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# A free radical synthesis of Y-lactones using tri-n-butylstannyl iodoesters

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A FREE RADICAL SYNTHESIS OF GAMMA-LACTONES USING TRI-N-BUTYLSTANNYL IODOESTERS

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# A free radical synthesis of γ-lactones using tri-n-butylstannyl iodoesters

by

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TABLE OF CONTENTS

# I. INTRODUCTION

Interest in the use of free radical reactions in synthetic organic chemistry has greatly intensified in recent years. An increased ability to control free radical reactions, thus avoiding unwanted by-products, has contributed to the confidence with which the synthetic chemist can now use them. Furthermore, the development of several new reaction sequences has enlarged the reservoir of tools available to effect carbon-carbon bond formation and various functional group transformations. Finally, the growing popularity of free radical chemistry in synthesis has perhaps heightened the awareness of its often important role as complement to cation and anion chemistry.

We have developed a new free radical approach to the synthesis of γ-lactones. Treatment of olefins with tri-n-butylstannyl iodoacetate in the presence of a catalytic amount of the free radical initiator 2,2'-azobis(2-methyl-propionitrile)(AIBN) in refluxing benzene results in good yields of 4-substituted-γ-lactones. We have also extended this reaction to the synthesis of bicyclic lactones via the intramolecular cyclizations of appropriately constructed tri-n-butylstannyl iodoesters under the same reaction conditions. The mild reaction conditions employed allow for

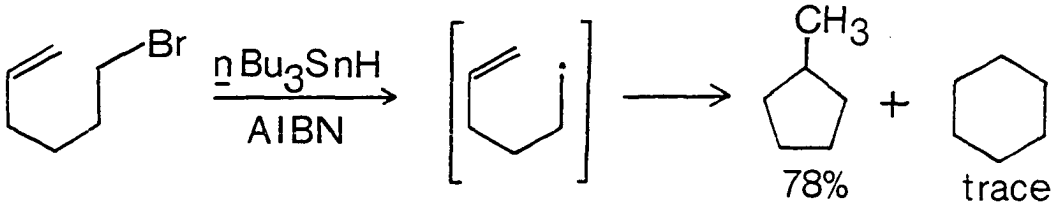
the introduction of a variety of functional groups at the 4-position including alcohols, ethers, and even alkylsilanes and silyl ethers.

This dissertation will focus on the development, scope, and limitations of this new reaction and will offer some reasonable mechanistic suggestions.

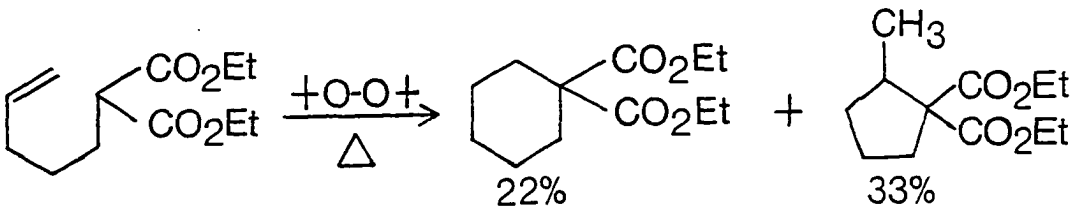
# II. HISTORICAL

## A. Recent Developments in Free Radical Organic Synthesis

Many recent developments in free radical organic synthesis have focused on the generation of cyclic systems via the intramolecular addition of a free radical center across a carbon-carbon multiple bond. An excellent review article concerning this subject has been written by Hart (1). One of the classic examples of such a reaction is known as the 5-hexenyl radical cyclization. This reaction involves the generation of a 5-hexenyl radical which cyclizes to form methylcyclopentane and a trace amount of cyclohexane as shown below (2). By placing substituents at various points on

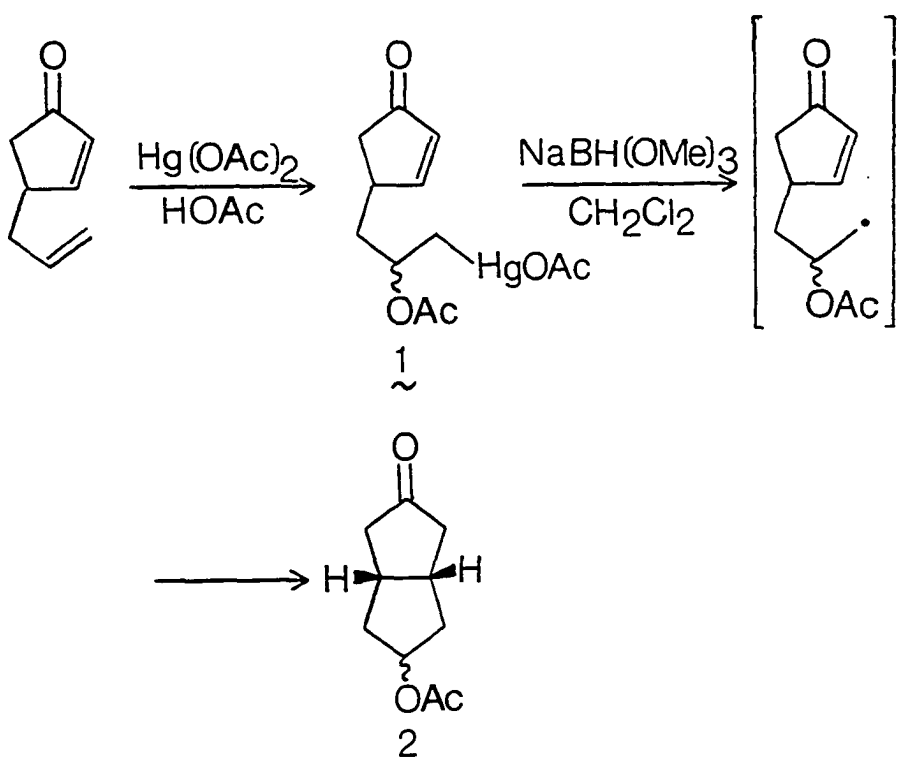



the 5-hexenyl radical, the regiochemistry can be altered to form more of the six-membered ring product, although it is still the minor one. Julia and Maumy have shown that two carboethoxyl groups attached to the carbon atom bearing the incipient radical increase the yield of six-membered ring product dramatically (3). Further modification of this classic



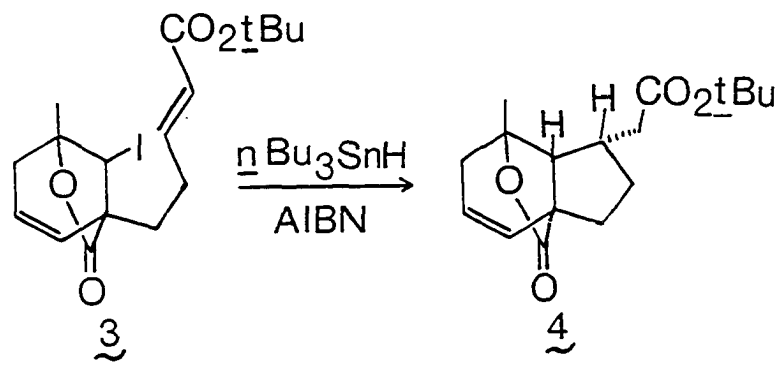

reaction scheme have enabled chemists to broaden its scope to a point whereby a variety of cyclic systems can be generated.

Danishefsky et al. have synthesized the bicyclo[3.3.0]-octane 2 via a route involving reduction of the mercurial 1 producing a 5-hexenyl type radical intermediate which adds to the β-position of the cyclopentenone moiety (4). Note that

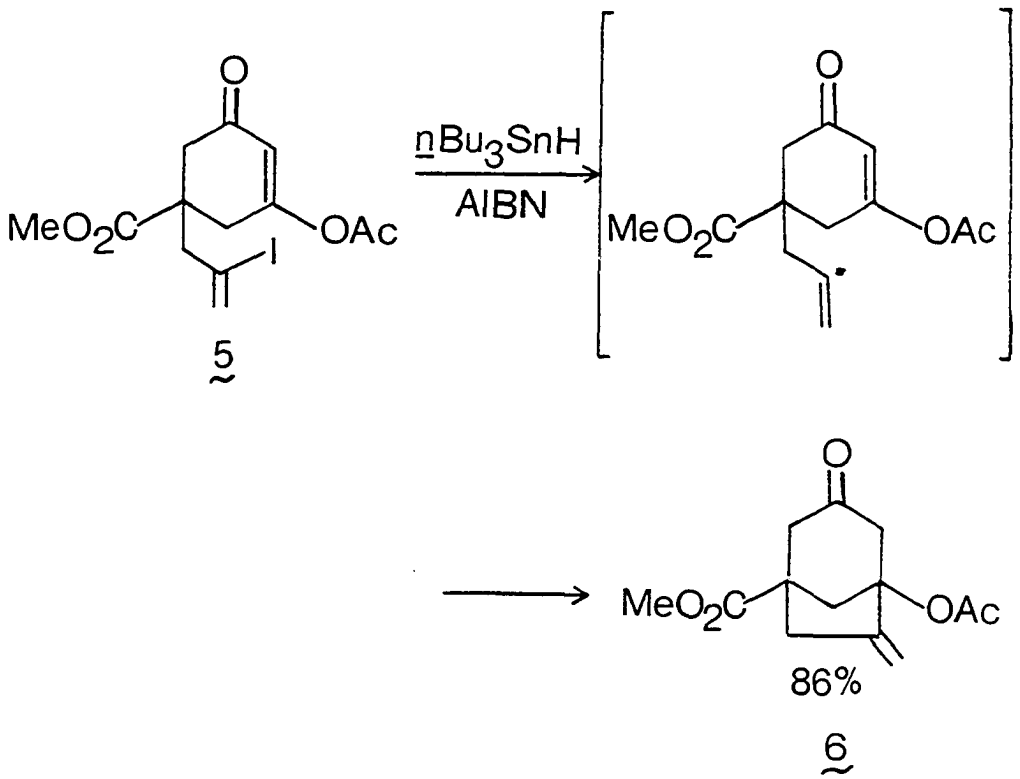


the β-acetoxyl radical intermediate formed in this reaction does not eliminate to form an alkene, a process which certainly would have occurred had the reactive intermediate been a carbanion. This general tendency of β-alkoxyl radicals to resist elimination is almost certainly due to the high energy carboxyl or alkoxyl radicals which would result, and is precisely one of the characteristics of free radical reactions which makes them so useful in synthesis.

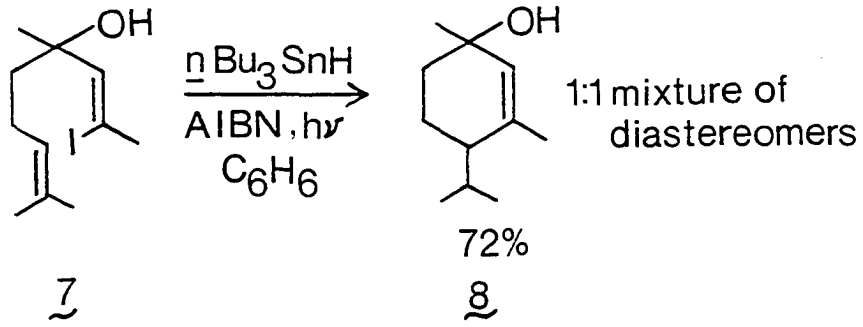
Another example of a β-alkoxyl radical which resists elimination is provided by Chuang and Hart from their work on the synthesis of highly functionalized perhydroindans (5). Treatment of 3 with tri-n-butylstannane and AIBN produces a 5-hexenyl type radical which cyclizes to form 4. A synthesis




of the gibberellic acid-related bicyclo[3.2.1]octane 6 could be accomplished via vinyl radical formation and cyclization of iodide 5; no products resulting from elimination of the acetoxyl group were observed (6).

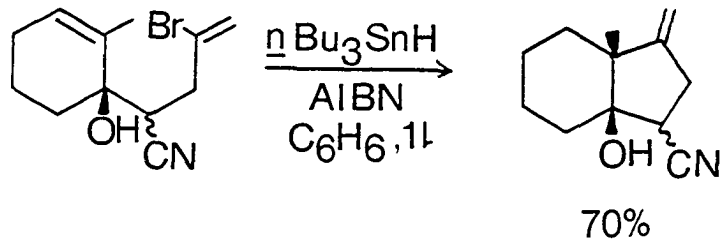



The use of vinyl radicals in cyclizations was recently reported by Stork and Baine who stressed the importance of this method in allowing the introduction of a double bond at a predictable position in a molecule (7). As shown below, vinyl iodide 7 was transformed into 8 by treatment with AIBN and tri-n-butylstannane. Another example shows the formation



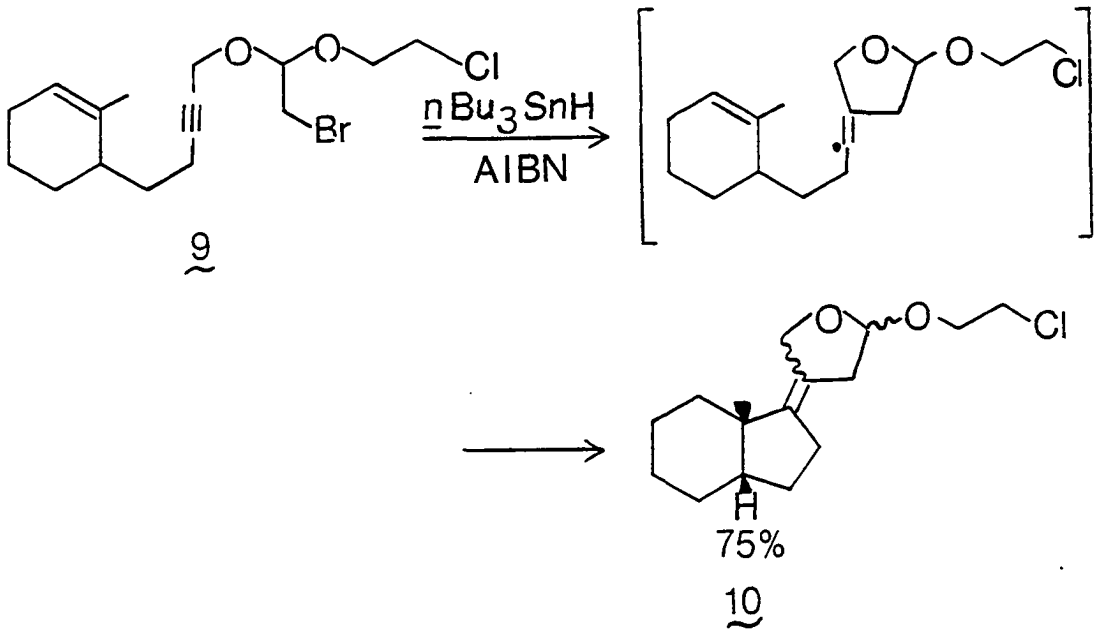

7 8

of a bicyclic system containing an exocyclic double bond (8).




Still another example provided by Stork and Mook concerns the synthesis of the protected tricyclic lactol 10 from the bromide 9 in which a vinyl free radical intermediate resulted from a preceding homolytic attack on the acetylenic portion of the molecule (8).

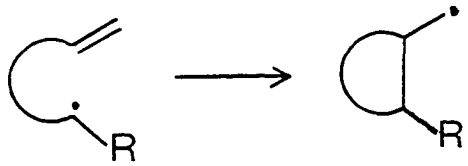
The success of this particular strategy hinges partly on the generality of another aspect of radical cyclization chemistry already hinted at above, that is, the preference



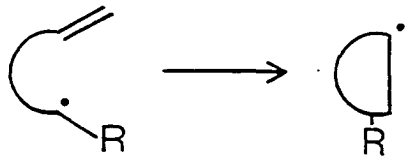

9

10

for exo- rather than endo-attack at a multiple bond. Except in cases where steric hindrance discourages exo-attack, or when the free radical resulting from endo-attack can be stabilized by resonance, the major products of radical cyclizations are those resulting from exo-attack.(9-11).



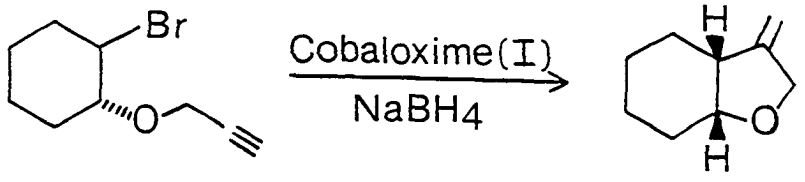

cycloalkylcarbinyl radical from exo-attack




cycloalkyl radical from endo-attack

This observation is puzzling, since cycloalkylcarbinyl radicals are generally thermodynamically less stable than cycloalkyl radicals (10). Nevertheless, ample documentation of this phenomenon in the chemical literature has allowed chemists to predict with confidence the products of given radical cyclization reactions. In Stork and Mook's conversion of 9 to 10 (8), as well as in every other example provided above, products resulting from exo-attack at the multiple bond predominated.

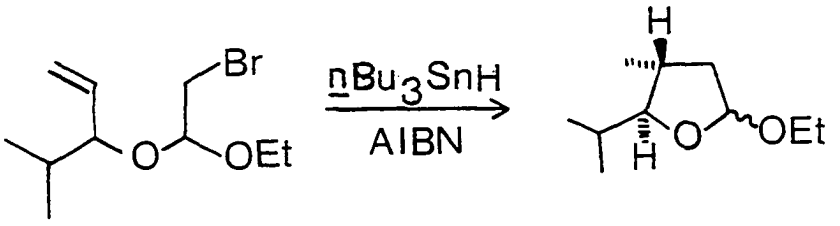
Substitution of an oxygen atom for one of the methylenes in a 5-hexenyl (or 5-hexynyl) system should constitute a cyclic ether synthesis. Indeed, for reasons which are not clear, this substitution actually increases the rate of the cyclization (12). Several years ago, Okabe et al. presented a synthesis of cyclic ether 12 from the bromoacetylene 11 (13). Here, the cobalt species served as a catalyst for homolysis of the carbon-bromine bond.




64%

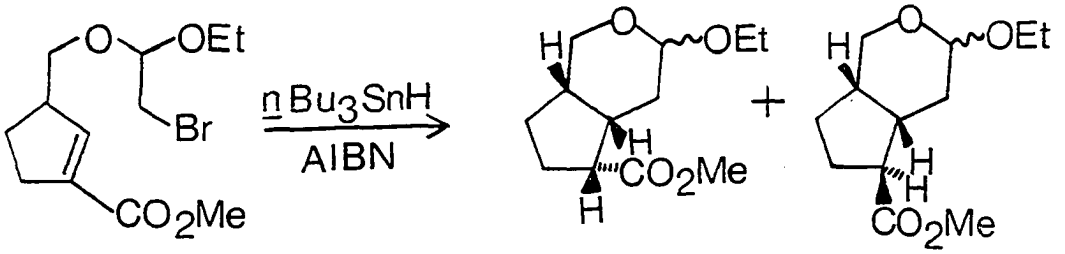
11 12

More recently, Stork et al. developed a procedure for the construction of cyclic acetals (14). Treatment of the mixed bromoacetal 13 derived from vinylisopropylcarbinol with tri-n-butylstannane and AIBN gave cyclic acetal 14 in 81% yield. Further modifications in the starting bromoacetal




13 14

have enabled them also to prepare bicyclic acetals containing a 6-membered ring. Conversion of 15 into 16 and 17 (85:15 mixture), for example, proceeded in 90% yield (14). The

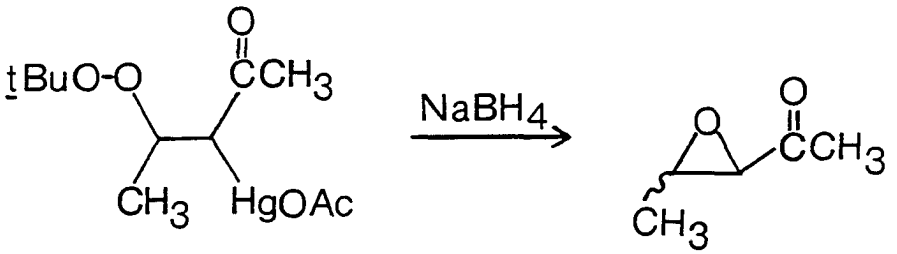



15 16 17

carboethoxyl substituent on the double bond was of crucial importance; in its absence, low yields of cyclic acetals were observed due to the occurrence of 1,5-hydrogen atom transfer.

