane). The mixture was acidified with hydrochloric acid (2.0 M) and the white solid was separated by filtration. The solid was washed with water (3 x 20 mL) and dried overnight at 50°C under high vacuum to afford a mixture of (*Z*)- and (*E*)-3-(phenylthio)-2-propenoic acid **184**[133] (1.70 g, 94%) in a 54:46 ratio (^{1}H NMR) respectively: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 5.70 (d, J = 15 Hz, 0.46 H), 6.00 (d, J = 10 Hz, 0.54 H), 7.24--7.70 (m, 5.54 H), 8.00 (d, J = 15 Hz, 0.46 H), 11.48 (br s, 1 H).

(*Z*)- and (*E*)-3-phenylthio-2-propenoyl chloride (189).[133]

A solution of (*Z*) and (*E*) acids **184** (524.0 mg, 2.91 mmol) and thionyl chloride (0.43 mL, 5.82 mmol) in carbon tetrachloride (7 mL) was stirred at room temperature for 14 h under argon. The excess of thionyl chloride and carbon tetrachloride were removed and Kugelrohr distillation [bp 133°C (5.5 mm)] gave a mixture of acid chlorides **189** (513.0 mg, 89%) as a slightly yellow liquid: IR (film) 3060, 1740 (broad) cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 5.83 (d, J = 15.0 Hz, 0.58 H), 6.25 (d, J = 10.0 Hz, 0.42 H), 7.23--7.75 (m, 5.42 H), 8.16 (d, J = 15.0 Hz, 0.58 H).

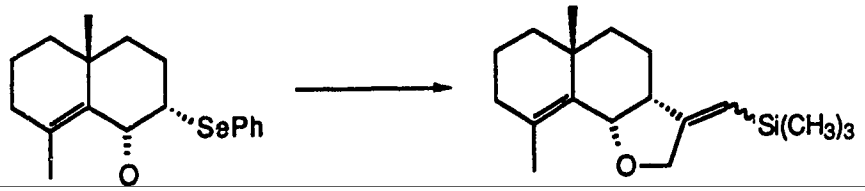
[1R-(1α,2α,4aβ)]- and [1S-(1α,2α,4aβ)]-1,2,3,4,4a,5,6,7-Octahydro-4a,8-dimethyl-2-(phenylseleno)-1-[[3-(trimethylsilyl)-2-propynyl]oxy]naphthalene (190).



Sodium hydride (60% dispersion in oil, 59.2 mg, 1.48 mmol) was added in one portion to a stirred solution of phenylseleno alcohol **173** (330 mg, 0.985 mmol) in THF (15 mL). Stirring at room temperature was continued for 45 min and then 3-bromo-1-trimethylsilyl-1-propyne[144] (1.13 g, 5.91 mmol) in THF (7 mL) was added rapidly. The mixture was heated at

chromatography of the residue over silica gel (3 x 18 cm) with hexane afforded the silyl ether **174** (154.0 mg, 38%). Continued elution with 2% ethyl acetate--hexane afforded the phenylseleno ether **190** (179.0 mg, 41%), which was a colorless, homogeneous (TLC, silica, 2% ethyl acetate--hexane) oil: FT-IR ($CDCl_3$ cast) 3050, 2176, 1656 cm^{-1}; ^1H NMR($CDCl_3$, 200 MHz) δ 0.20 (s, 9 H), 1.12 (s, 3 H), 1.27--2.31 [series of m (including a singlet at 1.88), 13 H], 3.84 (q, J = 4.0 Hz, 1 H), 4.17 and 4.30 (AB system, J = 16.0 Hz, 2 H), 4.75 (br s, 1 H), 7.21--7.32 (m, 3 H), 7.56--7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ -0.11, 18.73, 20.26, 25.62, 27.87, 34.50, 36.46, 37.34, 40.49, 50.75, 56.51, 76.63, 91.28, 102.34, 126.84, 128.85, 130.46, 130.84, 131.49, 134.13; exact mass, *m/z* calcd for $C_{24}H_{34}OSeSi$ 446.1548, found 446.1541.

(*Z*)-[3a*R*-(3aα,5aα,9bα)]- and (*Z*)-[3a*S*-(3aα,5aα, 9bα)]-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-5a,9-di-methyl-3-(trimethylsilylmethylene)naphtho[1,2b]furan (191) and (*E*)-[3a*R*-(3aα,5aα,9bα)]- and (*E*)-[3a*S*-(3aα,5aα, 9bα)]-2,3,3a,4,5,5a,6,7,8,9b-Decahydro-5a,9-di-methyl-3-(trimethylsilylmethylene)naphtho[1,2b]furan (192).



A solution of phenylseleno ether **190** (74.0 mg, 0.166 mmol), triethylborane (1.0 M solution in hexane, 0.183 mL, 0.183 mmol), and tributyltin hydride (53.15 mg, 0.049 mL, 0.183 mmol)[101] was stirred at room temperature for 4 h. The solvent was evaporated and flash chromatography of the residue over silica gel (2 x 18 cm) with 2% ethyl acetate--hexane afforded the starting material (13 mg, 17%), the (*Z*)-isomer **191** (17 mg, 35.5%) as a colorless oil and the (*E*)-isomer **192** (19 mg, 39.5%) also as a colorless oil. The (*Z*)-isomer had: FT-IR ($CDCl_3$ cast) 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 9 H), 1.00 (s, 3 H), 1.23--1.40 (series of m, 3 H), 1.45--1.64 (series of m, 3 H), 1.65--1.85 [series of m (including a singlet at 1.77), 4 H], 1.87--2.16 (m, 3 H), 2.74--2.84 (m, 1 H), 4.23 (part of AB system, ddd, J = 13.5, 2.2, 1.0 Hz, 1 H), 4.33 (part of AB system, dt, J = 13.5, 2.0 Hz, 1 H), 4.61 (d, J = 5.2 Hz, 1 H), 5.39 (q, J = 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ -0.46, 18.76, 19.82, 23.54, 25.95, 33.11, 35.13, 39.04, 44.63, 68.67, 77.47, 115.91, 132.18, 132.32, 163.64, (two signals are coincident in this spectrum); exact mass, *m/z* calcd for $C_{18}H_{30}OSi$ 290.2076, found 290.2071.