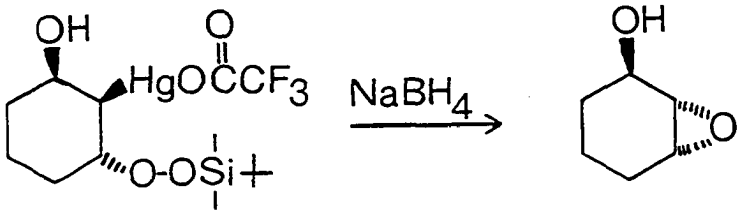
A variety of other cyclic ether syntheses have evolved whose strategies are quite different from the modifications of the 5-hexenyl (and 6-heptenyl) reactions discussed above.

Corey et al. (15) have modified a reaction originally observed by Bloodworth and Bylina for the preparation of epoxides (16). Treatment of 18 in THF at 0°C with a slight excess of sodium borohydride in basic aqueous solution afforded a mixture of the diastereomers 19 (15). Additionally,



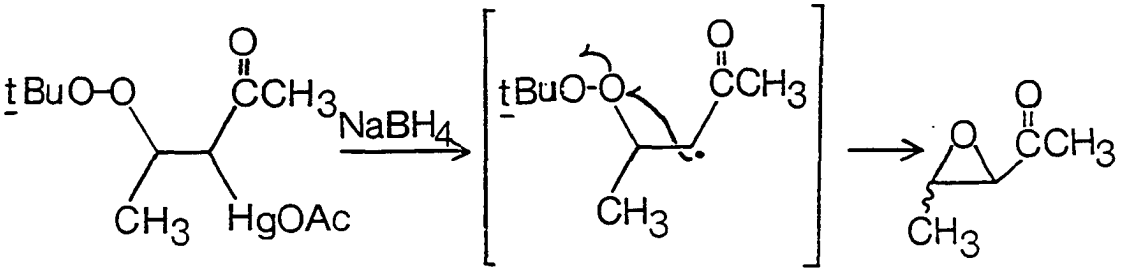

18 19

20 could be converted to trans-2,3-epoxycyclohexanol, 21, in 66% yield (15). The mechanism of this reaction almost

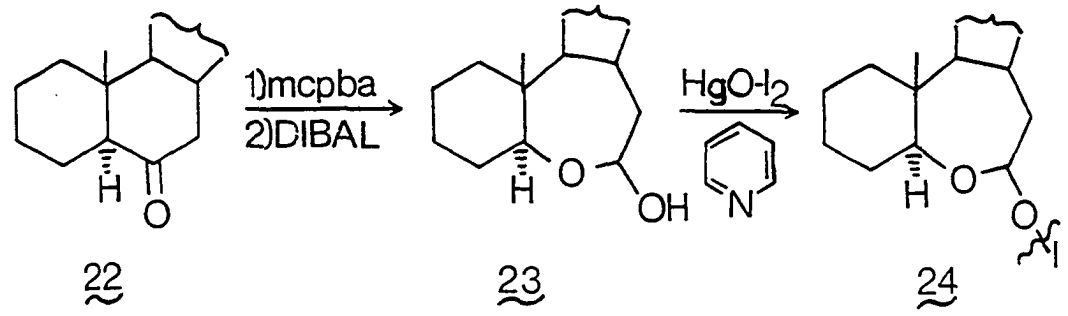



20 21

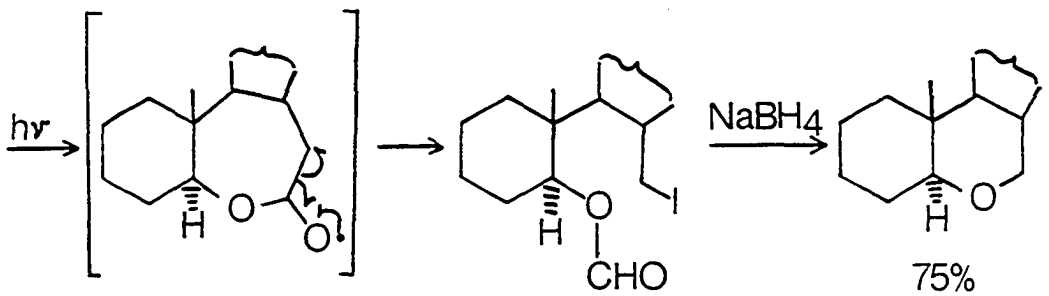
certainly involves an $S_Hi$ displacement at oxygen by the free radical resulting from sodium borohydride reduction of the carbon-mercury bond (15,16).



A very creative cyclic ketone to cyclic ether transformation has been reported by Suginome and Yamada (17). In this synthesis, a cyclic ketone such as 22 is converted to the lactol 23. Reaction of 23 with $HgO-I_2$ and pyridine affords a hypoiodite 24 which can be homolytically cleaved in the presence of light. The resulting free radical intermediate undergoes β-scission to yield an iodoformate 25 which, when reduced with sodium borohydride, yields a cyclic ether via an $S_Ni$ process. Yields range from 44 to 75% and the stereochemical integrities of chiral centers adjacent to the carbonyl group are maintained.



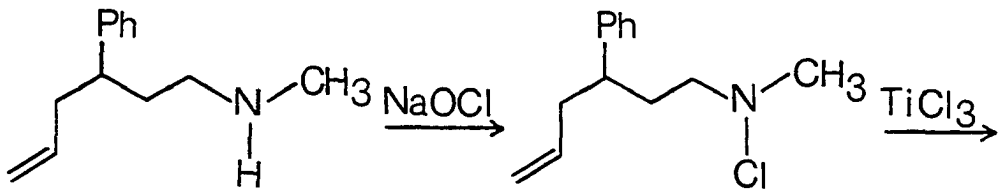

22 23 24



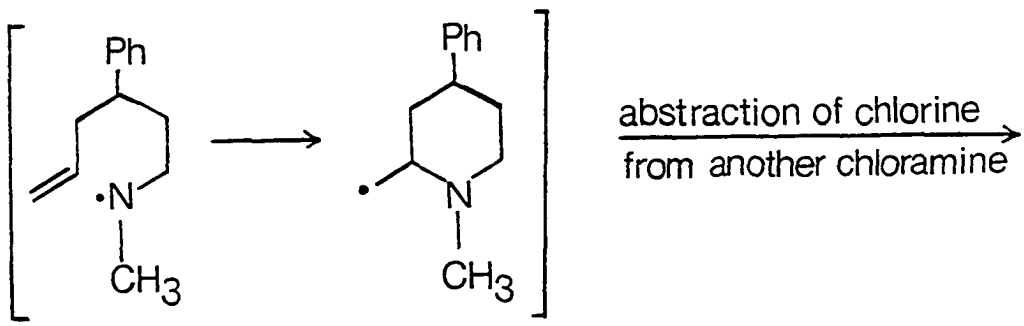

25

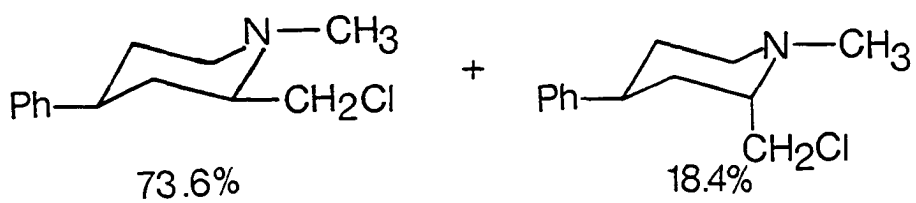
A number of papers have appeared recently concerning the synthesis of cyclic amines and lactams. In their synthesis

of 2-methyl-6,7-benzomorphane 31, a compound structurally related to morphine, Stella et al. used in a key step the intramolecular addition of an amino radical to a double bond (18). Treatment of the 2° amine 26 with aqueous sodium hypochlorite gave the N-chloramine 27, a good amino radical precursor. Homolytic fission of the nitrogen-chlorine bond with aqueous titanium trichloride produced the amino radical intermediate which cyclized to give a 4:1 mixture of 28 and 29.




26 27

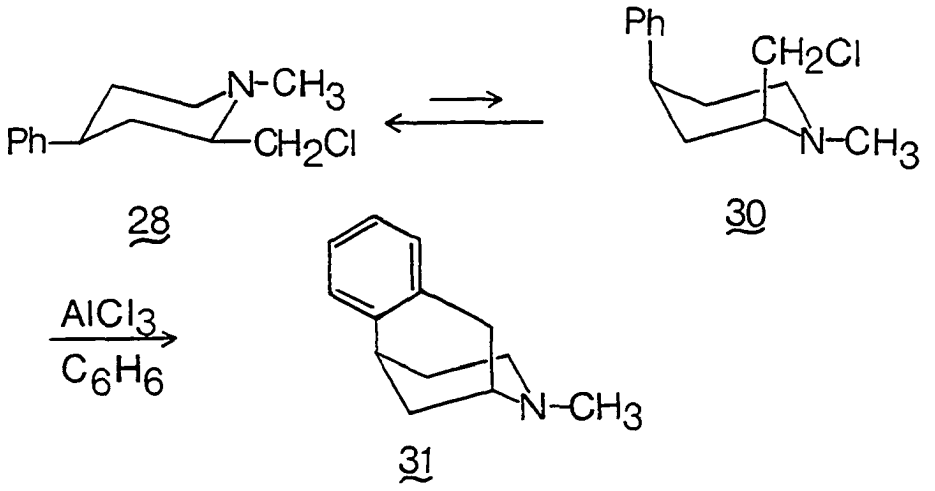



73.6% 18.4%

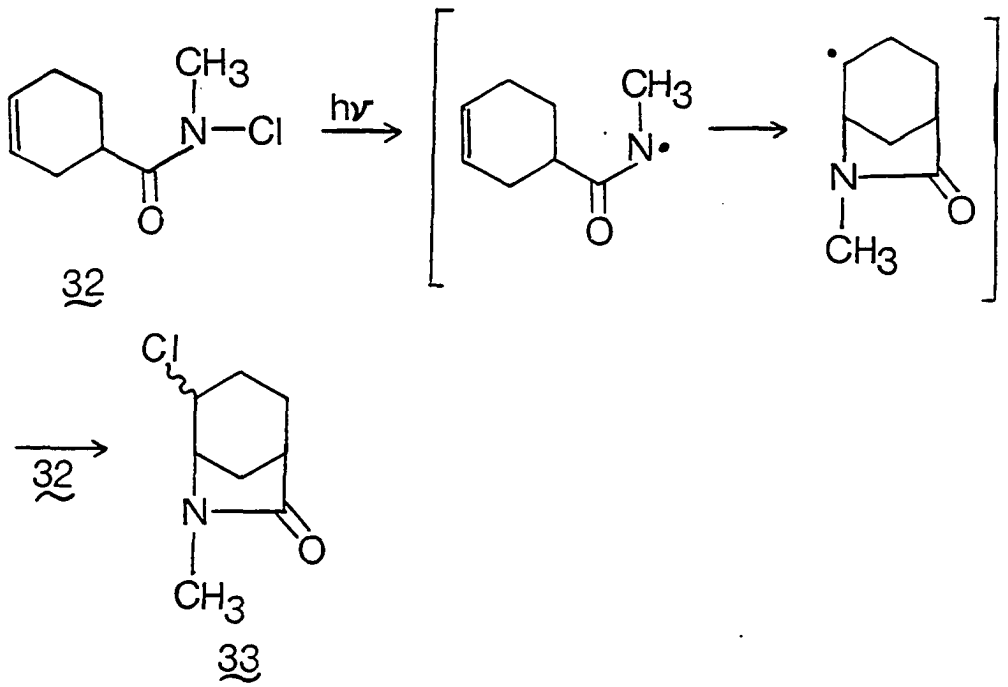
28 29

Finally, 28, which is in equilibrium with 30, was turned into tricyclic 31 via a Friedel-Crafts reaction.

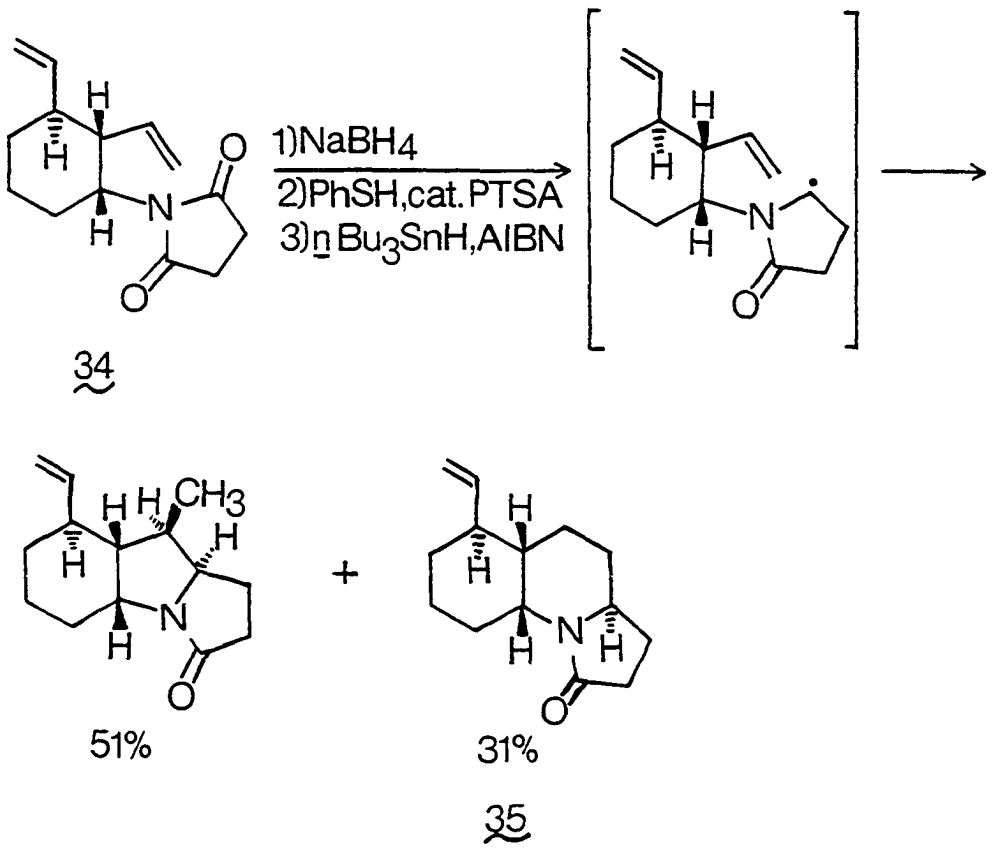



The photolysis of N-nitrosamides and N-chloramides yields amido radicals which can cyclize to give lactams. The bicyclic γ-lactam 33 shown below was produced in 91% yield from 32 via a chain process involving nitrogen-chlorine bond homolysis, cyclization, and chlorine atom abstraction from another molecule of 32 (19). A process similar to this can also explain the presence of chlorine in products 28 and 29 above.

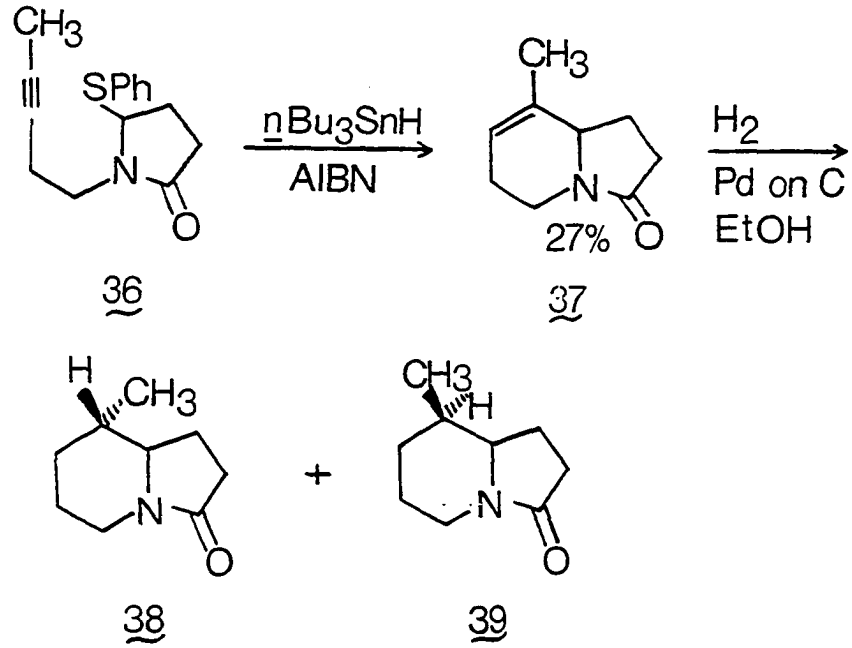
A greater number of lactam syntheses, however, have utilized α-acylamino free radical cyclizations. Hart and Tsai have developed a site-specific method for generating these



radicals which calls for reduction of an imide such as 34 with sodium borohydride, displacement of the alcohol with thiophenol, and finally homolysis of the carbon-sulfur bond using tri-n-butylstannane in the presence of AIBN (20). A separable mixture of 5- and 6-membered ring products resulted in this case. Compound 35 was identical to an intermediate used earlier by Hart in his synthesis of the Dendrobatid alkaloid gephyrotoxin (21).

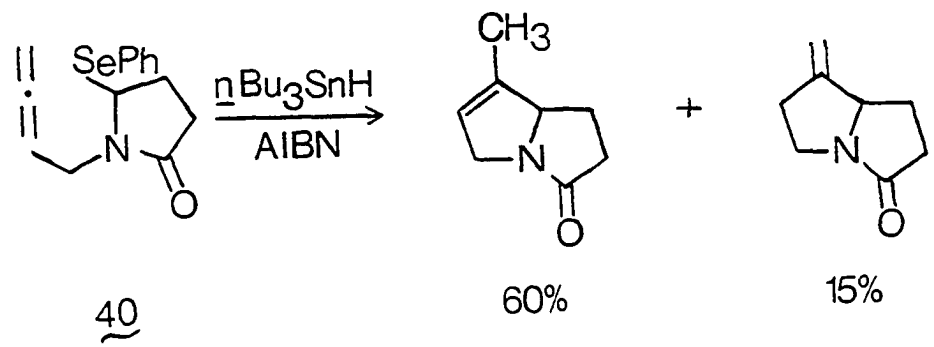



An interesting, albeit low-yielding synthesis of the indolizidinones 38 and 39 was accomplished by Choi et al. in which a key step utilized a 2-aza-5-hexynyl radical cyclization of thiophenoxy lactam 36 (22). It is noteworthy that the only cyclic product observed was 37, resulting from endo-attack on the triple bond. In contrast, substitution of the trimethylsilyl or neopentyl group for methyl in



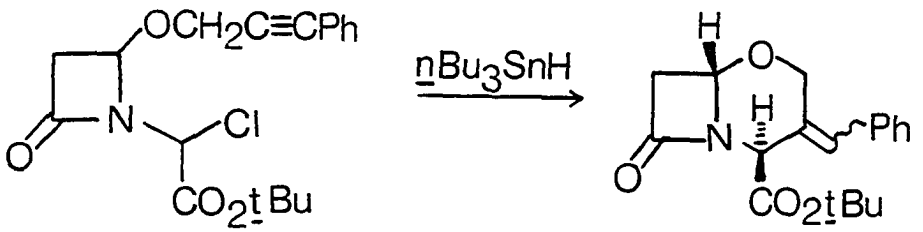

36 37 38 39

compound 36 resulted in only 5-membered cyclic products. Similarly, cyclization of allene 40 gave 5-membered cyclic products (22). The reasons for the apparently anomalous behavior of 36 are not clear, but perhaps are related to some poorly understood subtle steric and/or electronic effects (23).



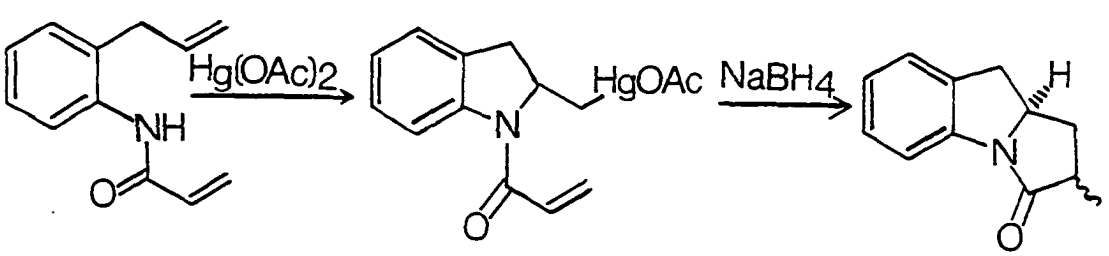

40

The mild reaction conditions used in these acylamino radical cyclizations have enabled even such sensitive molecules as the β-lactam antibiotics to be synthesized. Bachi and Hoornaert have prepared the 3-benzylidine-1-oxacepham 42 from the acylamino free radical derived from 41 (24).



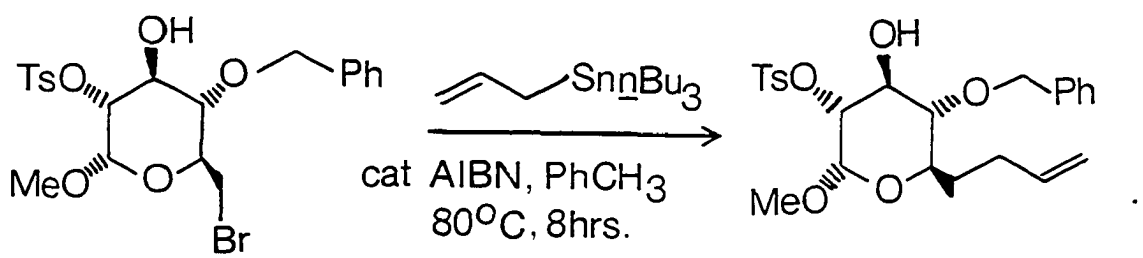

41 42

Finally, Danishefsky and Taniyama have developed a route to lactams from mercury-substituted acrylamides (25). When compound 43 was treated with mercuric acetate, and the presumed intermediate 44 treated with sodium borohydride, a 45% yield of 45 was obtained.

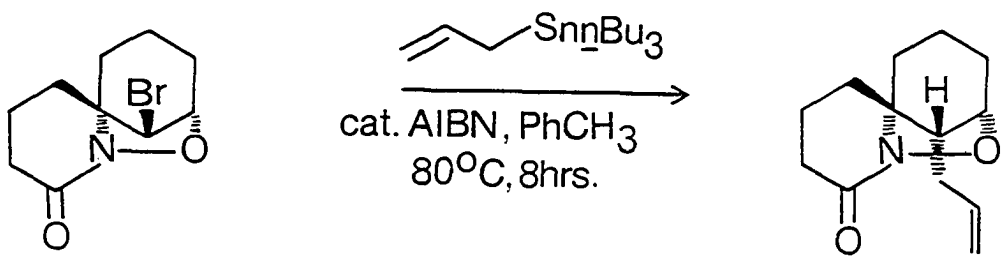



43 44 45

Two new methods for the substitution of a halide by an unsaturated three carbon unit have been reported recently. The substitution of an allyl group for halogen using allyltri-n-butylstannane has been reported by Keck and Yates (26). This reaction proceeds via initial carbon-halogen bond homolysis followed by addition of the carbon free radical to the terminal position of the double bond in allyltri-n-butylstannane. After β-scission of the tri-n-butylstannyl radical, the chain process is continued through carbon-halogen bond cleavage by the tri-n-butylstannyl radical itself. The two examples shown below testify to the wide variety of functional groups which can tolerate the reaction conditions.

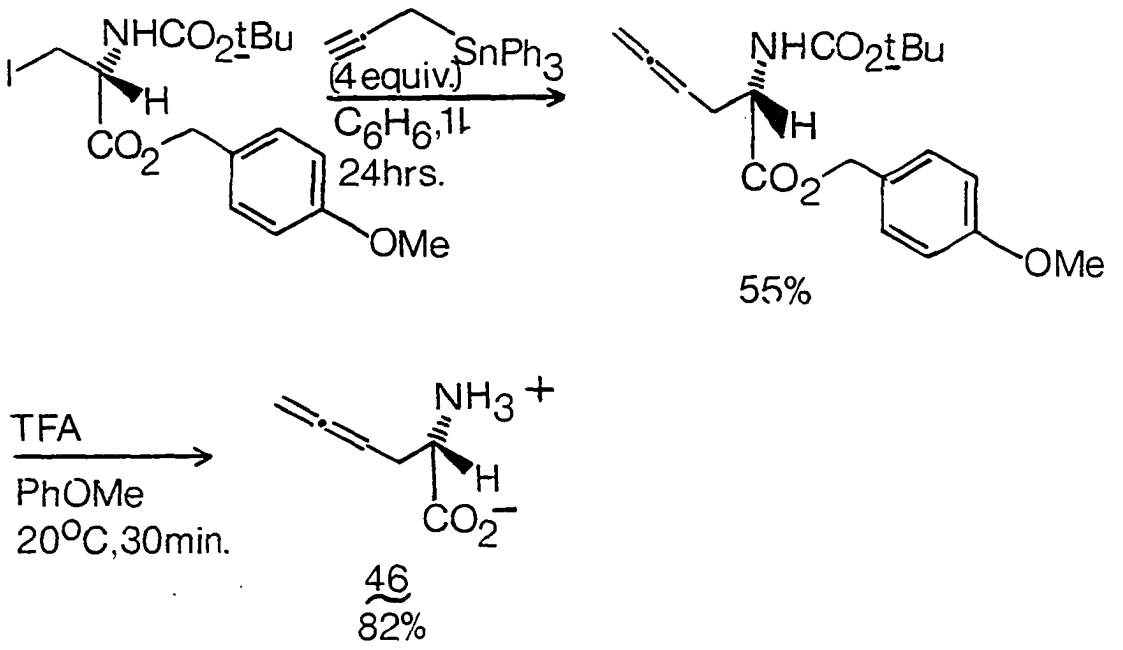



74%



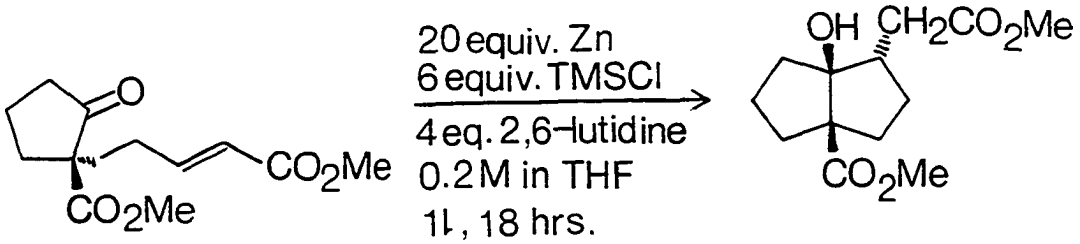

93%

In a reaction occurring by a similar mechanism, Baldwin et al. have used triphenylprop-2-ynylstannane for the transfer of an allene unit to organic compounds (27). The example shown below illustrates the use of this reaction in the synthesis of the unusual naturally occurring amino acid S-2-aminohexa-4,5-dienoic acid 46 (27).



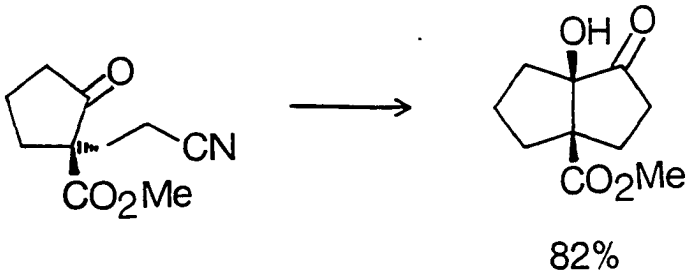

Exciting new results from Corey and Pyne have focused on the preparation of alcohols by chlorotrimethylsilane-zinc induced cyclizations of unsaturated ketones (28). In this reaction, the chlorotrimethylsilane-zinc system serves to generate an α-trimethylsilyloxyl radical (by electron transfer and silylation) which then adds to a multiple bond. Ketone

47, for example, gave 48 in 76% yield. The reaction can




47 48

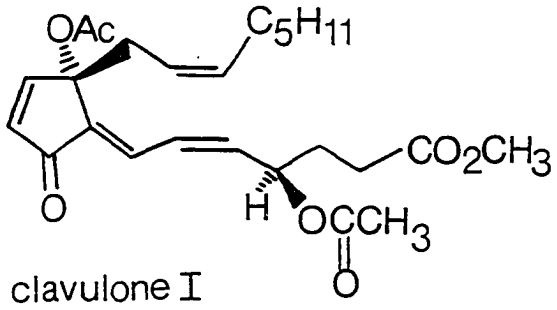
also be used to effect cyclizations on nitriles as shown below. This type of process is not entirely new, however,




82%

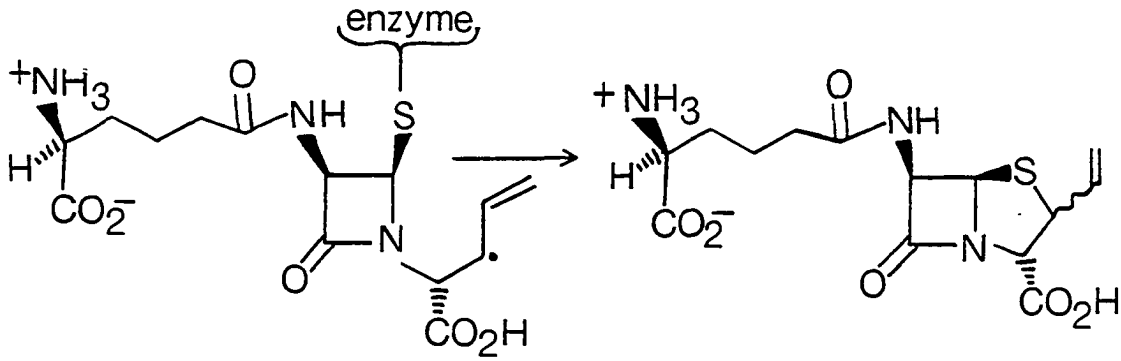
since other workers have used lithium naphthalenide (29), and electrolytic reduction (30,31), to carry out similar cyclizations.

Finally, it is perhaps pleasing to find that these free radical reactions which have enjoyed increasing popularity among laboratory chemists might also be occurring in nature. Corey et al. have proposed a biosynthesis of clavulone I, for example, which involves several free radical intermediates (15). Furthermore, 49 has been postulated to be




clavulone I

an intermediate in the biosynthesis of the vinylpenicillin 50 (32).




49 50

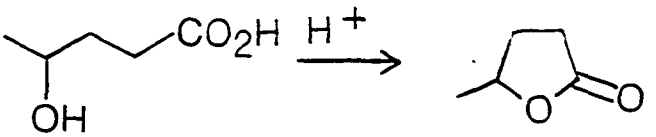
B. Methods of γ-Lactone Formation

1. Methods not involving free radicals

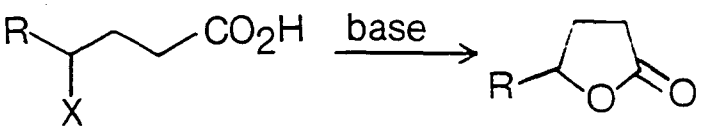
A great variety of reactions has been developed for the synthesis of γ-lactones; the intent of the author in this section is to provide a brief survey of some of the interesting and more common methods which do not involve free radical intermediates. Inasmuch, its incompleteness will be evident to many readers. However, its role as a backdrop on which to project some of the salient features

of free radical chemistry will be properly developed by providing standards for yields, scope, and reaction conditions which can be compared to those in the next section on free radical methods.

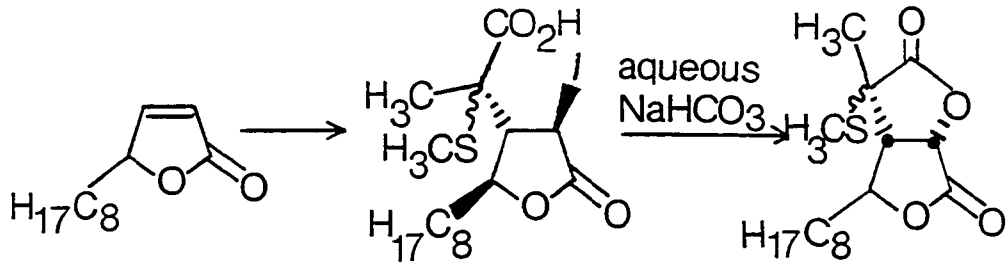
A mild and very direct method of γ-lactone formation involves closure of γ-hydroxy acids. Cyclization is usually effected by treatment with acid, but many γ-hydroxy acids form γ-lactones simply on standing at room temperature (33, p. 363).




Treatment of γ-halo acids with base also gives rise to γ-lactones (33, 367). In their synthesis of avenaciolide,

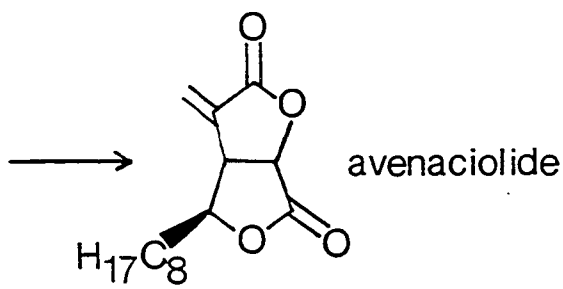



Herrmann et al. used such a reaction to produce 53 from 52 (34).

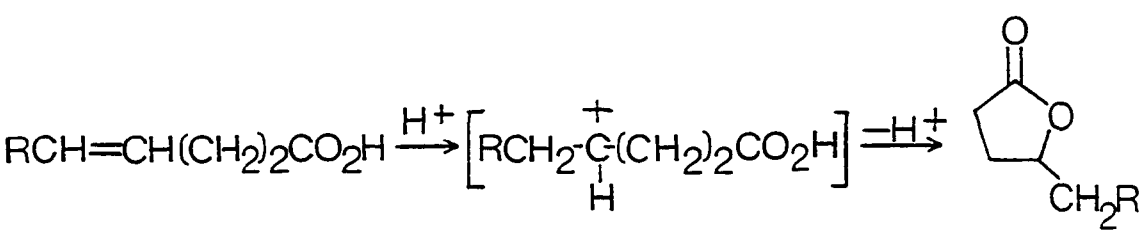



51 52 53

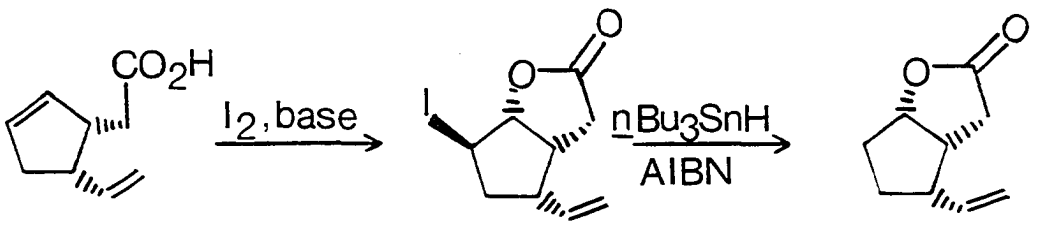
83%
from 51




The cyclization of an unsaturated acid to a γ-lactone can be accomplished by treating with a proton-donating acid such as outlined below (33, pp. 701-702). A similar reaction, which involves attack by a carboxylate anion on an iodonium ion, has been used by many chemists for the synthesis of



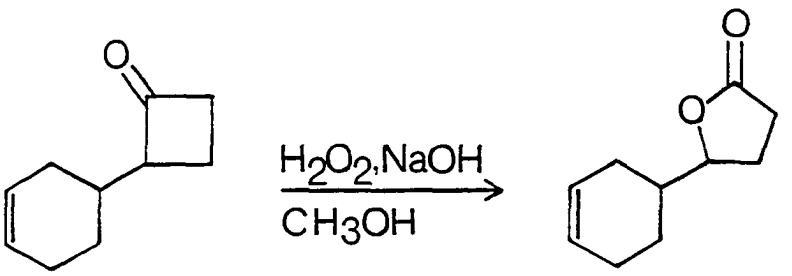
γ-lactones. This iodolactonization reaction was used by Paquette et al. in their synthesis of a prostaglandin precursor 55 from 54 which could be reduced to 56 with tri-n-butylstannane (35).



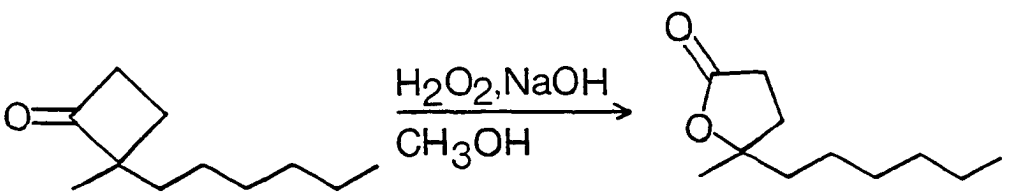

54 55 56

95% from 54

The Baeyer-Villiger oxidation of cyclobutanones also provides a route to γ-lactones. As shown below, excellent yields of lactones result from formal insertion of oxygen between the carbonyl and adjacent most highly substituted alpha position (36).

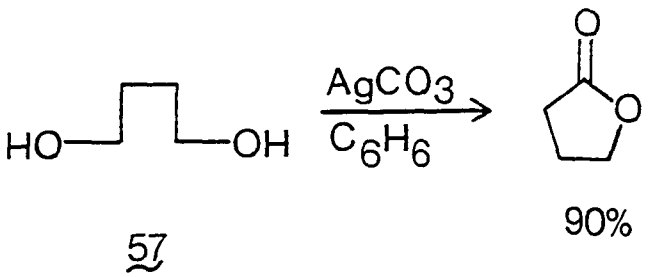



82%



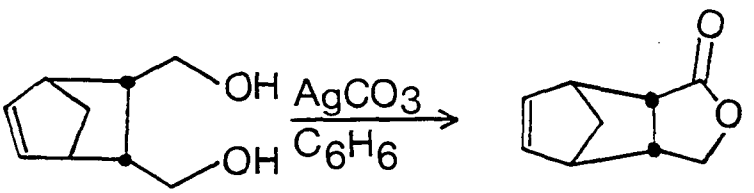

100%

Butane-1,4-diol derivatives are oxidized in good yields to the corresponding γ-lactones with silver carbonate precipitated on Celite (Fetizon's reagent). This reaction occurs under essentially neutral conditions and is particularly useful for the oxidation of symmetric diols such as 57 and 58 (37). Advantage can be taken of the preference for




57

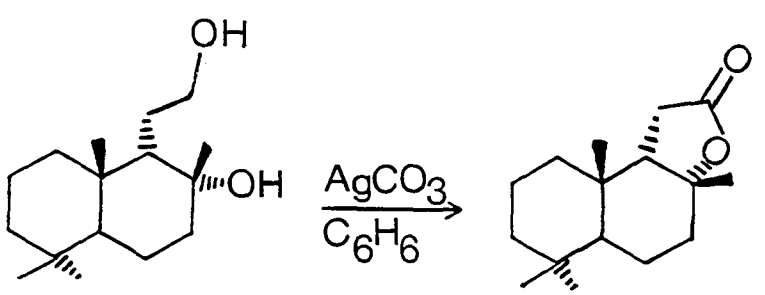
90%




58

96%

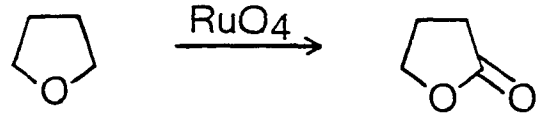
oxidation of 1° over 2° or 3° alcohols, however, for the regiospecific formation of γ-lactones from unsymmetrical diols such as 59 (37).




59

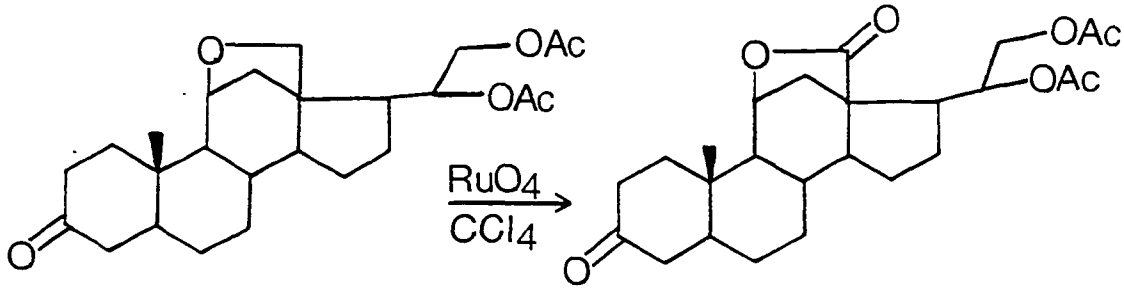
Berkowitz and Rylander have used the extremely potent oxidizing agent ruthenium tetroxide to transform cyclic

ethers into γ-lactones (38). A quantitative yield of γ-butyrolactone was obtained from tetrahydrofuran as shown below.