The (*E*)-isomer had: FT-IR ($CDCl_3$ cast) 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 9 H), 1.01 (s, 3 H), 1.29 (series of m, 4 H), 1.55--1.69 [series of m (including a singlet at 1.72), 4 H], 1.92--2.21 (series of m, 3 H), 2.88 (br quintet, J = 5.0 Hz, 1 H), 4.15 (part of AB system, dd, J = 13.5, 1.5 Hz, 1 H), 4.43 (part of AB system, br dt, J = 13.5, 1.5 Hz, 1

NMR ($CDCl_3$, 75.47 MHz) δ 0.04, 18.61, 19.17, 24.38, 25.55, 31.84, 32.21, 34.70, 38.45, 39.03, 71.39, 77.61, 115.55, 132.47, 133.65, 164.76; exact mass, *m/z* calcd for $C_{18}H_{30}OSi$ 290.2061, found 290.2067. A second run was done (reaction time: 1.5 h) on 2.3 times the above scale. A mixture of both isomers in a 1:1 ratio (^1H NMR) was obtained in 94% yield.

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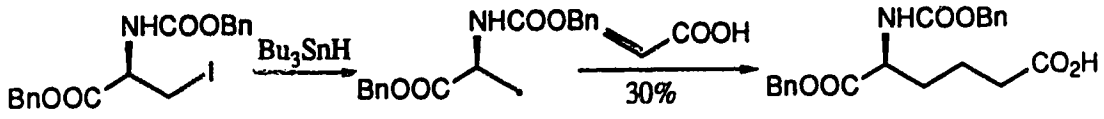
CHAPTER 2

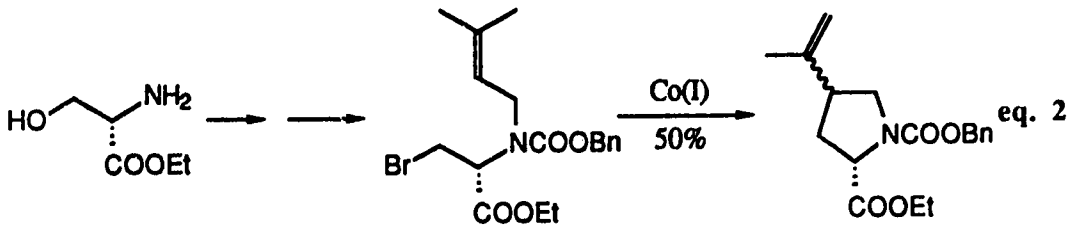
Preliminary studies on the use of intermolecular radical addition for the synthesis of amino acids

I INTRODUCTION

Very little work has been reported on the use of free radical techniques for the construction of amino acids and peptides.[1] An intact amino acid unit (already containing the α-stereogenic center) can be converted into a radical species, which can be trapped intermolecularly, as shown in equation 1,[2] or intramolecularly, as summarized in equation 2.[3]