100%

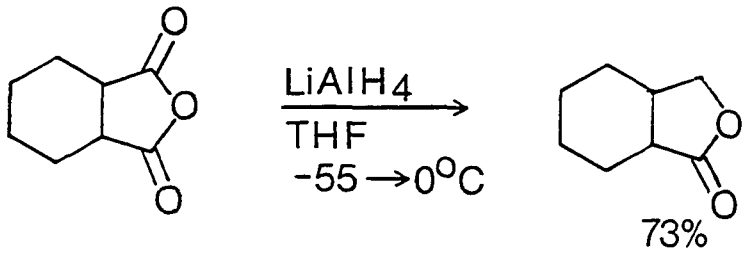
Another group of workers used this reaction in their synthesis of the steroid derivative 60 (39).



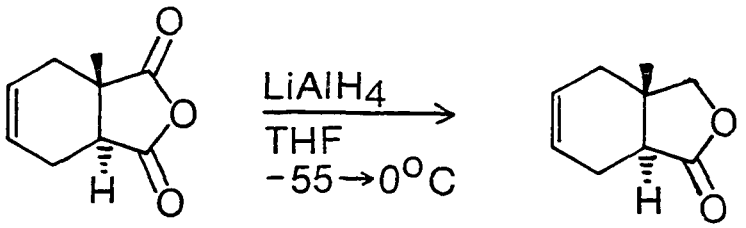

60

42%

Bloomfield and Lee have reported several examples of γ-lactone formation by reduction of cyclic anhydrides (40). In unsymmetrical anhydrides, reduction occurs at the more sterically congested carbonyl group as shown for anhydride 61.



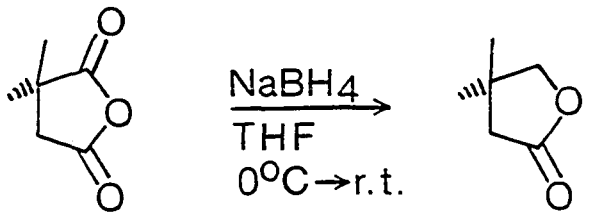

73%




61

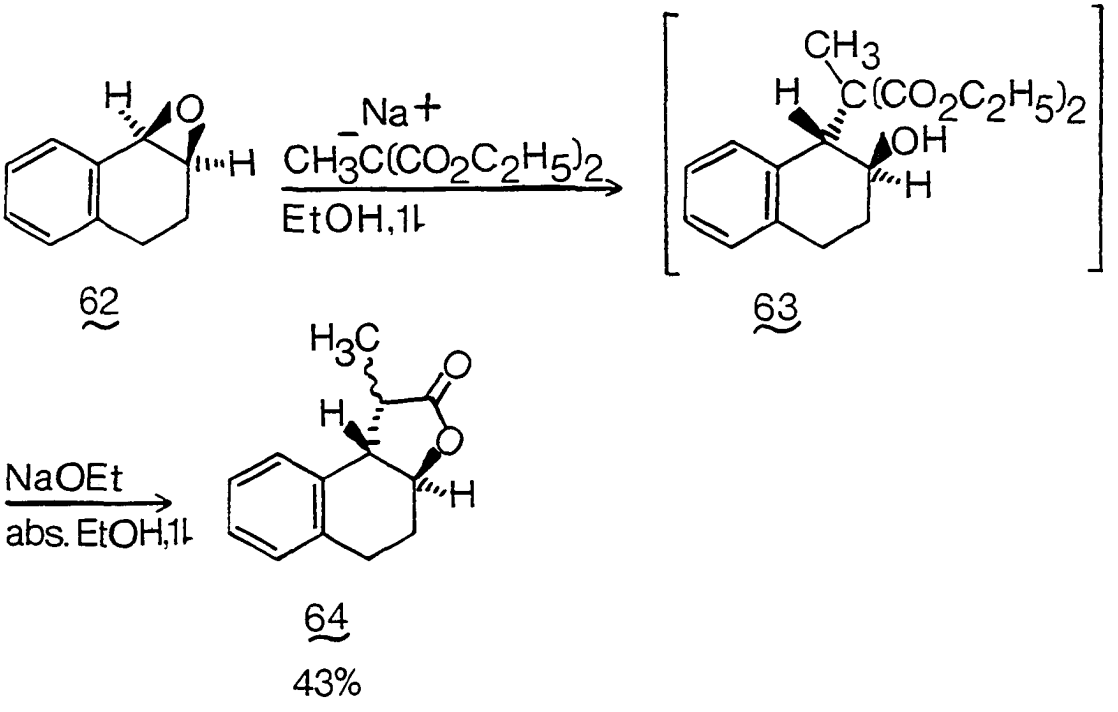
70%

Sodium borohydride is also a convenient reagent for effecting the same type of transformation (41).

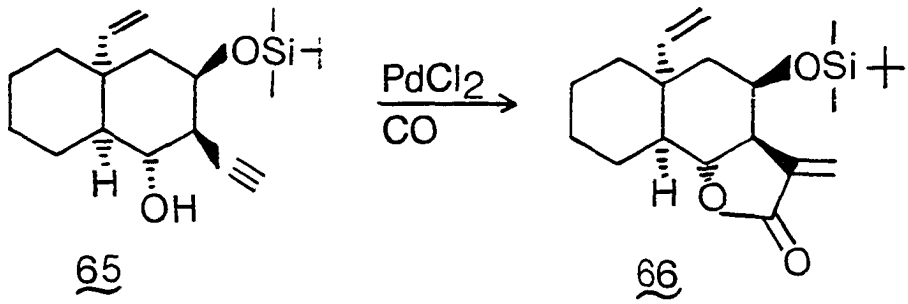



74%

An epoxide ring may be opened by a variety of nucleophiles including malonate anions to afford γ-lactones. Epoxide 62, for example, gives intermediate 63 upon treatment with the anion of diethyl methylmalonate which, upon heating, produces diethyl carbonate and γ-lactone 64 (42).



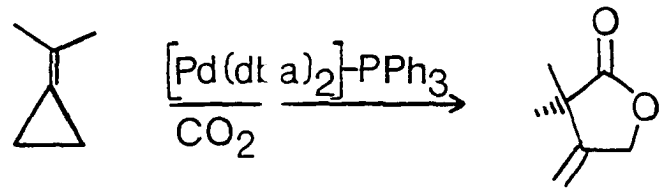

Finally, the field of organotransition metal chemistry offers a variety of procedures for γ-lactone formation. Shown below are two examples which involve the formal insertion of carbon monoxide and carbon dioxide into organic molecules. In a synthesis of vernolepin, a 50% yield of the α-methylene-γ-butyrolactone 66 was obtained by treating 65 with palladium chloride and carbon monoxide (43). A palladium




65 66

50%

catalyst was also used for the conversion of isopropylidene-cyclopropane to 6 in 69% yield (44).



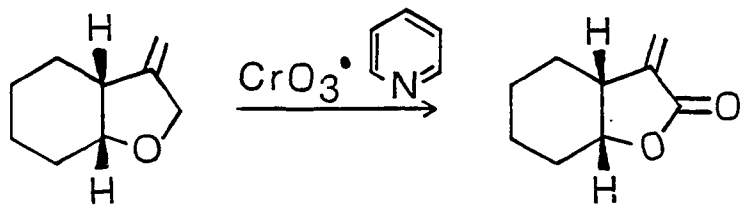

dba=dibenzylideneacetone 67

That many procedures are available for the generation of γ-lactones which do not involve free radical intermediates is evident from the foregoing discussion. In spite of the excellent yields which can be obtained from those reactions, however, there is still a need for free radical methods. Aside from allowing the synthetic chemist opportunities for bond disconnections in retrosynthetic analyses which may be incompatible with ionic reaction conditions, free radical methods of lactone formation are often necessary when acid-

or base-sensitive functional groups present in a given molecule prevent the use of those reactions discussed above. In the following section, a few examples of free radical γ-lactone syntheses will be presented which will hopefully testify as to their importance in synthetic organic chemistry.

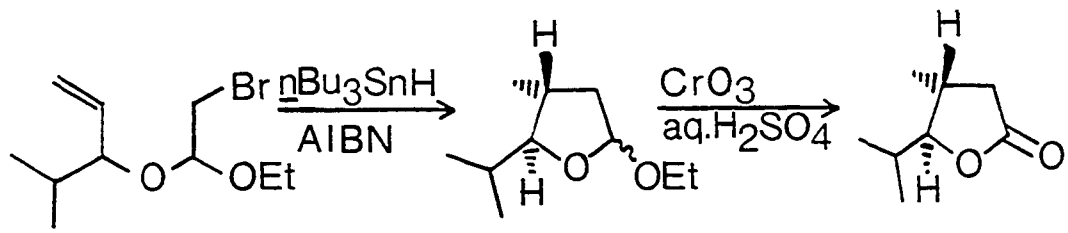
2. Free radical methods

Modifications of two reactions already discussed can be used for the preparation of γ-lactones. An ether such as 12, prepared via free radical cyclization, can be transformed easily into the corresponding α-methylene-γ-lactone by oxidation (13). Furthermore, hydrolysis and oxidation of an




12

acetal such as 14 produced by free radical cyclization affords a γ-lactone in good yield (14).

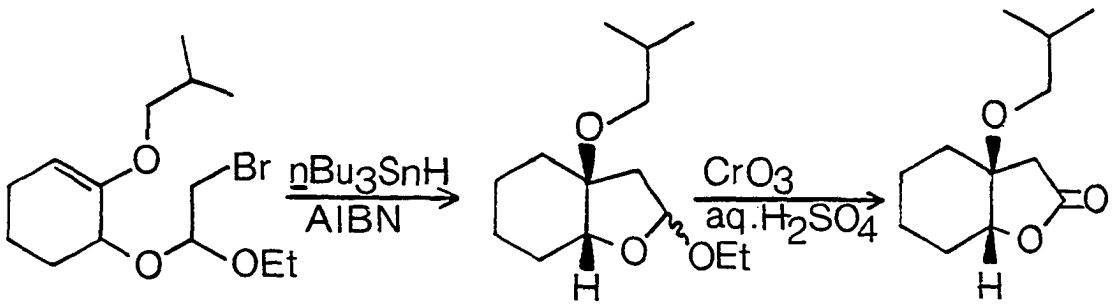



14

81%

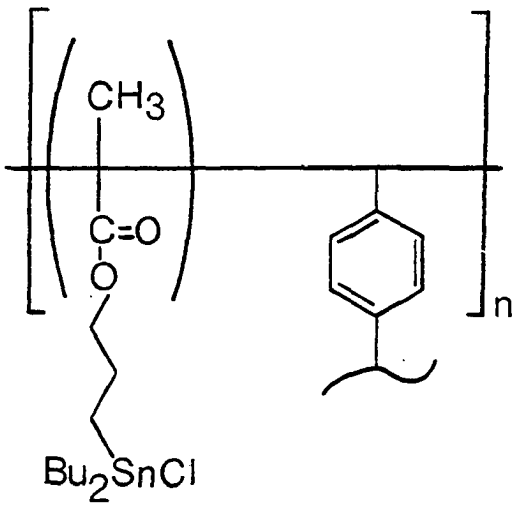
100%

In a similar reaction sequence, Ladlow and Pattenden treated 68 with tri-n-butylstannane and AIBN to obtain acetal 69 (45). This compound was then oxidized with Jones' reagent to the β-alkoxy-γ-butyrolactone 70. Comparable yields were obtained for several other similar systems.

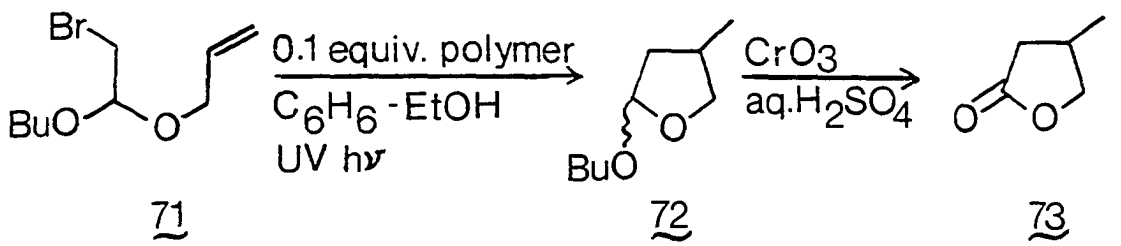



68 69 91% 70 70%

A problem often associated with these free radical cyclizations is the difficulty in separating the desired product from bromotri-n-butylstannane when tri-n-butylstannane is used as the free radical initiator. A procedure developed by Ueno et al. circumvents this problem by utilizing the polymer-supported organotin catalyst shown below (46). Treatment of bromoacetal 71 with the polymer and sodium borohydride followed by ultraviolet irradiation provided 72 in 91% yield; a lower (59%) yield was obtained when

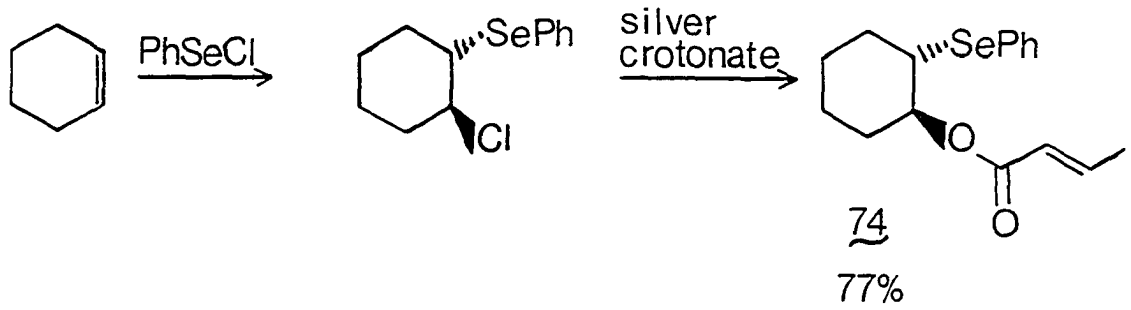



tri-n-butylstannane was used as the initiator. The product, 72, was isolated by a simple filtration step. Lactone 73 was then produced in excellent yield by oxidation with Jones' reagent.




71 72 73

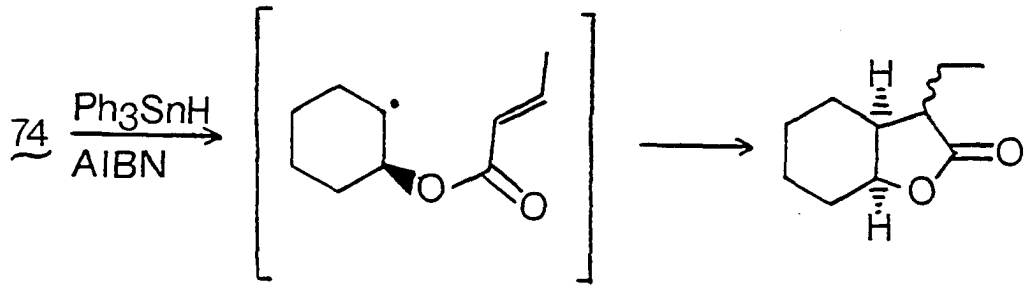
Clive and Beaulieu have developed an interesting method of γ-lactone synthesis from γ-phenylselenocrotonates (47). One synthesis they reported began by treating cyclohexene with phenylselenenyl chloride; subsequent treatment with silver crotonate yielded 74. Slow injection of a triphenyl-




74

77%

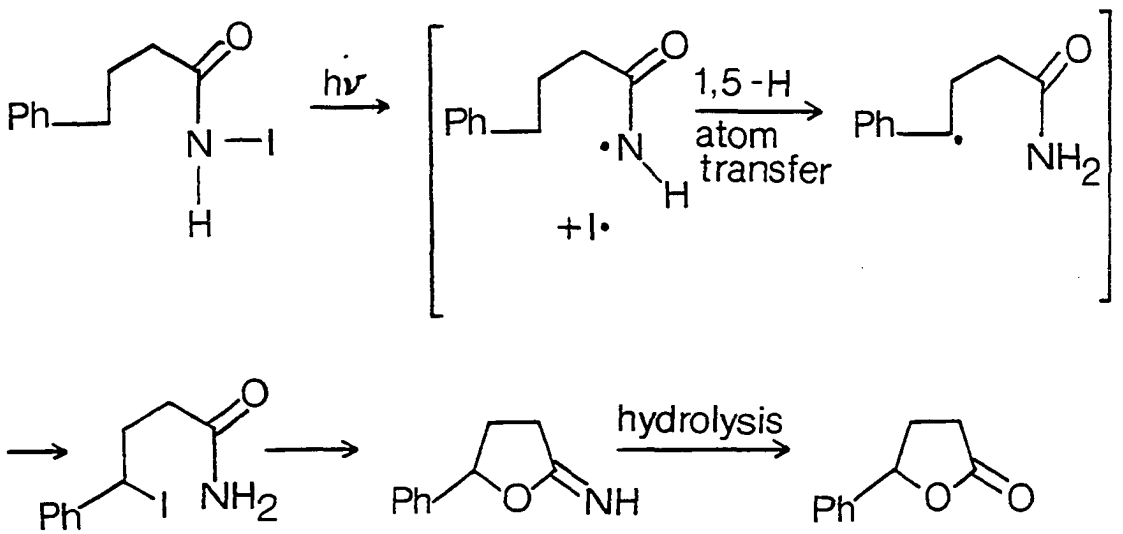
stannane/AIBN mixture into 74 in benzene resulted in a 63% yield of γ-lactone 75. Yields observed for other similar



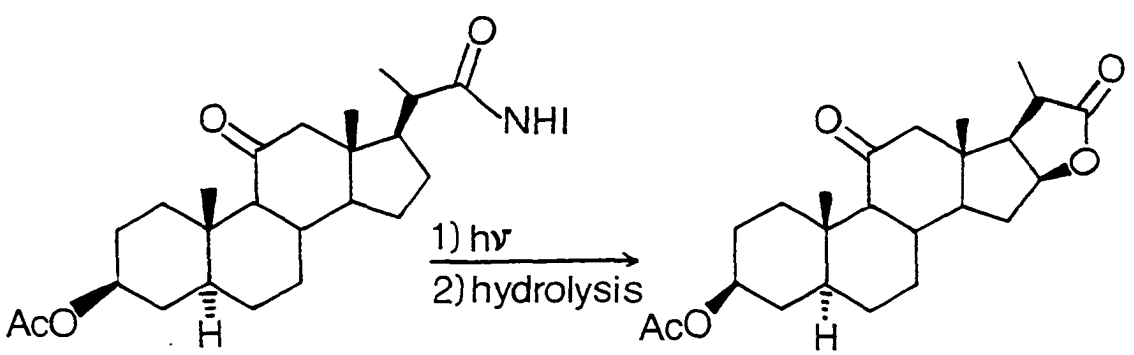

75

systems ranged from 24 to 65%.

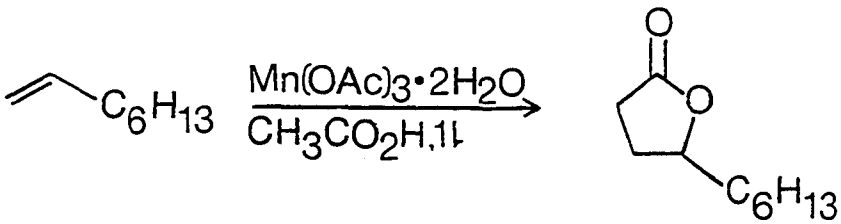
An older, yet interesting reaction enables the formation of γ-lactones from N-iodoamides. Photolysis of N-iodo-4-phenylbutyramide in benzene gave, after hydrolysis, 4-phenyl-γ-butyrolactone in modest yield (48). The proposed mechanism is outlined below. Similarly, photolysis of a steroid




derivative gave the corresponding γ-lactone in 28% yielo (48). Certainly, the low yields observed for this reaction sequence have discouraged its frequent use in organic synthesis.