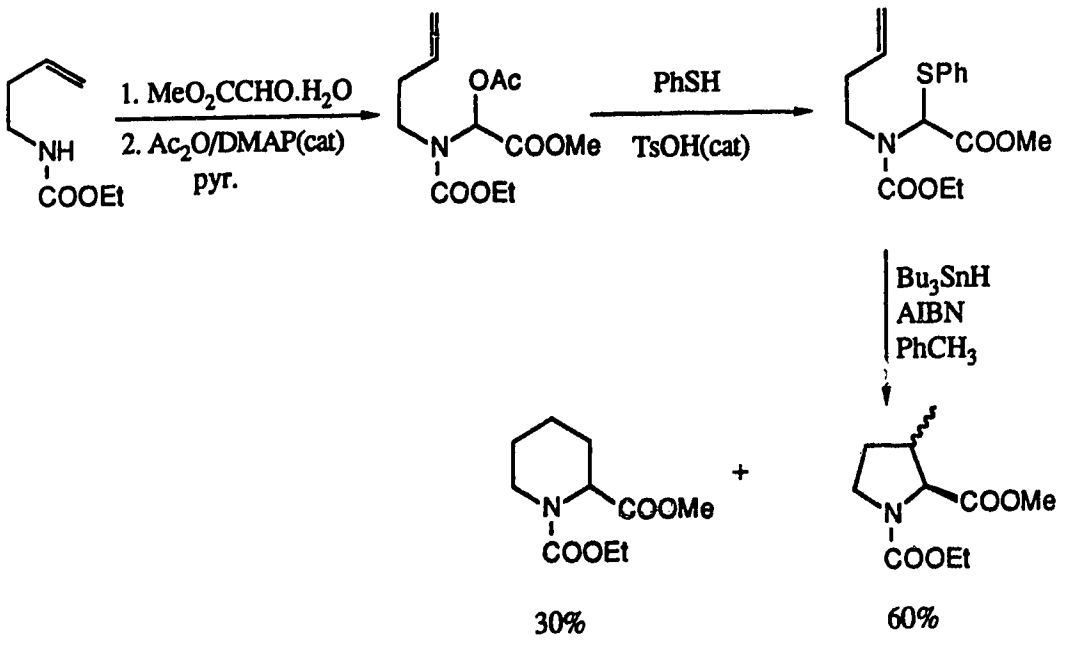
eq. 1



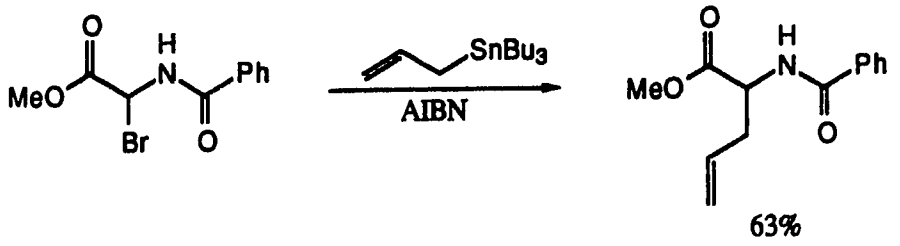
eq. 2

Both stannane- and cobalt(I)-mediated processes can be used, as illustrated above. A related approach, shown in Scheme 1,[4] represents the construction of *cyclic* amino acid derivatives, but with low diastereoselectivity.

SCHEME 1



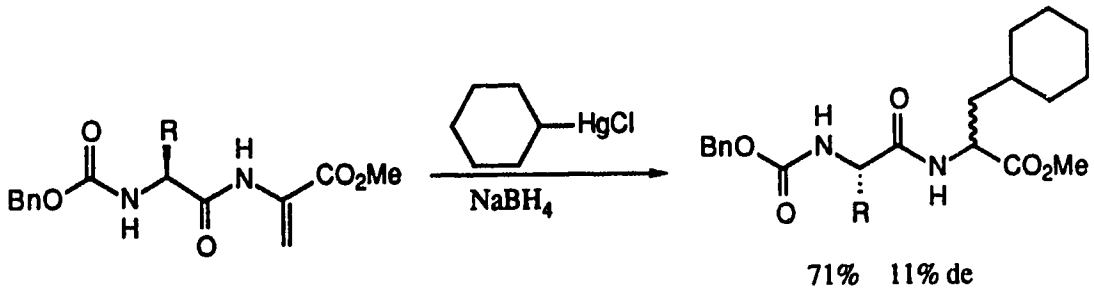
Several instances are known in which the α-stereogenic center is generated in the radical process. For example, Easton formed 2-glycinyl radicals and found that they undergo addition to allylic stannanes (equation 3).[5] Interestingly,



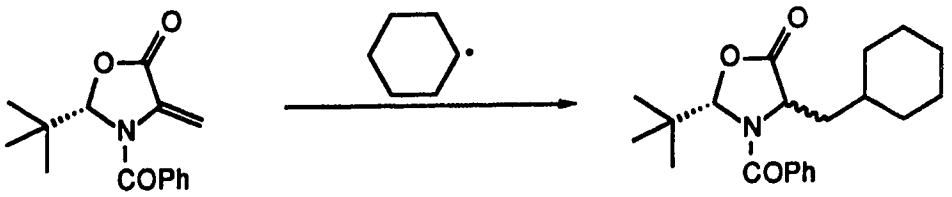
eq. 3

the reaction can be done in carbon tetrachloride. In the process of equation 3 a new carbon-carbon bond is formed at the alpha position of the glycine residue.

There are two other reports in which the newly formed bond is at the beta position. Each of these studies (equations 4 and 5) involved radical addition to a dehydroalanine derivative and, while the example of equation 4[6] proceeded with poor diastereoselectivity, a diastereomeric excess of greater then 75% was obtained with the example of equation 5.[7]



eq. 4



eq. 5

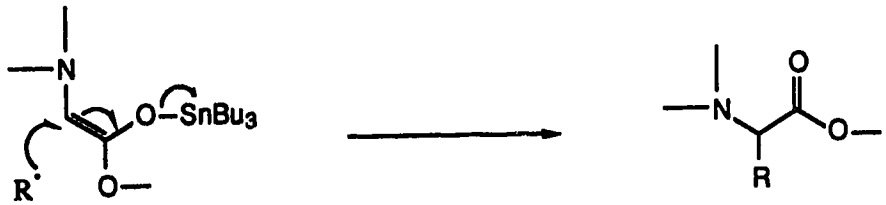
Clearly, the application of radical chemistry to the synthesis of amino acids is at a very early stage of development, and further progress is to be expected in view of the importance of amino acids and the current intense interest in free radical methods.

II DISCUSSION

In the following experiments we sought to develop a method of attaching a carbon unit to the alpha position of an amino acid substructure as depicted in Schemes 2 and 3. If

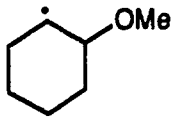
SCHEME 2

SCHEME 3

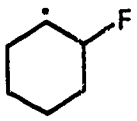


either of these processes could be reduced to practice, then a method would be available for making amino acids in which the group R contains heteroatom substituents alpha to the site of attachment of R to the glycine residue. For example, the radicals **1** and **2** could be used in such schemes; in

contrast the corresponding carbanions would undoubtedly expel the adjacent heteroatom substituents.

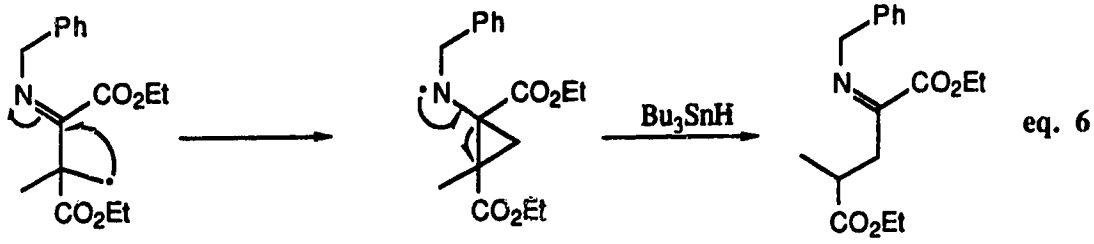


1

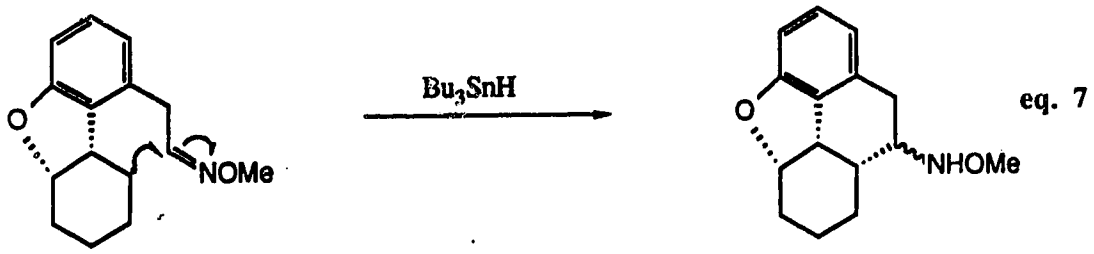


2

There was some guidance in the literature that suggested that the routes of both Schemes 2 and 3 would be viable processes. There are several examples of intramolecular addition of a radical to a carbon-nitrogen double bond and the cases known to me are summarized in equations 6,[8] 7,[9] 8,[10] 9,[11] and 10.[12] One example of an intermolecular addition has been reported (equation 11[10]).

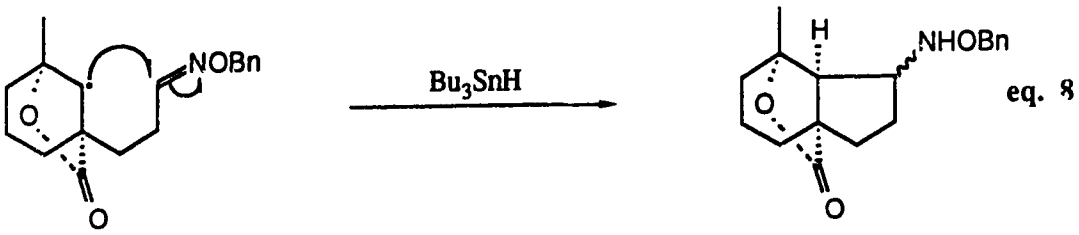


eq. 6

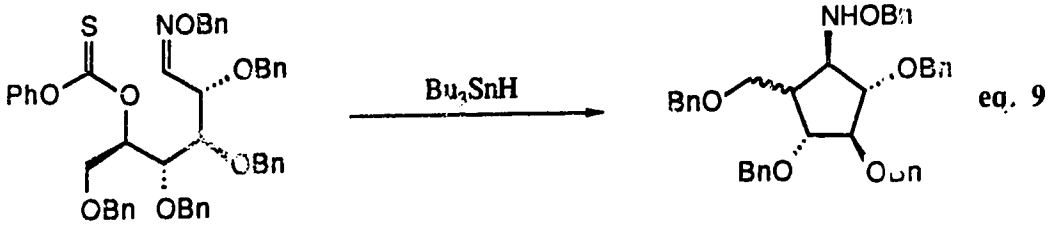


eq. 7

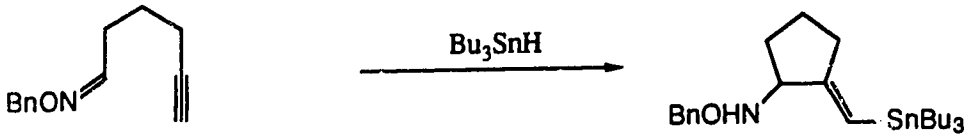
The results of equations 8, 9, and 11 were known at the outset of the present investigation.