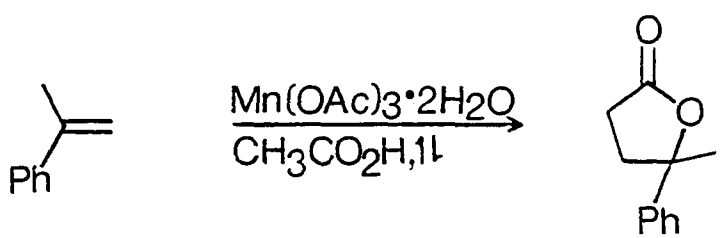



Finally, Heiba et al. have reported a synthesis of γ-lactones which involves treating olefins with two equivalents of manganic acetate dihydrate in refluxing glacial acetic acid (49). Thus, 1-octene gave γ-lactone 76 in 74% yield.



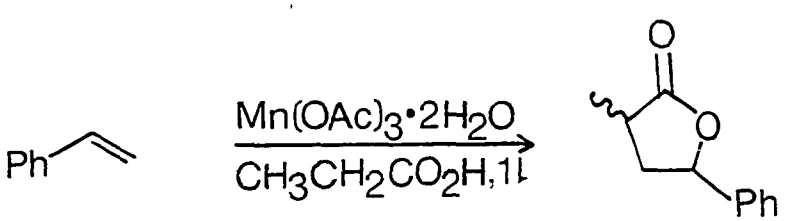

76

Similarly, α-methylstyrene gave 77, also in 74% yield. Other



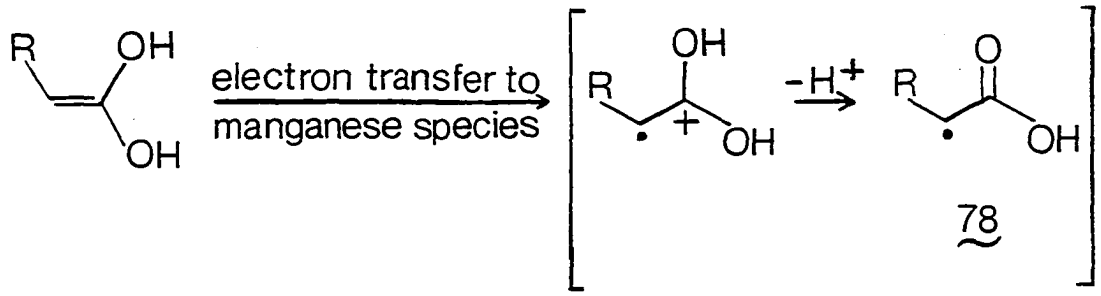

77

acids containing α-hydrogens, such as propionic acid, were also effective in producing γ-lactones as shown below (49).



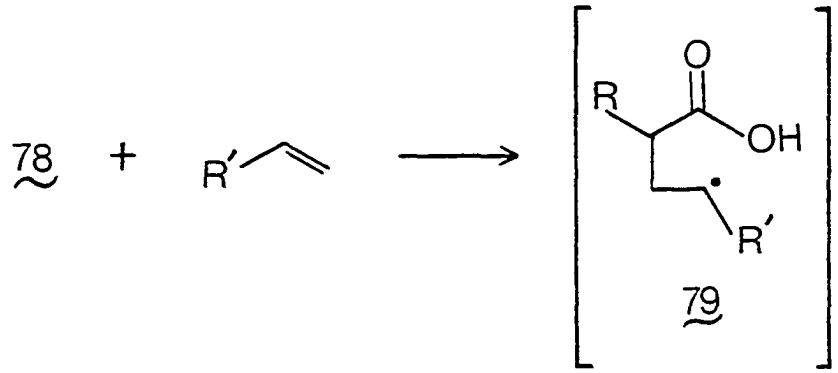

50%

The proposed mechanism involves production of a carboxyalkyl radical, 78, by electron transfer from the enol form of the acid to the manganese species. This radical then adds to



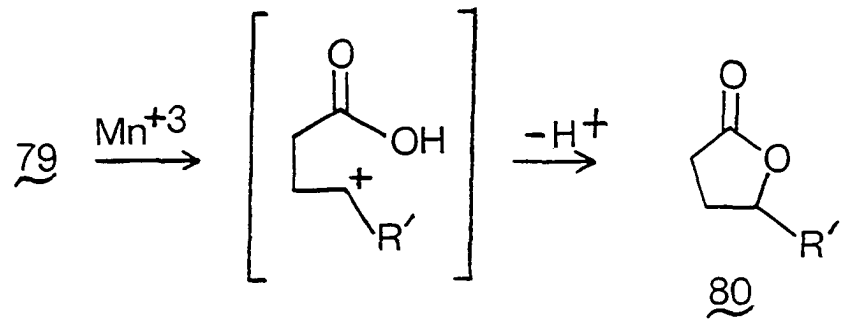

78

the terminal or least sterically crowded end of the olefin to produce 79. Rapid oxidation by $Mn^{+3}$ of 79 to a carbo-



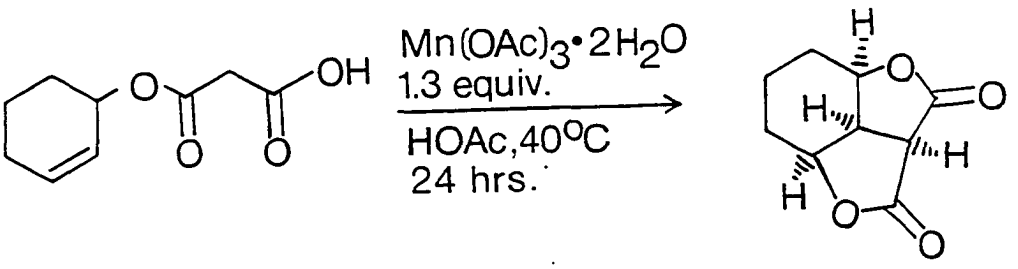

79

cation followed by cyclization and loss of a proton lead to the γ-lactone 80.




80

Recently, Corey and Kang have published an important extension of this basic reaction (50). Reasoning that an electron-withdrawing group attached to the carbon atom bearing the incipient radical might facilitate enolization and electron transfer, and taking advantage of the rate increase expected for an intramolecular reaction, they synthesized the tricyclic bis(γ-lactone) 81 shown below.




81

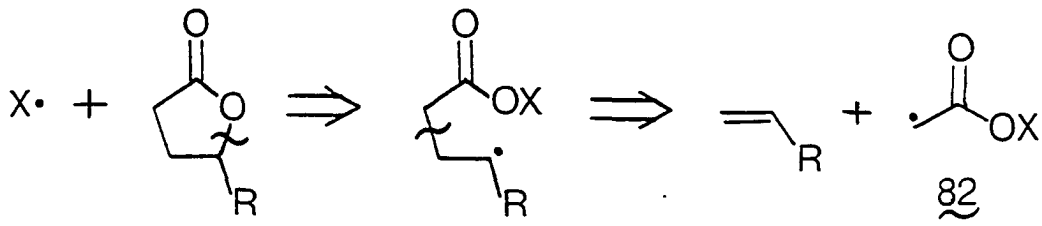
This type of reaction offers good yields and has a broad scope due to the variety of olefins and acids which can be used together to produce an almost unlimited number of γ-lactones. Further, since the starting materials are often commercially available or are trivial to prepare, it is more convenient than many of the other methods described above which require halo- or seleno-substituted precursors. One limitation of the reaction which might prevent its use in the synthesis of some lactones, however, is its incompatability with acid-sensitive functional groups. This problem, as well as the success of the reaction generally,

prompted us to seek a similar convergent approach to γ-lactones which would allow their formation under essentially neutral conditions. Our efforts toward that goal are described in the next section.

# III. RESULTS AND DISCUSSION

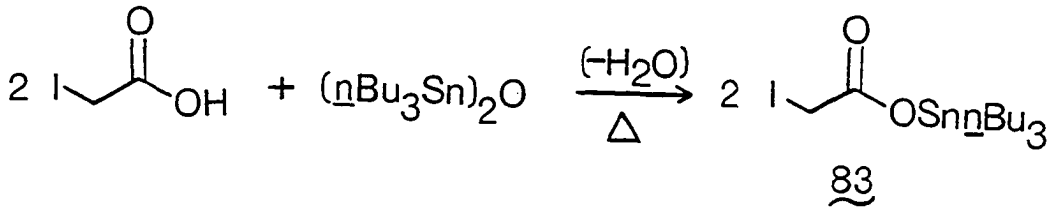
## A. Intermolecular Free Radical Lactonizations Using Tri-n-butylstannyl Iodoacetate

Our interest in developing a free radical approach to γ-lactones which would occur under neutral conditions prompted us to consider the following retrosynthetic scheme.

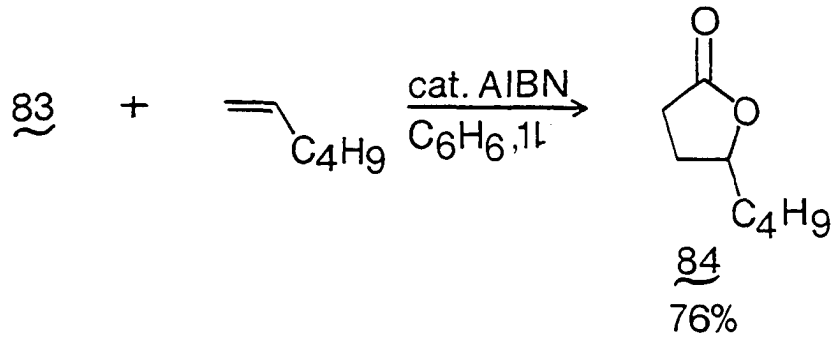



Such an approach would be similar to that of Heiba et al. (49) in that the carbon-carbon bond would be formed via a free radical process, but differs since ours might involve a free radical process for carbon-oxygen bond formation as well. We hoped also to find a suitable group X which, once eliminated, could initiate the formation of another carboxyalkyl radical 82; such a chain of events would permit us to use small amounts of free radical initiator.

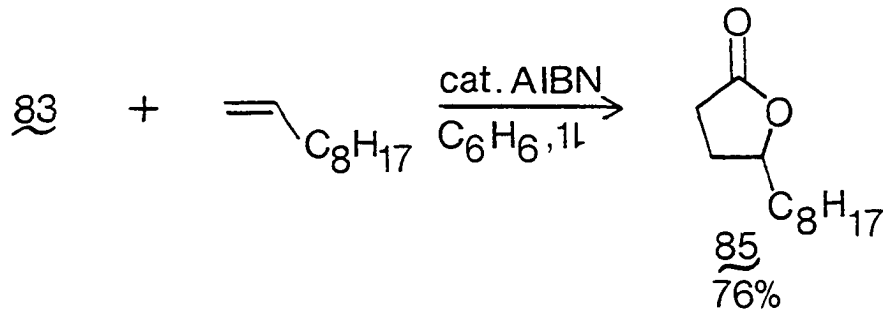
We chose tri-n-butylstannyl iodoacetate, 83, as the progenitor to 82. Tri-n-butylstannyl iodoacetate was prepared by the condensation of iodoacetic acid and inexpensive hexa-n-butyldistannoxane (51). When 83 was



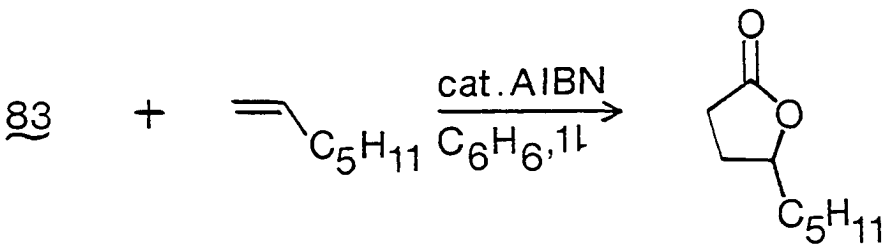
refluxed for 8 hrs in benzene with 3 equivalents of 1-hexene and 0.05 equivalent AIBN, a 76% yield of 4-n-butyl-γ-butyrolactone, 84, was obtained (52). The γ-lactone was separated from nonpolar by-products by partitioning between acetonitrile and hexanes (53). Further purification by column chromatography gave pure 84. Similarly, 4-n-octyl-γ-butyrolactone,



85, and 4-n-pentyl-γ-butyrolactone, 86, were prepared from 1-decene and 1-heptene, respectively. Interestingly, 85 is a pheromone produced by the rove beetle (54) and lactone

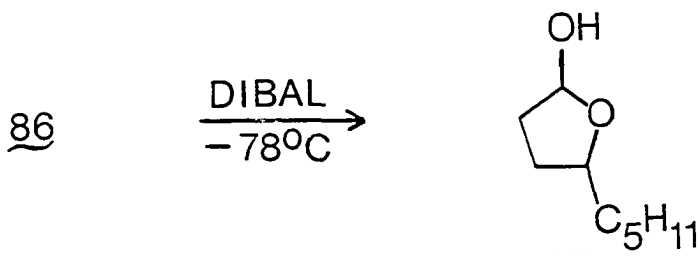



85
76%



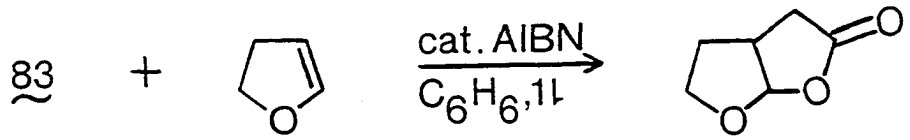

86
72%

86, when reduced with diisobutylaluminum hydride (DIBAL), gave the watermelon flavor constituent 87 (55).

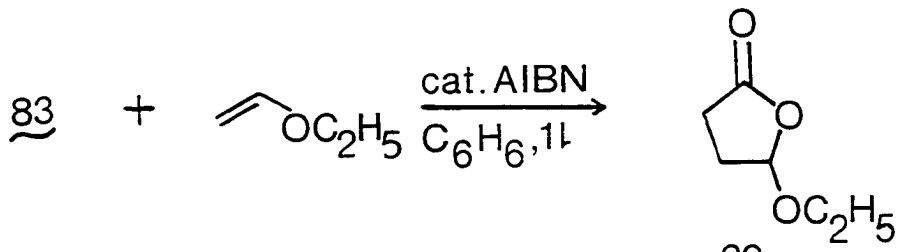



87
80%

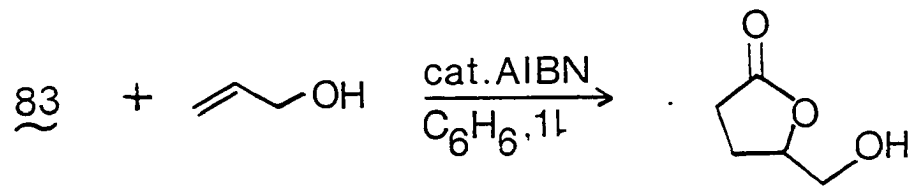
That a variety of functional groups are compatible with the reaction conditions is evident from the examples given below. Thus, bicyclic lactone 88 was prepared in



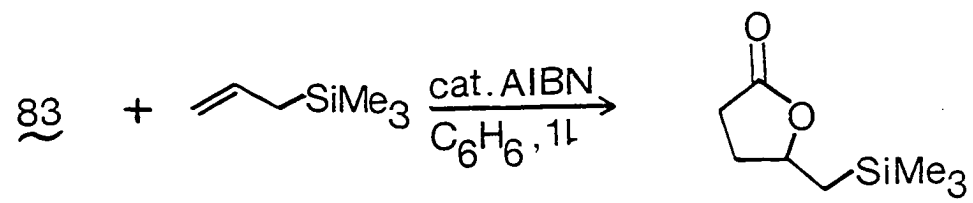

88
78%




89
36%




90
73%



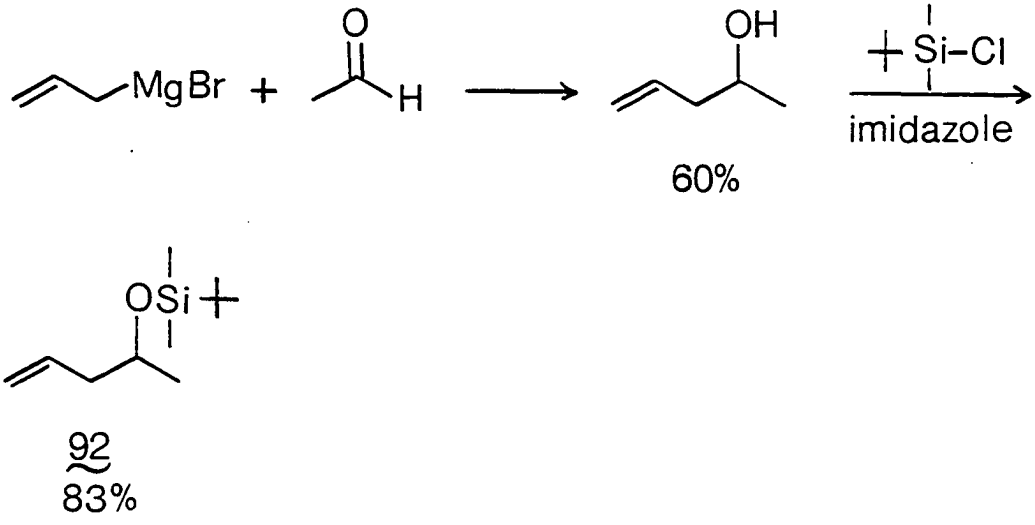

91
56%

good yield from 2,3-dihydrofuran. An equal amount of an unidentified by-product was formed in addition to 89 when ethyl vinyl ether was used as the olefinic component. Finally, the formations of 90 and 91 show the compatibilities of hydroxyl and trialkylsilyl groups with the reaction conditions.

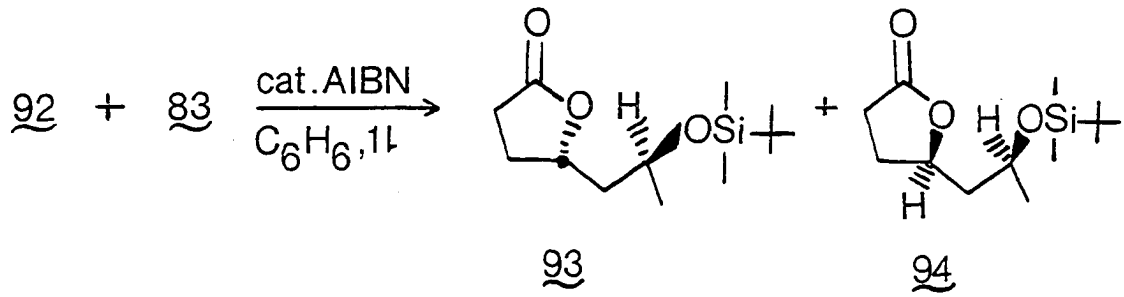
Several alternate initiation procedures for the reaction were studied. Although a catalytic amount of tri-n-butylstannane was effective when AIBN was also present, its use did not improve yields. Photochemical initiation, either at 25°C or 80°C, led to the formation of several by-products. Thus, a catalytic amount of AIBN alone proved to be an effective and convenient free radical initiator.

Use of more than 3 equivalents of olefin did not improve yields significantly. However, drastically lower yields of γ-lactones were obtained when only 1 or 2 equivalents of olefin were used. Degassing the benzene solutions with argon or nitrogen also did not significantly affect yields.