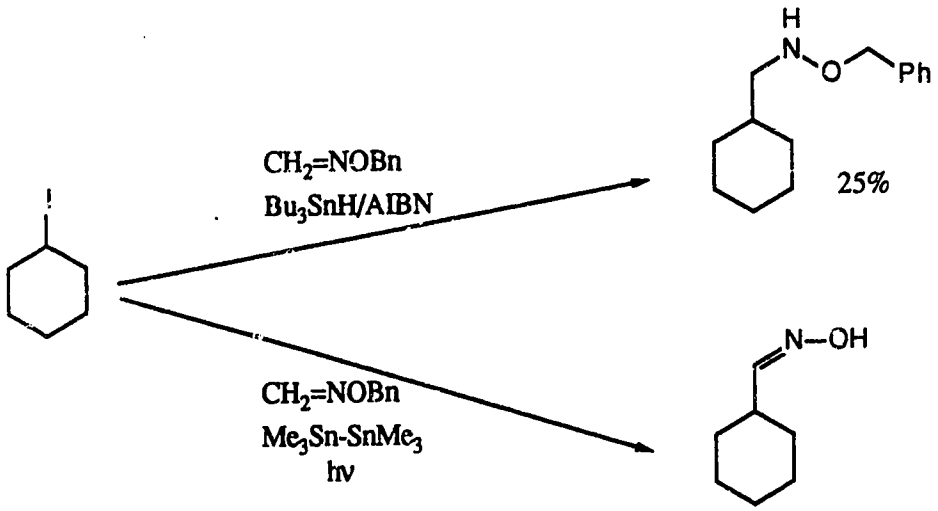
eq. 8



eq. 9



eq. 10



eq. 11

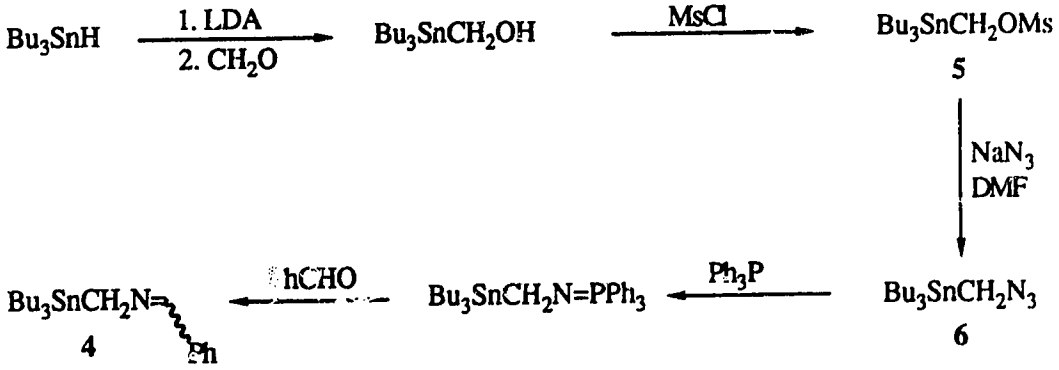
In our initial experiments we sought to add a radical to

12. With the result shown in that equation as an analogy,

eq. 12

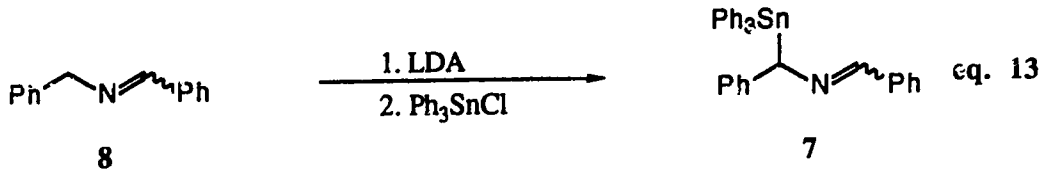
we prepared compound **4** (Scheme 4). This material, which was made by the literature route shown in the Scheme, was obtained as a single compound whose stereochemistry was

SCHEME 4



not established. When the imine **4** was heated in toluene with AIBN and cyclohexyl bromide no attack on the imine was

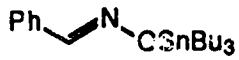
hope that the presence of a benzene ring on the carbon carrying the tin unit would make the carbon-tin bond weaker. Compound **7** was made by the simple method of equation 13.



8 **7** eq. 13

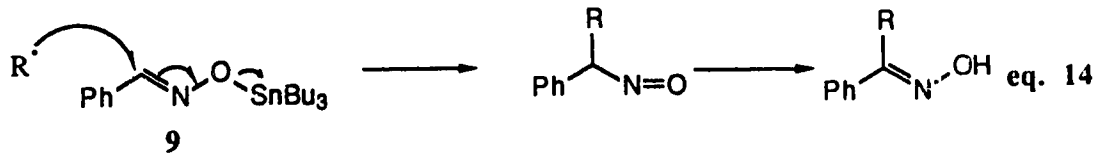
Once again the geometry was not established, but the material appeared to be a single isomer. When subjected to the same conditions tried with the simpler imine **4**, the present compound failed to react (^{1}H NMR) and the same observation was made when triethylborane was used as the radical initiator.[15] Photolysis of **7** in quartz apparatus (using a high pressure mercury lamp) in the presence of cyclohexyl bromide led to no identifiable product after acid hydrolysis of the total reaction mixture. If any of the desired reaction had taken place we would have found α-cyclohexyl-

classical allyl stannane system, and we prepared the *O*-stannyl oxime **9**.[16] We hoped that it would react as shown in



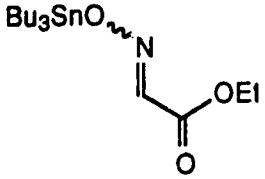
9

equation 14, in which the initial adduct tautomerizes to an oxime. In the event, compound **9** was not attacked by cyclohexyl or benzyl radicals. In each experiment the



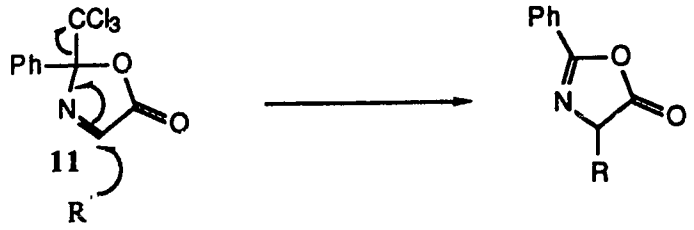
9 eq. 14

compound was heated for 48 hours in toluene with cyclohexyl or benzyl bromide in the presence of AIBN, the initiator being added periodically during the thermolysis. We also examined the *O*-stannyl oxime **10**, which was prepared from the corresponding oxime[17] by the same method used for **9**. Notwithstanding the presence of an additional electron withdrawing group on the imine carbon of **10**, the material was just as inert as the simpler oxime **9**.



10

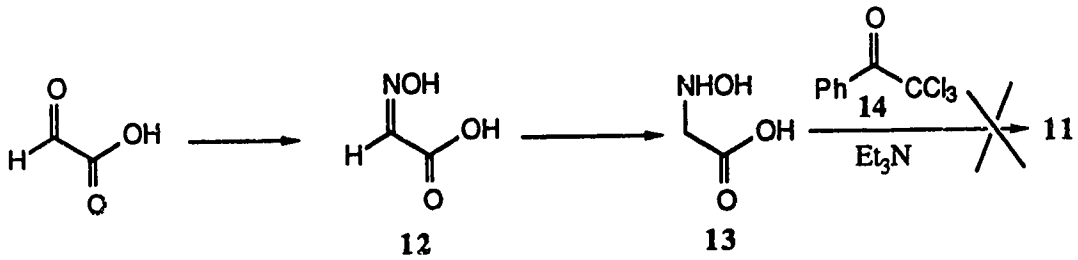
We then decided to try the same principle (see equation 15), but using the cyclic imine **11**. Our approach to this



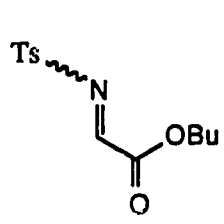
eq. 15

cyclic imine is summarized in Scheme 5. The last step, condensation with trichlomethyl phenyl ketone is based on a close analogy,[18] but unfortunately the condensation did not work with our ketone.

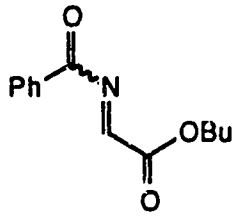
SCHEME 5



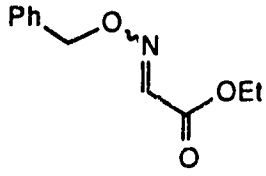
Our final studies with imine and oxime derivatives involved compounds **15**, **16**, and **17**. The preparation of **15** proved troublesome, but we eventually found that the route of Scheme 6 works well. The difficulties we experienced were associated with the first step shown in the Scheme 6. The



15



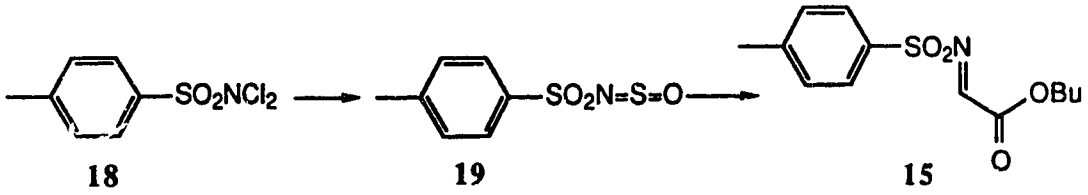
16



17

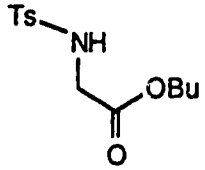
literature procedure[19] involves treating *p*-toluenesulfonamide with thionyl chloride, with or without a catalytic amount of *N,N*-dichloro-*p*-toluenesulfonamide. We found it best to

SCHEME 6



18 19 15

use *N,N*-dichloro-*p*-toluenesulfonamide as a stoichiometric starting material. When compound **15** was treated with tributyltin hydride and cyclohexyl bromide, a reaction did take place, but we were disappointed to discover that the the crystalline product **20** was the result of simple reduction of

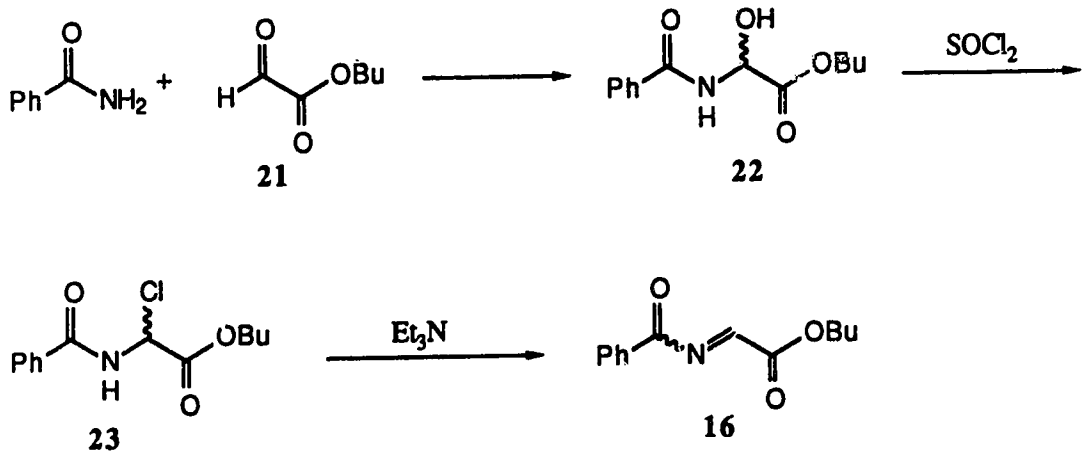


20

the carbon-nitrogen double bond of **15**. The rate of addition of the stannane had no effect on the outcome.

As stated above, we also prepared the *N*-benzoyl imine **16** according to the method of Scheme 7, but we found the compound to be extremely moisture-sensitive and also thermally unstable. We obtained a very small amount that served for characterization, but we did not pursue the matter further.

SCHEME 7

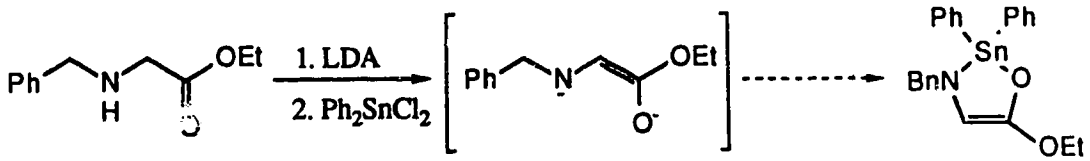


The *O*-benzyl oxime **17** was easily prepared and because of the observed reduction with **15** we avoided the use of tributyltin hydride, and treated **17** with cyclohexyl bromide in the presence of bis(trimethylstannyl)benzopinacolate[10] in refluxing benzene. The oxime was consumed but no cyclohexyl adduct could be identified.

Our next approach (see Scheme 8) was thwarted in the

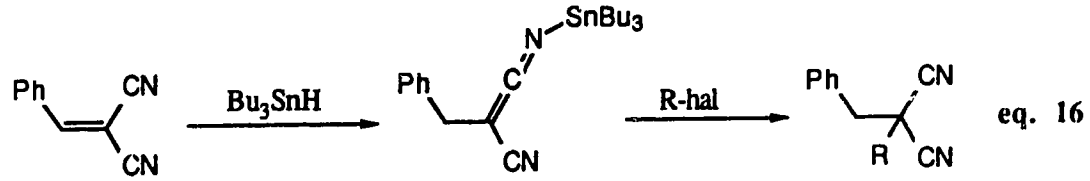
first step, as no tin adduct could be isolated from treatment of the bis anion **25** with dichlorodiphenyltin.