To determine if any degree of diastereoselectivity would result from the reaction of tri-n-butylstannyl iodoacetate with an olefin containing an asymmetric center, we prepared silyl ether 92. Grignard reaction of allylmagnesium bromide with acetaldehyde gave 4-penten-2-ol in 60% yield. Subsequent protection of the alcohol afforded 92 in good yield. We hoped that the bulky t-butyldimethylsiloxyl




protective group, through a 1,3-steric interaction, would direct carbon-oxygen bond formation to afford a preponderance of the diastereomer 93. In fact, a 68% yield of a 1:1

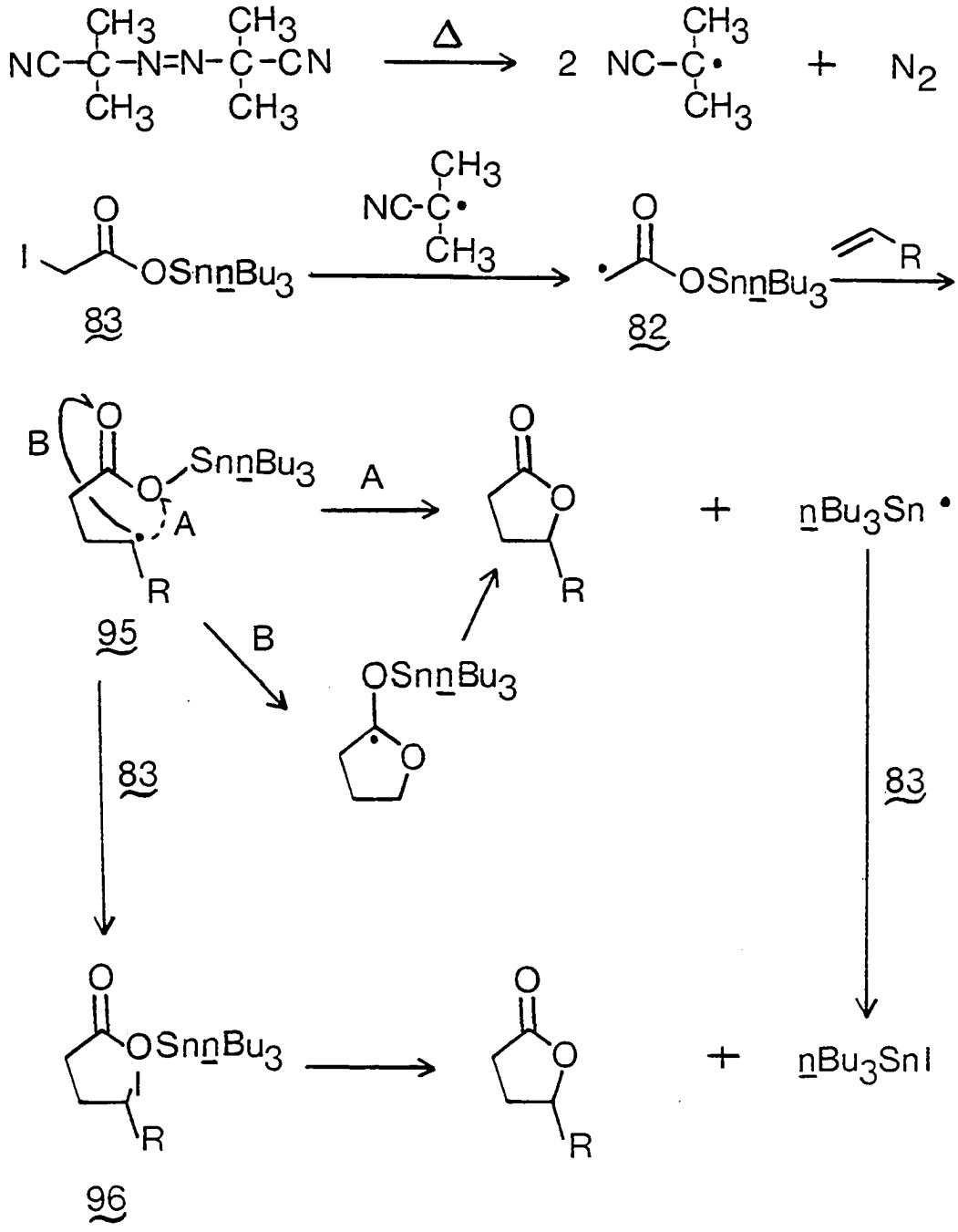



mixture (as determined by 300 MHz NMR) of 93 and 94 was produced; thus, no diastereoselectivity was observed. Analogous results were obtained using the t-butyldimethyl-silyl ether of 3-buten-2-ol.

We were initially surprised that several olefins did not react to give γ-lactones under these reaction conditions. Cyclohexene, 2-methyl-1,3-butadiene, and isopropenyl acetate were recovered unchanged. Ethyl cinnamate and 83, even after heating to 200°C in a sealed tube containing benzene and AIBN were similarly recovered unchanged. Styrene and ethyl acrylate produced polymeric substances. 1-Heptyne also did not react with 83 under these conditions.

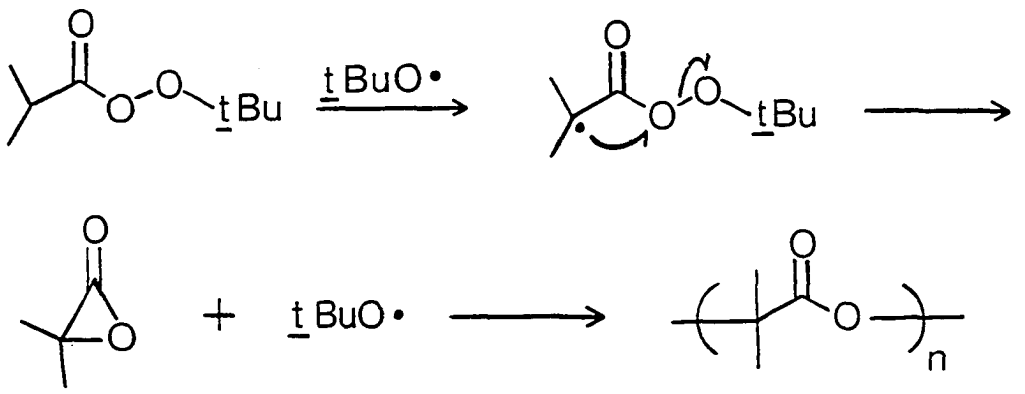
## B. Mechanistic Considerations

The possibilities which seem most reasonable for the mechanism of this novel lactonization are illustrated on the next page. The first step, dissociation of AIBN into a pair of 2-cyanopropyl radicals, is well documented in the chemical literature (56, p. 514). Iodine atom abstraction by this radical from 83 forms 82 (57), which then adds to the terminal carbon of the olefin to form 95. This addition step seems reasonable since similar addition reactions of the acetonyl radical have been observed (58). In fact, addition reactions of most free radicals to monosubstituted olefins occur at the unsubstituted position, thus avoiding the greater steric compression associated with forming a new bond at the internal position (59).

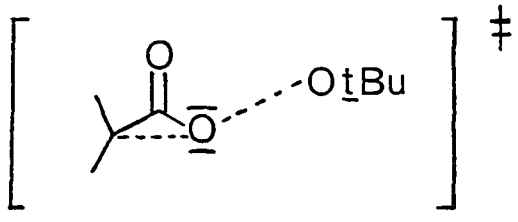

NC–C(CH3)2–N=N–C(CH3)2–CN
Δ
2 NC–C•(CH3)2
+ N2
I–CH2–C(=O)–OSnnBu3
83
NC–C•(CH3)2
•CH2–C(=O)–OSnnBu3
82
R
B
SnnBu3
A
95
R
+ nBu3Sn•
B
OSnnBu3
O
83
83
OSnnBu3
I
R
96
+ nBu3SnI

The failure of 82 to react with electron deficient olefins is most likely a consequence of the presumed polarity of the transition state for this addition step. The importance of polar forces in determining the course of free radical reactions is well documented (59). Thus, 82, an "electron acceptor" radical, is a poor candidate for addition reactions to electron deficient olefins such as 2-methyl-1,3-butadiene, isopropenyl acetate, ethyl cinnamate, styrene, and ethyl acrylate.

At least three pathways should be considered for the transformation of 95 to a γ-lactone. Path A involves homolytic attack at oxygen with elimination of the tri-n-butylstannyl radical. Homolytic substitution reactions at oxygen in peroxides and peresters are well known; one example involves the decomposition of t-butylperisobutyrate to a polyester of γ-hydroxyisobutyric acid. An α-lactone, resulting from $S_Hi$ reaction at perester oxygen, is considered to be an intermediate (60).

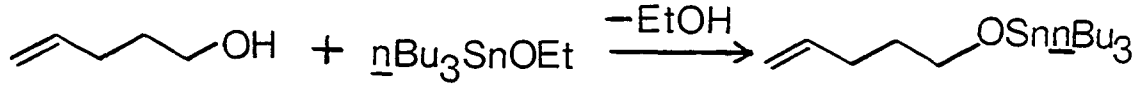


This $S_Hi$ process might initially seem unreasonable, since the transition state could be considered to involve a hypervalent oxygen atom. However, the weakness of the



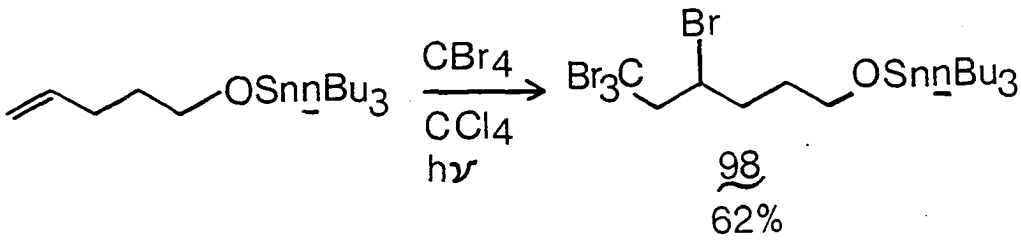
oxygen-oxygen bond apparently allows for an early transition state in which bond cleavage has progressed to a further extent than carbon-oxygen bond formation (60).

In order to test whether homolytic attack at a tin-oxygen bond is feasible, we prepared the tri-n-butylstannyl ether 97 from ethoxytri-n-butylstannane and 4-penten-1-ol (61). Reasoning that addition of a free radical to the terminal



97
98%

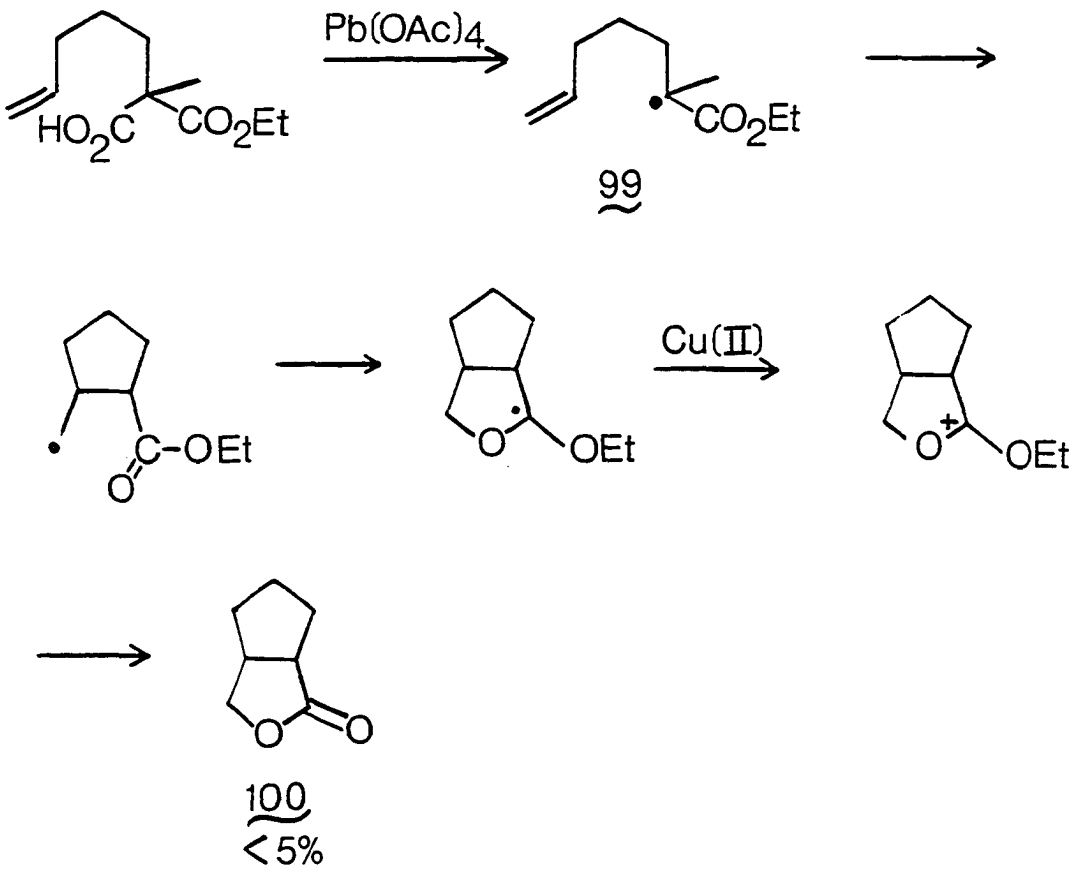
end of the olefin in 97 would produce an intermediate which could close to a cyclic ether via an $S_Hi$ process, we attempted the addition of the tribromomethyl radical (62). Recovery of the tetrabromide 98 indicated that such an $S_Hi$ process does not occur under the reaction conditions for stannyl ethers. Apparently, the greater strength of the tin-oxygen



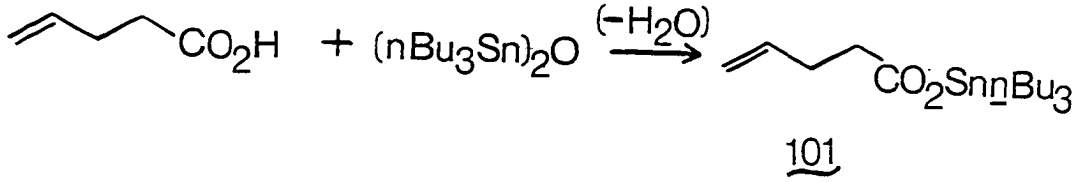

bond in stannyl ethers (and presumably also in stannyl esters) discourages the $S_Hi$ process to such an extent that simple addition reactions occur instead.

Path B involves homolytic attack at the carbonyl oxygen to give an acetal type radical intermediate which fragments to form a γ-lactone. The formation of this intermediate, a 5 endo-trig process, appears to violate Baldwin's rules (63). However, there are many exceptions to these rules; one in particular involves the preparation of bicyclic lactone 100, albeit in low yield, from radical intermediate 99 via the mechanism shown below (64).

In order to determine if intermediate 95 can cyclize to a γ-lactone, we decided to prepare some of its analogs by adding various free radicals to stannyl ester 101, prepared by condensation of 4-pentenoic acid and hexa-n-butyl-distannoxane (51). We felt that intermediate 102, an

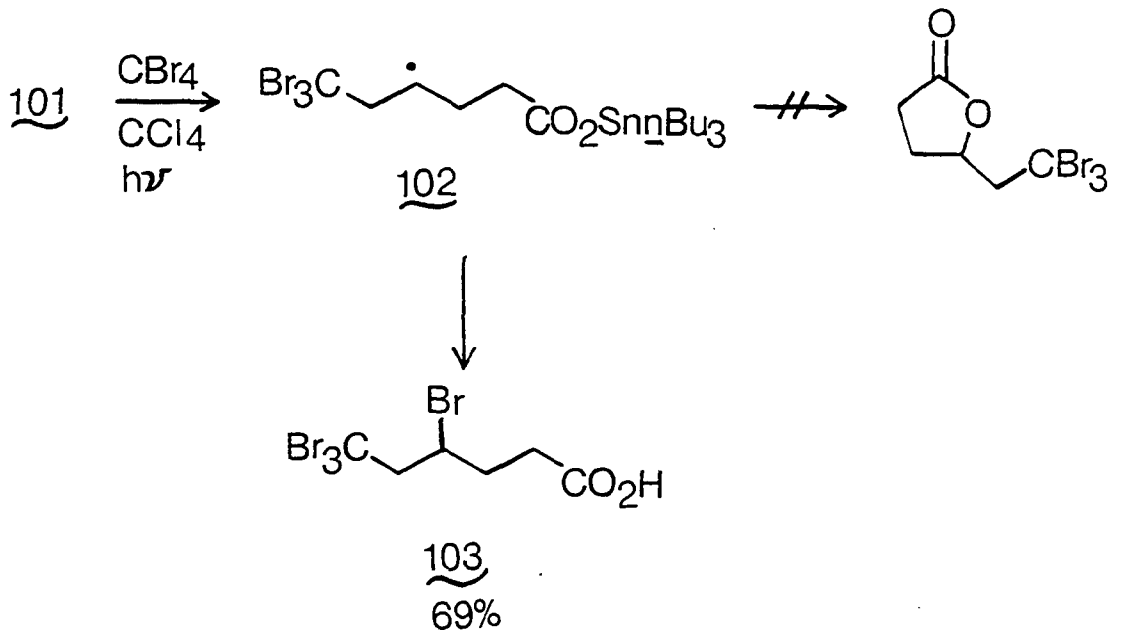



analog of 95 obtained by the addition of the tribromomethyl radical to 101, should cyclize to give a γ-lactone. Instead, we obtained only the tetrabromo acid 103. Treatment of 101

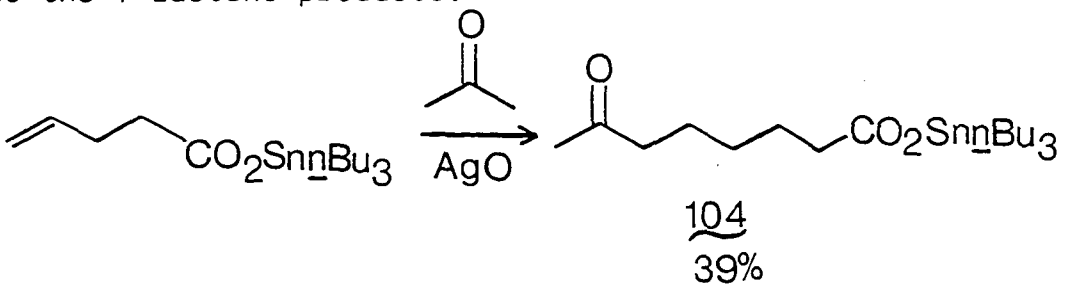


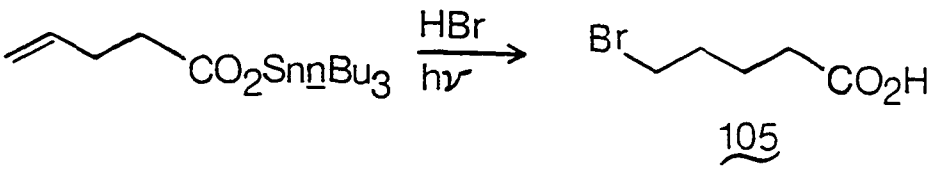

101

with the acetonyl radical (58) gave a product resulting from addition of acetone across the double bond. Similarly,

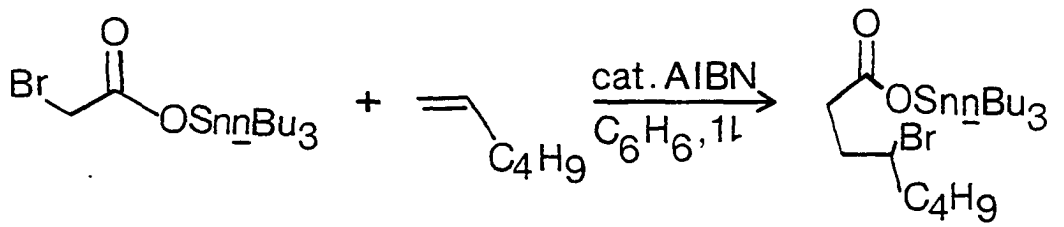


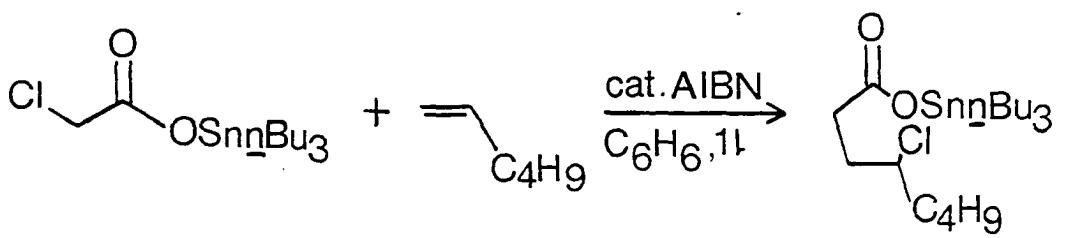

hydrogen bromide was ineffective in promoting lactonization. Apparently, intermediate 95 does not proceed directly to the γ-lactone products.