SCHEME 8



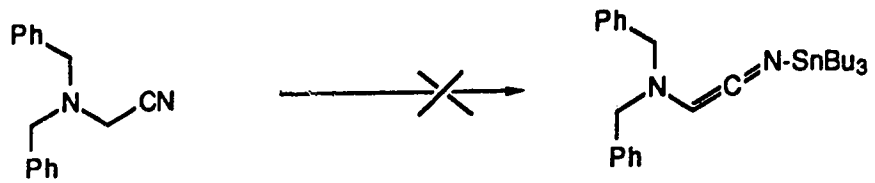
24 **25** **26**

Finally, we examined an approach based on the observation of Neumann[20] that *N*-stannyl keteneimines such as **27** (equation 16) are easily prepared, and that they react with active alkyl halides as shown in the equation. The

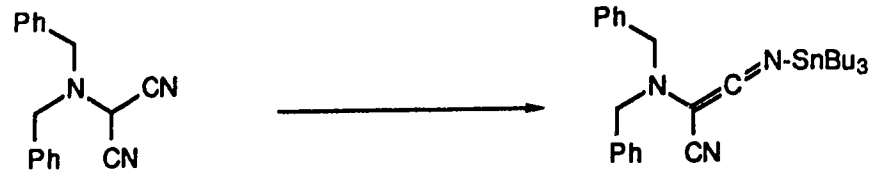


27 eq. 16

mechanism of the reaction with alkyl halides is not known but we felt that a radical mechanism could operate. On this basis then, we decided to attempt the stannylations shown in equations 17 and 18 in the hope that radical addition to the keteneimines, followed by nitrile hydrolysis would furnish *N,N*-dibenzyl amino acids. The requisite starting materials for this project were easily prepared.



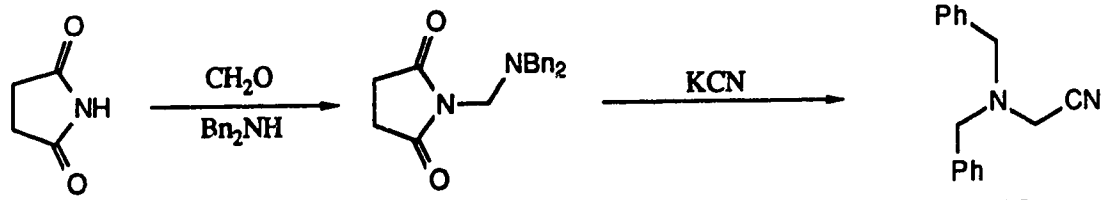
28



29

Compound **28** is a known substance, accessible by the simple route of Scheme 9. Deprotonation with sodium hydride

SCHEME 9



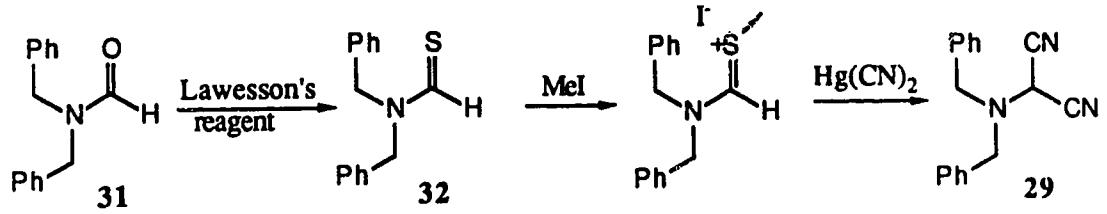
30 28

and quenching with triphenyltin chloride gave a stannylated substance, but the tin group was not on nitrogen as no vinyl hydrogen was detectable in the ^{1}H NMR spectrum of the crude product.

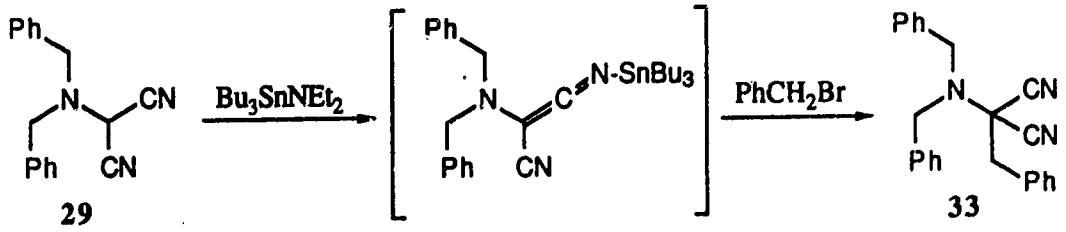
The synthesis of compound **29** started (see Scheme 10) with *N,N*-dibenzylformamide **31** and involved conversion to the thio analogue **32** followed by methylation on sulfur and

displacement with cyanide ion. Deprotonation of **29** with

SCHEME 10



sodium hydride and quenching with triphenyltin chloride, followed by addition of benzyl bromide led, after workup, only to the starting dinitrile. However, when the dinitrile **29** was treated with (tributylstannyl)diethylamine, a new substance was formed that showed characteristic keteneimine IR absorption.[21] This material was warmed with benzyl bromide and afforded the desired product **33** (equation 19). Further work is in progress in this laboratory to optimize the reaction conditions, determine its mechanism, and deal with the problem of hydrolyzing the compound to an amino acid derivative. If the process is indeed a radical reaction then it would constitute a general route to amino acids.

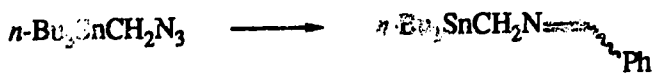


eq. 19

III. Experimental

General Procedures: The same general procedures were used as described on page 100.

N-(Phenylmethylene)-1-(tributylstannyl)-methanamine (4).[22]



A solution of azido stannane **6** (see later for preparation) (1.0 g, 2.89 mmol) in dry benzene (3 mL) was added dropwise over *ca* 5 min to a stirred solution of triphenylphosphine (0.76 g, 2.89 mmol) in dry benzene (15 mL) at room temperature under argon. After evolution of nitrogen has ceased (3 h), benzaldehyde (0.3 mL, 2.89 mmol) was added in one portion and stirring was continued for further 12 h under the same conditions. The solvent was evaporated and the solid residue was washed with petroleum ether (3 x 10 mL). The solvent was evaporated and Kugelrohr distillation of the oily residue [170°C (1 mm)] afforded the imino stannane **4** (0.88 g, 75%) as a slightly yellow, low melting solid: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.50--2.00 (m, 27 H), 3.88 (s, 2 H), 7.18--7.43 (m, 3 H), 7.50--7.80 (m, 2 H), 8.40 (s, 1 H).

(Tributylstannyl)methanol methanesulfonate (5).[23]

$$n\text{-}Bu_3SnH \longrightarrow n\text{-}Bu_3SnCH_2OMs$$

The literature procedure[23] was followed: Tributyltin hydride (2.9 g, 2.64 mL, 10 mmol) was added dropwise over *ca* 5 min to a stirred and cooled (0°C) solution of LDA [prepared from diisopropylamine (1.6 mL, 11.42 mmol and *n*-butyllithium (1.5 M in hexanes, 7 mL, 10.5 mmol) in dry THF (20 mL)]. Stirring was continued for a further 30 min at 0°C and paraformaldehyde (0.31 g, 10 mmol) was added portionwise. The mixture was allowed to warm to room temperature and, after 3 h, it was cooled to -78°C, and methanesulfonyl chloride (1.0 mL, 13 mmol) was added dropwise over *ca* 5 min. Stirring was continued for a further 5 min and water (50 mL) was added in one portion. The mixture was extracted with hexane (4 x 30 mL) and the combined organic extracts were washed with water (4 x 50 mL), and brine (1 x 50 mL), dried (Na_2SO_4), and evaporated. The crude product was filtered rapidly through a pad of silica (40 g) using 10% ethyl acetate--hexane as eluent. Evaporation of the solvents afforded the methanesulfonate **5** as a colorless liquid (2.8 g, 72%): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.5 Hz, 9 H), 1.00 (t, J = 7.5 Hz, 6 H), 1.28 (sextet, J = 7.5 Hz, 6 H), 1.50 (quintet, J = 7.5 Hz, 6 H), 2.9 (s, 3 H), 4.28 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 9.35, 13.60, 27.16, 28.80, 35.60, 59.66.

(Azidomethyl)tributylstannane (6).[22]

A solution of tributylstannylmethanol methanesulfonate (2.8 g, 7 mmol) and sodium azide (0.912 g, 14 mmol) in dimethylformamide (100 mL) was stirred under argon in the dark for 3 h (TLC control). The mixture was taken up in ether (300 mL), washed with water (3 x 150 mL), dried (Na_2SO_4), and evaporated at 20°C under water pump vacuum. Flash chromatography of the residue over silica gel with petroleum ether afforded azido stannane **6** (2.0 g, 82%) as a colorless oil: IR (film) 2960, 2170, 2075 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.65--2.00 (m, 27 H), 3.1 (s, 2 H).

***N*-(Phenylmethylene)-1-(triphenylstannyl)-benzylamine (7).**

A general literature procedure[14] was followed. A solution of imine **8** (see later for preparation) (2.90 g, 20 mmol in THF (10 mL) was added dropwise over *ca* 15 min to a stirred and cooled (-78°C) solution of LDA [prepared from diisopropylamine (3.0 mL, 21.42 mmol) and *n*-butyllithium (1.6 M in hexanes, 12.8 mL, 20.48 mmol) in dry THF (40 mL) and *n*-

heptane (10 mL)]. The color of the solution turned deep red. Stirring was continued for a further 30 min at -78°C and a solution of triphenyltin chloride (7.70 g, 20 mmol) in THF (10 mL) was added in one portion. After 5 min, the resulting colorless solution was quenched with saturated aqueous ammonium chloride (40 mL), followed by addition of ether (400 mL). The organic layer was separated and the aqueous phase was extracted with ether (1 x 100 mL). The combined organic extracts were washed with water (4 x 400 mL), dried (Na_2SO_4), and evaporated. The oily yellow residue was crystallized from pentane to afford imino stannane **7** (9.14 g, 84%) as a white solid: mp 93-97°C; IR (KBr) 3056, 3024, 2848, 1648 cm^{-1}; ^1H NMR ($CDCL_3$, 200 MHz) δ 5.60 (s, 1 H), 7.20--7.70 (m, 25 H), 8.10 (s, 1 H); MS (CI) *m/z* 545 (M^+).

N-(Phenylmethylene)benzylamine (8).[24]

A mixture of benzaldehyde (10.17 mL, 0.1 mol), benzylamine (10.92 mL, 0.1 mol), benzene (100 mL), 3Å molecular sieves (20 g), and *p*-toluenesulfonic acid monohydrate (200 mg) was stirred for 12 h at room temperature. The solids were filtered off and washed with benzene (2 x 20 mL), and the filtrate was evaporated. Kugelrohr distillation of the residue afforded imine **8** (18 g, 92%) as a light yellow liquid: bp 170°C (1.0 mm) [lit.[24] 200-202°C (10-20 mm)]; ^1H