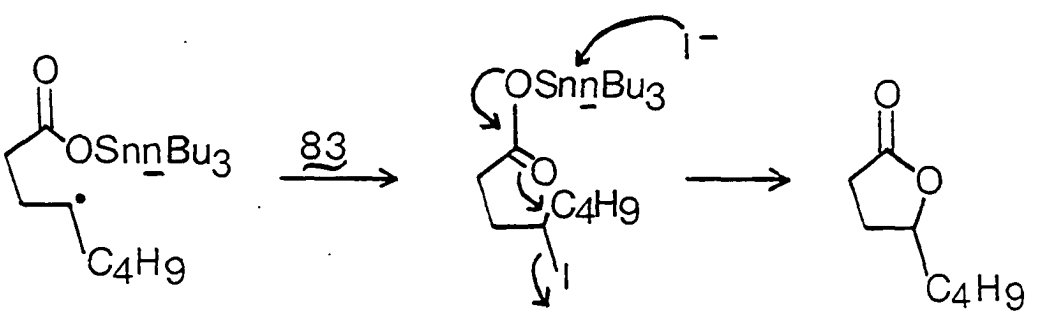



Recently, Prof. B. Maillard (65) has studied our lactone forming reaction and has concluded that intermediate 95 is transformed into 96, presumably by abstraction of an iodine atom from a molecule of 83. He found that reactions of tri-n-butylstannyl bromoacetate and tri-n-butylstannyl chloroacetate with 1-hexene gave the halides shown below. The corresponding iodide could not be isolated from the

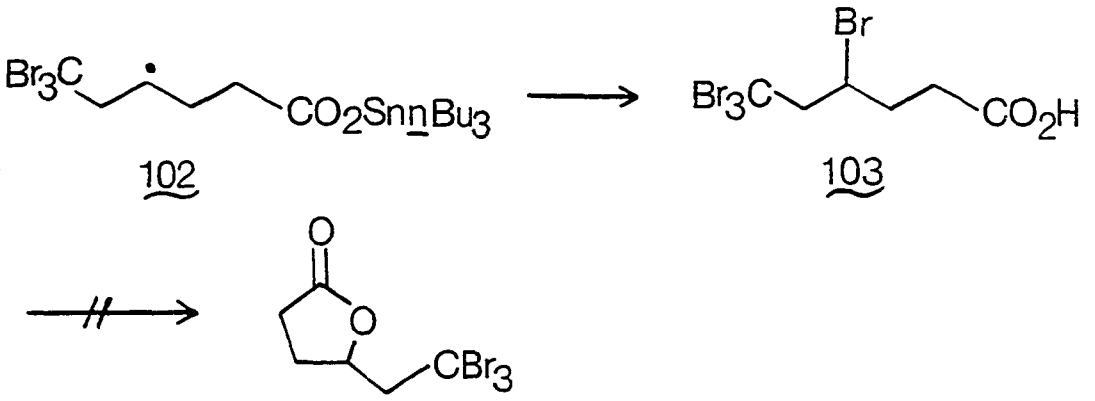



reaction of 1-hexene and tri-n-butylstannyl iodoacetate; instead, 4-n-butyl-γ-butyrolactone was produced presumably via the mechanism shown below (65).



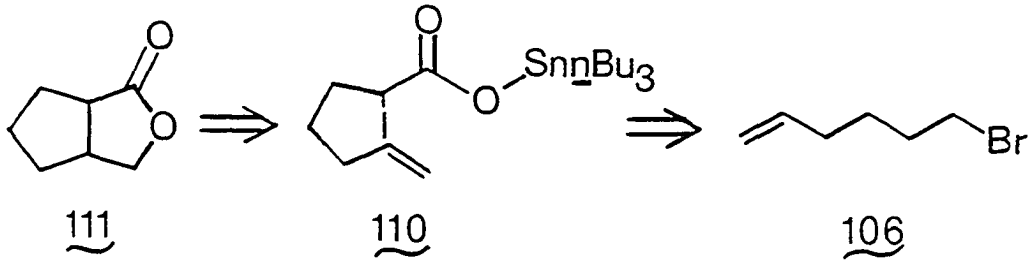
This mechanism explains the failure of our attempts to prepare cyclic ethers via an $S_Hi$ process, and further enables one to rationalize the inability of intermediate 102 to cyclize to a γ-lactone. Apparently, bromide is not a good enough leaving group to lead from 103 to the desired tribromo lactone.




C. Intramolecular Free Radical Lactonizations

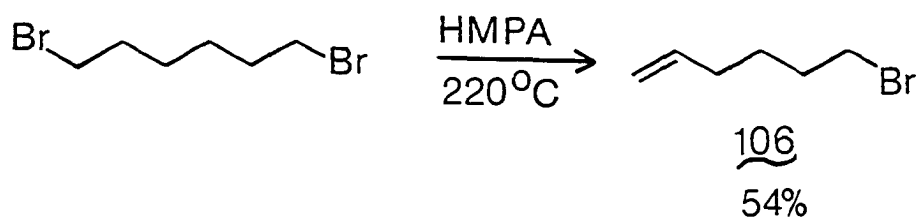
1. Synthesis of 3-oxabicyclo[3.3.0]octan-2-one

Encouraged by the successful results obtained for the intermolecular version of our novel lactone forming reaction, we chose to develop a short synthesis of 3-oxabicyclo[3.3.0]-octan-2-one, 111, to show the utility of its intramolecular counterpart. The retrosynthetic analysis for 111 is given below.



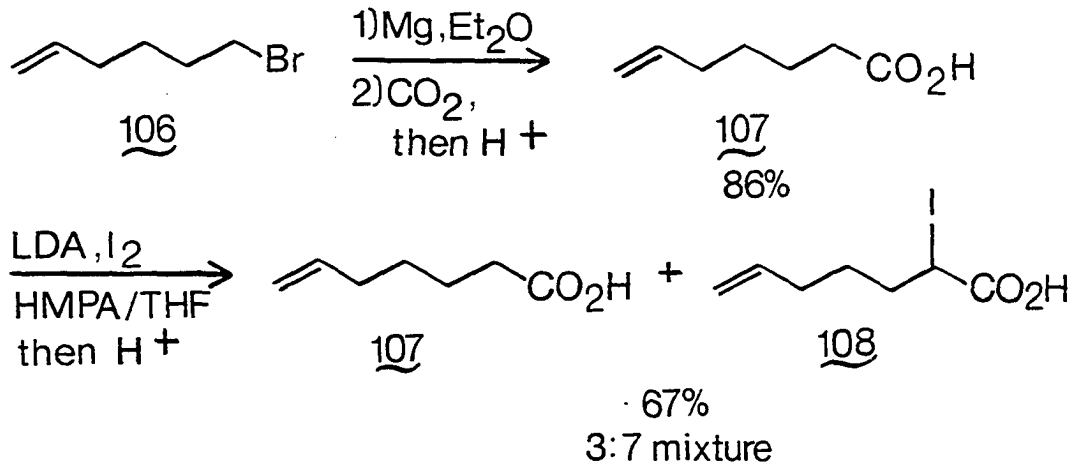

111 110 106

The starting material, 6-bromo-1-hexene, although commercially available, is expensive. Thus, we designed a method for its preparation from inexpensive 1,6-dibromohexane (66). Slow addition of hexamethylphosphoric triamide (HMPA) to the dibromide at high temperature resulted in the elimination of one molecule of hydrogen bromide to give 106 in 54% yield. The crude product, obtained by distillation of the reaction mixture during the addition of HMPA, could be purified by an additional simple distillation. In a similar manner, 5-bromo-1-pentene and 4-bromo-1-butene were prepared from the corresponding dibromides in comparable yields (66).

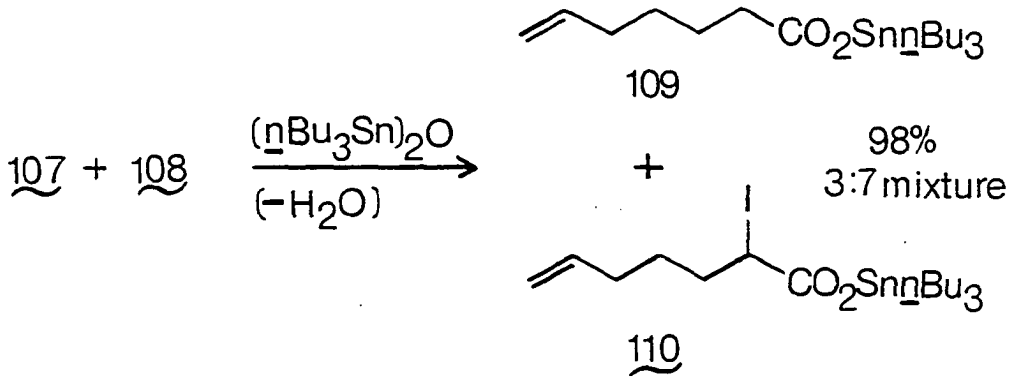



106
54%

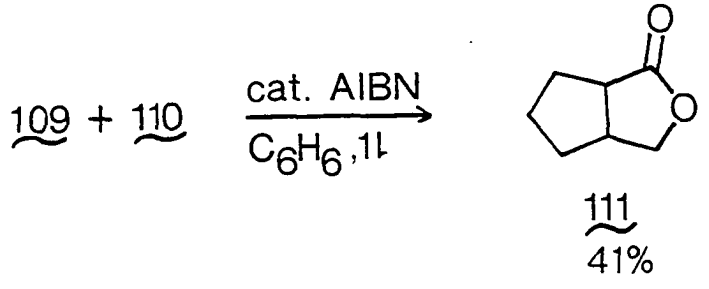
Grignard reaction of 106 with carbon dioxide produced 6-heptenoic acid which was iodinated according to a literature procedure (67) to give a 3:7 mixture of 107 and 108 in 67% yield. Since these two compounds were inseparable by flash




chromatography, and distillation resulted in decomposition of 108, the mixture was taken on to stannyl esters 109 and 110 by treatment with hexa-n-butyldistannoxane.

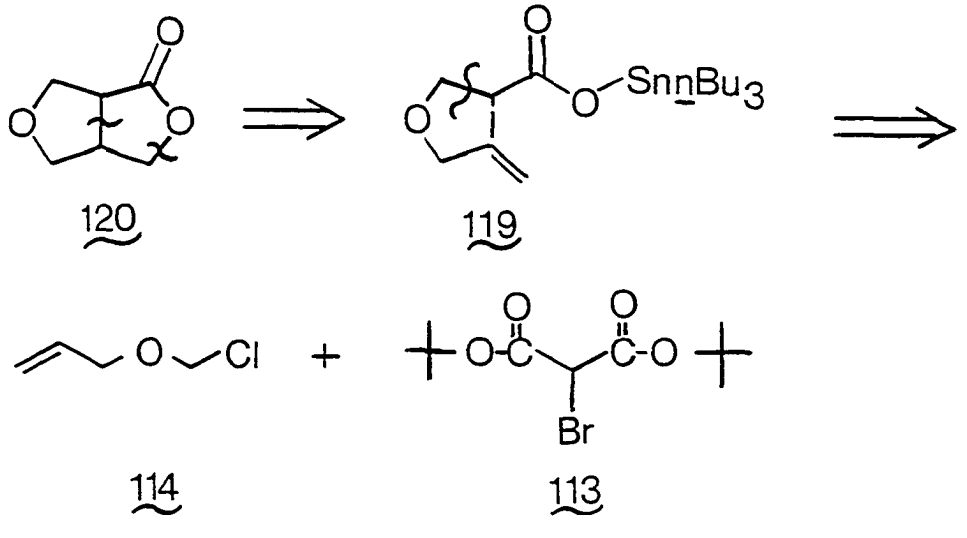



The final step in the synthesis, free radical cyclization, was accomplished by refluxing 109 and 110 in benzene in the presence of AIBN. A 41% yield of bicyclic lactone 111 was obtained after flash chromatography.



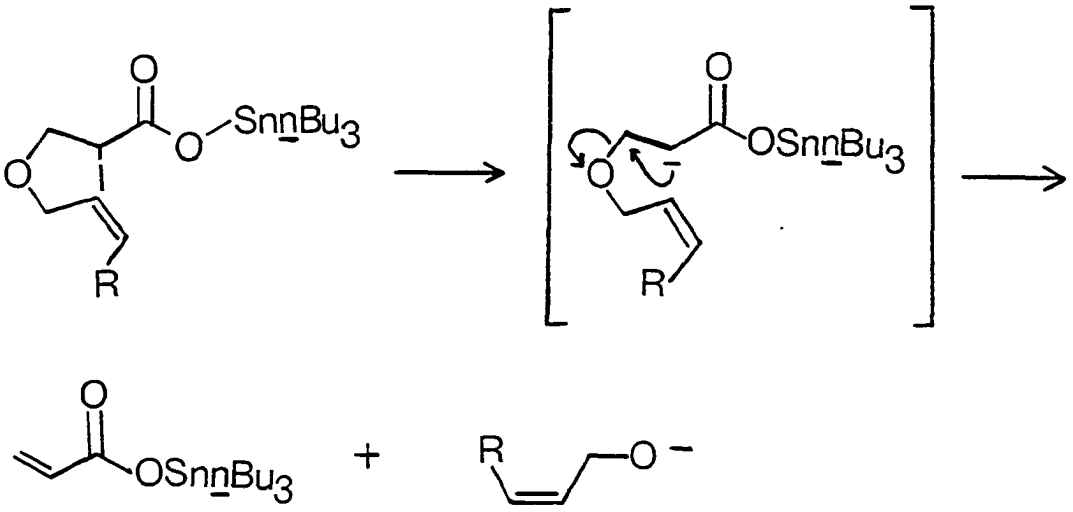

2. Synthesis of 3,7-dioxabicyclo[3.3.0]octan-2-one

A synthesis of 3,7-dioxabicyclo[3.3.0]octan-2-one, 120, was undertaken to show the utility of our intramolecular lactonization in the synthesis of bicyclic lactones containing additional functionality. The retrosynthetic analysis for 120 is given below. It is noteworthy that the crucial



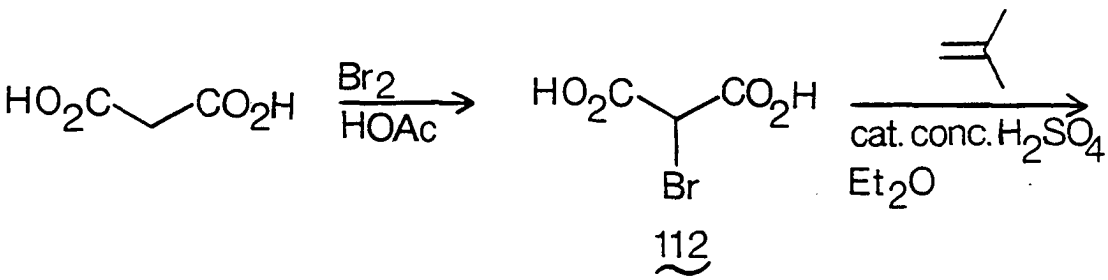

carbon-carbon bond formation which occurs as 119 proceeds to 120 is particularly well suited to free radical methods. Formation of the first 5-membered ring (the tetrahydrofuran portion of the molecule) should occur rapidly due to the

rate-accelerating effect of the ethereal oxygen (12). Of course, this carbon-carbon bond formation would have little chance for success were the reactive intermediate a carbanion, even if the double bond were appropriately modified, due to the competitive elimination of an alkoxide anion as illustrated below.

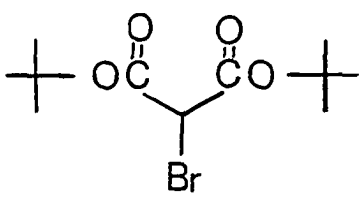



R = electron-withdrawing group

Bromination of malonic acid (68) resulted in the formation of 112 which was converted to the di-t-butyl ester 113 (69). Chloromethyl allyl ether, 114, was prepared

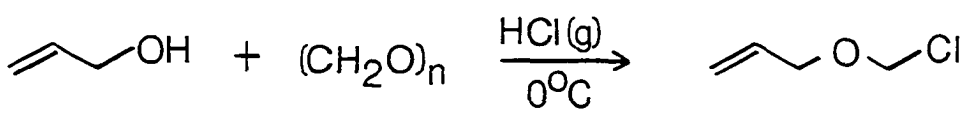



112




113

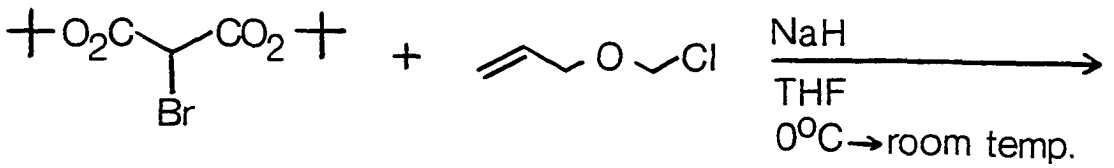
in 41% yield by treating allyl alcohol with formaldehyde and gaseous hydrogen chloride (70). This compound was then

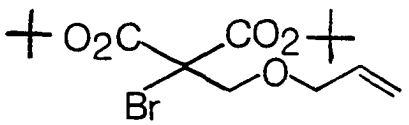



114

41%

used as an electrophile in the synthesis of diester 115.

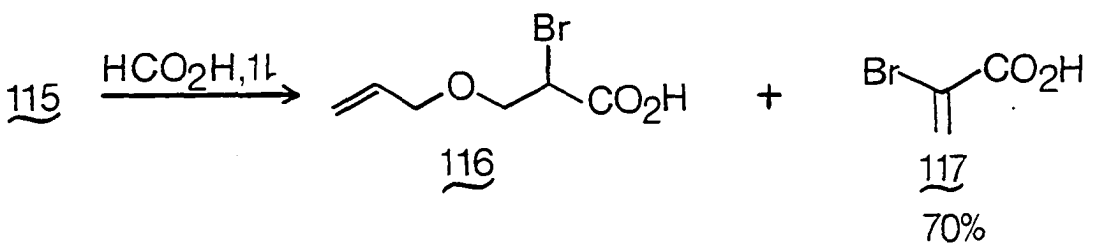


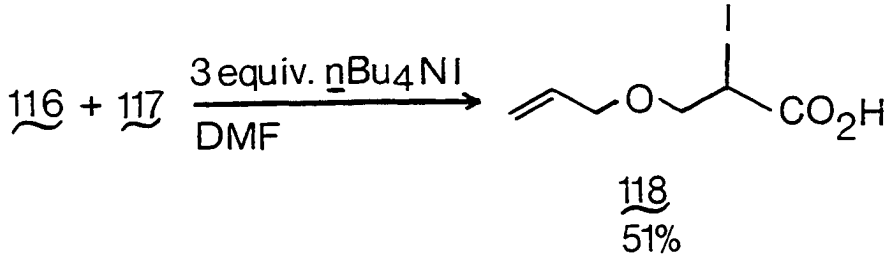

115

87%

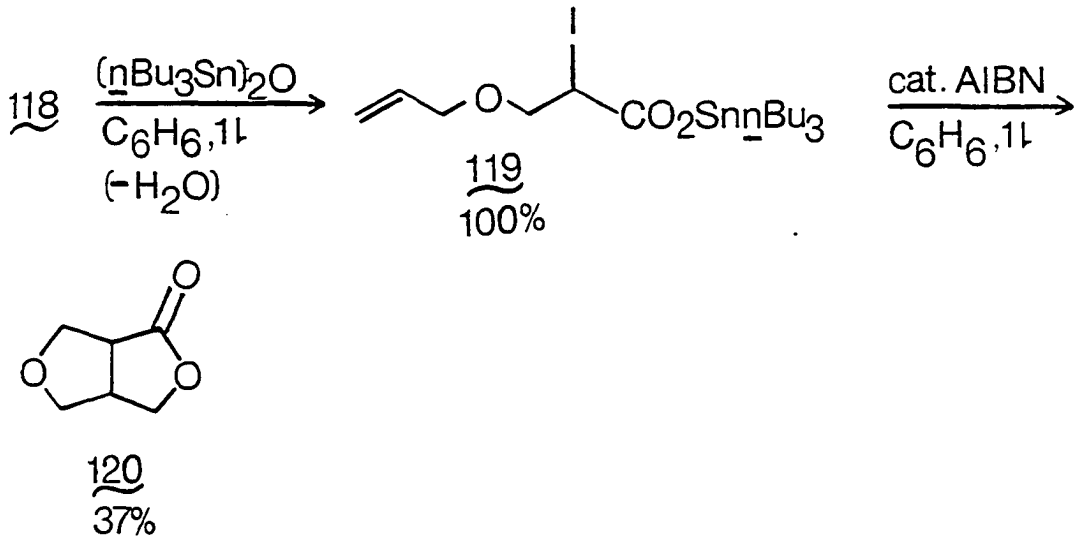
Deprotection and decarboxylation of 115, accomplished by treatment with formic acid, afforded in good yield (70%) a 67:33 mixture of 116 (71) and 117, the minor product apparently arising by elimination of allyl alcohol subsequent




to the decarboxylation step. The bromide 116 was converted to iodide 118 by treatment with tetra-n-butylammonium iodide. Contaminant 117 was no longer present as determined by NMR and IR spectroscopy. Formation of the tri-n-butylstannyl




ester 119 and subsequent treatment with AIBN in refluxing benzene afforded bicyclic lactone 120 in 37% yield, thus completing the synthesis.



# IV. CONCLUSION

The free radical reactions of α-iodostannyl esters with olefins has proven to be an effective method for the synthesis of γ-lactones. The esters are prepared from inexpensive starting materials and the reaction is conducted under neutral conditions. Thus, a variety of functional groups are able to tolerate the conditions of the reaction.

The modern synthetic organic chemist has at his disposal literally thousands of reactions for various functional group transformations and methods of carbon-carbon bond formation. Yet, only a few of those stand out in the chemist's mind as being efficient and convenient enough to be used regularly. It is hoped that as refinements are made in this novel lactone-forming reaction, and as its great utility is more thoroughly uncovered through use in the synthesis of more complex and sensitive organic molecules, it will become widely used.

# V. EXPERIMENTAL

## A. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to usage. Methylene chloride was distilled from phosphorus pentoxide. Benzene was distilled from lithium aluminum hydride. N,N-Dimethylformamide (DMF) was dried over 4 Å molecular sieves. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous sodium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a stream of nitrogen or was dried in an oven at 150°C for 12 hrs. Flash chromatography was performed on Kreselgel 60, mesh 230-400. Column chromatography was performed on Grace silica gel, grade 62, mesh 60-200. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-4250 or Acculab 2 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in $\delta$ relative to tetramethylsilane as

an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra were determined on a Nicolet Magnetics Corporation NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm). High resolution mass spectra were recorded on an AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

1. Tri-n-butylstannyl iodoacetate 83

Iodoacetic acid (9.30 g, 50.0 mmol) and hexa-n-butyldistannoxane (14.902 g, 25.0 mmol) were combined in an open 100 ml round bottom flask. The mixture was stirred at 130°C for 30 min and then cooled to room temperature. The resultant beige solid was recrystallized from hot hexanes to afford 12.59 g (53%) of 83 as a white solid which was stored in the dark (mp 74-75°C). NMR ($CDCl_3$) δ 0.8-1.8 (br m, 27 H), 3.7 (s, 2 H). IR (Nujol mull) 2970, 2940, 2865, 1600, 1580, 1470, 1430, 1385 $cm^{-1}$. High resolution mass spectrum for $C_{10}H_{20}SnO_2I(M^+-C_4H_9)$ requires 418.95301; measured 418.95281.

2. 4-n-Butyl-γ-butyrolactone 84

1-Hexene (1.008 g, 12.0 mmol), 83 (1.90 g, 4.0 mmol), and AIBN (0.033 g, 0.20 mmol) were dissolved in 4 ml benzene

in a 25 ml round bottom flask equipped with a reflux condenser. The stirring solution was refluxed for 8 hrs, then cooled to room temperature. After stirring for an additional 8 hrs, the solution was diluted with 25 ml acetonitrile and washed six times with 25 ml portions of hexanes. The acetonitrile layer was concentrated in vacuo and purified by flash chromatography using 2:1 hexane/ether affording 0.43 g (76%) of 84 as a pale yellow liquid. NMR ($CDCl_3$) δ 0.8-1.2 (t, 3 H), 1.3-1.9 (br m, 8 H), 2.2-2.8 (m, 2 H), 4.2-4.7 (br m, 1 H). IR (neat) 2960, 2920, 2860, 1780-1770, 1460, 1350, 1190-1160.

3. 4-n-Octyl-γ-butyrolactone 85

Synthesis of 85 was accomplished by subjecting 1-decene to the same reaction conditions developed for the synthesis of 84. Flash chromatography using 2:1 hexane/ether afforded 0.60 g (76%) of 85 as a pale yellow liquid. NMR ($CDCl_3$) δ 0.8-1.1 (t, 3 H), 1.2-1.9 (br m, 16 H), 2.2-2.8 (m, 2 H), 4.2-4.7 (br m, 1 h). IR (neat) 2960, 2930, 2860, 1790-1770, 1460, 1200-1150. High resolution mass spectrum for $C_{12}H_{23}O_2(M^+ + H)$ requires 199.16981; measured 199.16955. Elemental analysis calculated for $C_{12}H_{22}O_2$: C, 72.68, H, 11.18. Found: C, 72.61, H, 11.28.

4. 4-n-Pentyl-γ-butyrolactone 86

Synthesis of 86 was accomplished by subjecting 1-heptene to the same reaction conditions developed for the synthesis

of 84. Flash chromatography using 2:1 hexane/ether afforded 0.45 g (72%) of 86 as a yellow liquid. NMR, 300 MHz ($CDCl_3$) δ 0.86-0.94 (t, 3 H), 1.30-1.90 (br m, 10 H), 2.30-2.36 (m, 1 H), 2.50-2.56 (dd, 1 H), 4.47-4.52 (m, 1 H). C-13 NMR ($CDCl_3$) 13.82, 22.38, 24.80, 27.91, 28.74, 31.42, 35.47, 80.91, 177.51 ppm. IR (neat) 2950, 2930, 2860, 1790-1760, 1450, 1350, 1175 $cm^{-1}$. MS, m/e (%) 155 (1), 113 (3), 85 (67), 69 (100), 55 (7). High resolution mass spectrum for $C_9H_{15}O_2(M^+-H)$ requires 155.10720; measured 155.10716.

5. 2-Hydroxy-5-n-pentyltetrahydrofuran 87

Diisobutylaluminum hydride (1.50 ml of a 1 M solution in hexane, 1.50 mmol) was added in 0.5 ml portions to 86 (0.234 g, 1.50 mmol) in 5 ml toluene at -78°C. When the reaction was completed, as determined by TLC, the contents of the reaction vessel were poured into a rapidly stirring mixture of 10 g ice and 2 ml glacial acetic acid. Chloroform (15 ml) was added and the two phase system stirred vigorously for 10 min. Another 30 ml chloroform was added and the mixture was stirred vigorously for an additional 2 hrs. The chloroform layer was then washed twice with 25 ml portions of aqueous saturated sodium bicarbonate and twice with 25 ml portions of aqueous saturated sodium chloride solutions. The chloroform layer was then dried, concentrated in vacuo,

and purified by flash chromatography using varying proportions of hexane/ethyl acetate to afford 0.19 g (80%) of 87 as a colorless liquid. NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.0-2.2 (br m, 13 H), 3.8-4.4 (m, 1 H), 4.9-5.6 (m, 1 H). IR (neat) 3400 (br) $cm^{-1}$.

6. 2,8-Dioxabicyclo[3.3.0]octan-3-one 88

Synthesis of 88 was accomplished by subjecting 2,3-dihydrofuran to the same reaction conditions developed for the synthesis of 84. Flash chromatography using varying proportions of hexane/ether afforded 0.40 g (78%) of 88 as a colorless liquid. NMR ($CDCl_3$) δ 1.6-3.3 (br m, 5 H), 3.8-4.2 (m, 2 H), 6.0-6.2 (d, 1 H). IR (neat) 3080, 3000, 2900, 1780, 1360, 1270 $cm^{-1}$. High resolution mass spectrum for $C_6H_7O_3(M^+-H)$ requires 127.03952; measured 127.03997. Elemental analysis calculated for $C_6H_8O_3$: C, 56.25, H, 6.29. Found: C, 56.03, H, 6.34.

7. 4-Ethoxy-γ-butyrolactone 89

Synthesis of 89 was accomplished by subjecting ethyl vinyl ether to the same reaction conditions developed for the synthesis of 84. Flash chromatography using varying proportions of hexane/ether afforded 0.19 g (36%) of 89 as a pale yellow liquid along with 0.16 g of an unidentified by-product. NMR ($CDCl_3$) δ 1.1-1.4 (t, 3 H), 2.1-2.8 (br m,

4 H), 3.4-4.0 (m, 2 H), 5.4-5.6 (m, 1 H). IR (neat) 3000, 2960, 2920, 1800-1780, 1460, 1360, 1170-1150 $cm^{-1}$.

8. 4-Hydroxymethyl-γ-butyrolactone 90

Synthesis of 90 was accomplished by subjecting 2-propen-1-ol to the same reaction conditions developed for the synthesis of 84. Flash chromatography using varying proportions of hexane/ether afforded 0.34 g (73%) of 90 as a yellow viscous liquid. NMR ($CDCl_3$) δ 1.8-2.7 (m, 4 H), 3.3-3.8 (br m, 3 H), 4.3-4.8 (br m, 1 H). IR (neat) 3600-3150 (br), 2960-2880 (br), 1780-1750, 1340, 1180-1140 $cm^{-1}$. MS m/e 116, 98, 85.

9. 4-Trimethylsilylmethyl-γ-butyrolactone 91

Synthesis of 91 was accomplished by subjecting allyltrimethylsilane to the same reaction conditions developed for the synthesis of 84. Flash chromatography using varying proportions of hexane/ether afforded 0.39 g (56%) of 91 as a pale yellow liquid. NMR ($CDCl_3$) δ 0.1 (s, 9 H), 0.8-2.6 (m, 6 H), 4.3-4.8 (m, 1 H). IR (neat) 2980, 2910, 1780-1770, 1450, 1340, 1250, 1180-1160 $cm^{-1}$. High resolution mass spectrum for $C_7H_{13}O_2Si(M^+-CH_3)$ requires 157.06848; measured 157.06802. Elemental analysis calculated for $C_8H_{16}O_2Si$: C, 55.79, H, 9.30. Found: C, 55.58, H, 9.26.

10. 4-t-Butyldimethylsiloxy-1-pentene 92

Magnesium powder (3.0 g, 123.4 mmol) was suspended in diethyl ether (150 ml) in a 250 ml round bottom flask equipped with a reflux condenser. Allyl bromide (15.09 g, 124.7 mmol) was added slowly and the solution was allowed to stir for 1 hr before being cooled to 0°C. Freshly distilled acetaldehyde (8.27 g, 187.7 mmol) was then added to this solution over 30 min and then stirred an additional 3 hrs at 0°C. The solution was diluted with 100 ml 1N HCl and extracted three times with 50 ml portions of diethyl ether. The combined ether layers were washed twice with aqueous saturated sodium chloride solution, dried, and concentrated in vacuo. The product, 4-penten-2-ol (6.38 g, 74.07 mmol), was dissolved in 70 ml DMF in a 250 ml round bottom flask. t-Butylchlorodimethylsilane (18.97 g, 125.9 mmol) and imidazole (15.12 g, 222.1 mmol) were then added and the contents were heated to 40°C for 24 hrs. This mixture was then poured into water and extracted four times with 50 ml portions of ether. The combined ether layers were washed with aqueous saturated sodium chloride, dried, concentrated in vacuo, and passed quickly through a chromatography column using hexane as the solvent to afford 12.30 g (83%) of 92 as a colorless liquid. NMR ($CDCl_3$) δ 0.2 (s,

6 H), 1.0 (s, 9 H), 1.2 (d, 3 H), 1.9-2.3 (m, 2 H), 3.6-4.1 (m, 1 H), 4.8-6.3 (m, 3 H). IR (neat) 3100, 2980, 2940, 2880, 1650, 1470, 1380, 1360, 1260, 1130 $cm^{-1}$.

11. 4-3(t-Butyldimethylsiloxy-n-propyl)-γ-butyrolactone 93 and 94

Synthesis of 93 and 94 were accomplished by subjecting 4-t-butyldimethylsiloxy-1-pentene to the same reaction conditions developed for the synthesis of 84. Flash chromatography using varying proportions of hexane/ether afforded 0.70 g (68%) of a 1:1 mixture of 93 and 94 as a pale yellow liquid. NMR, 300 MHz ($CDCl_3$) δ 0.00-0.03 (m, 6 H), 0.83-0.84 (d, 9 H), 1.10-1.17 (dd, 3 H), 1.7-1.9 (br m, 4 H), 2.25-2.55 (br m, 2 H), 3.95-4.05 (br m, 1 H), 4.55-4.65 (br m, 1 H). IR (neat) 2960-2920, 2850, 1780-1760, 1450, 1380-1350, 1240, 1170-1130 (br) $cm^{-1}$. MS, m/e (%) 257 (0.2), 243 (1), 201 (7), 158 (13), 157 (100), 75 (50), 73 (12). High resolution mass spectrum for $C_{12}H_{23}O_3Si$ ($M^+-CH_3$) requires 243.1416; measured 243.1413.

12. 4-Pentenyl tri-n-butylstannyl ether 97

4-Penten-1-ol (0.86 g, 10.0 mmol) and ethoxytri-n-butylstannane (2.2 g, 10.0 mmol) were combined in an open 25 ml round bottom flask. The mixture was stirred at 120°C for

3 hrs and then cooled to room temperature to afford 3.7 g (98%) of 97 as a clear liquid. NMR ($CDCl_3$) δ 0.7-2.3 (br m, 31 H), 3.6-3.9 (t, 2 H), 4.8-6.2 (m, 3 H). IR (neat) 2980, 2920, 2860, 1650, 1460, 1420, 1380, 1340, 1290, 1270, 1180, 1150 $cm^{-1}$.

13. 4,6,6,6-Tetrabromohexyl tri-n-butylstannyl ether 98

Tetrabromomethane (0.31 g, 0.93 mmol) and 97 (0.35 g, 0.93 mmol) were combined in a pyrex test tube and degassed with argon for 30 min. The mixture was irradiated for 8 hrs with a GE 475 watt sun lamp, diluted with 50 ml acetonitrile, and washed six times with 50 ml portions of hexanes. The acetonitrile layer was concentrated *in vacuo* to afford 0.41 g (62%) of 98 as a yellow liquid. NMR ($CDCl_3$) δ 0.9-2.9 (br m, 31 H), 3.6-3.9 (dd, 2 H), 4.1-4.4 (br m, 1 H). IR (neat) 2990, 2920, 2870, 1470, 1420, 1380, 1340, 1295, 1270 $cm^{-1}$

14. Tri-n-butylstannyl-4-pentenoate 101

4-Pentenoic acid (3.0 g, 30.0 mmol) and hexa-n-butyldistannoxane (8.94 g, 15.0 mmol) were combined in an open 25 ml round bottom flask and heated to 130°C for 30 min and then cooled to room temperature to afford 11.47 g (98%) of 101 as a white solid (mp 52-54°C). NMR ($CDCl_3$) δ 0.8-1.8 (br m, 27 H), 2.2-2.4 (m, 4 H), 4.7-6.0 (m, 3 H). IR (Nujol mull) 2960, 2920, 2860, 1640, 1570, 1550, 1410 $cm^{-1}$. High

resolution mass spectrum for $C_{13}H_{25}O_2Sn(M^+-C_4H_9)$ requires 333.08766; measured 333.08697.

15. 4,6,6,6-Tetrabromohexanoic acid 103

Tetrabromomethane (1.33 g, 4.0 mmol) and 101 (1.56 g, 4.0 mmol) were combined in a pyrex test tube and degassed with argon for 30 min. The mixture was irradiated for 7 hrs with a GE 475 watt sun lamp, diluted with 50 ml acetonitrile, and washed six times with 50 ml portions of hexanes. The acetonitrile layer was concentrated in vacuo to afford 1.19 g (69%) of 103 as a yellow liquid. NMR ($CDCl_3$) δ 2.1-3.0 (br m, 4 H), 3.7-4.0 (dd, 2 H), 4.1-4.6 (m, 1 H), 11.4 (br s, 1 H). IR (neat) 3600-2800 (br), 1720, 1430, 1150, 910 $cm^{-1}$. High resolution mass spectrum for $C_6H_8O_2Br_3$ ($M^+$-Br) requires 348.80743; measured 348.80681.

16. Tri-n-butylstannyl-7-oxooctanoate 104

Silver(II) oxide (0.08 g, 0.65 mmol) and acetone (15 ml) were placed in a 25 ml round bottom flask equipped with a reflux condenser and degassed with argon for 30 min. To this solution was added 101 (0.60 g, 1.54 mmol). The mixture was refluxed for 48 hrs, cooled to room temperature, and filtered through Celite. The filtrate was diluted with 50 ml acetonitrile and washed six times with 50 ml portions of hexanes. The acetonitrile layer was concentrated in vacuo

to give 0.27 g (39%) of 104. NMR ($CDCl_3$) δ 0.8-1.8 (br m, 33 H), 2.0-2.6 (br m, 7 H). IR (neat) 2980, 2930, 2870, 1700, 1560, 1400, 1350, 1150 $cm^{-1}$.

17. 5-Bromopentanoic acid 105

Pentane (40 ml) was purified by stirring over concentrated sulfuric acid, washing with 40 ml water, drying, and distilling finally from calcium hydride. The purified pentane was placed in a 100 ml round bottom flask along with 101 (0.43 g, 1.1 mmol). Gaseous HBr was passed through a drying tube containing anhydrous magnesium perchlorate into this solution for 10 min, during which time the solution was also irradiated by a 450 watt medium pressure mercury lamp. The resultant solution was flushed with nitrogen, washed twice with 25 ml portions of aqueous saturated sodium thiosulfate solution, diluted with 50 ml acetonitrile and washed six times with 25 ml portions of hexanes. The acetonitrile layer was concentrated in vacuo to give 105. NMR ($CDCl_3$) δ 1.6-2.1 (m, 4 H), 2.3-2.5 (t, 2 H), 3.3-3.6 (t, 2 H), 11.8 (s, 1 H). IR (Nujol mull) 3700-2800 (br), 1750-1710 (br), 1650, 1500, 1460, 1410, 1250-1220 $cm^{-1}$.

18. 6-Bromo-1-hexene 106

A 25 ml round bottom 3-neck flask was fitted with an addition funnel and septum at one neck, a glass stopper at the middle neck, and a water-cooled short path distillation

apparatus with thermometer at the third neck. Connected to the distillation apparatus was a collection vessel cooled to -78°C. The round bottom flask was wrapped in aluminum foil, charged with 1,6-dibromohexane (20.4 g, 83.6 mmol) and immersed in a 195°C oil bath. HMPA (17.2 ml, 98.9 mmol) was then added to the reaction vessel via the addition funnel at a rate of about 1 drop each second as the temperature of the oil bath was increased to 220°C. Shortly after the addition of HMPA began, a cloudy liquid began to condense into the collection vessel. A further simple distillation of this crude product afforded 7.37 g (54%) of 106 as a colorless liquid (bp 149-151°C/760 mm Hg). NMR ($CDCl_3$) δ 1.3-2.3 (br m, 6 H), 3.3-3.6 (t, 2 H), 4.8-6.2 (m, 3 H). IR (neat) 3100, 3020-2880 (br), 2860, 1640, 1440, 1250 $cm^{-1}$.

19. 6-Heptenoic acid 107

6-Bromo-1-hexene (8.92 g, 54.7 mmol) was dissolved in diethyl ether (10 ml) and added via syringe to magnesium (1.86 g, 76.5 mmol) suspended in diethyl ether (35 ml) at room temperature in a 100 ml round bottom flask equipped with a reflux condenser. The reaction vessel was cooled to 0°C for 10 min, then allowed to warm to room temperature over 2 hrs during which time carbon dioxide was bubbled in through a drying tube containing calcium chloride. The mixture was

then diluted with 100 ml diethyl ether and acidified to pH 3 with aqueous 1N HCl sol'n. The aqueous layer was extracted three times with 50 ml portions of diethyl ether, and the combined ether layers were washed twice with 50 ml portions of aqueous saturated sodium chloride solution, dried, and concentrated in vacuo to afford 6.05 g (86%) of 107 as a colorless liquid. NMR ($CDCl_3$) δ 1.2-1.7 (m, 4 H), 1.8-2.2 (m, 2 H), 2.2-2.6 (t, 2 H), 4.8-6.2 (m, 3 H), 11.4 (s, 1 H). IR (neat) 3600-2840 (br), 1740-1700, 1640, 1420 $cm^{-1}$. MS, m/e (%) 128 (0.3), 127 (1.3), 110 (25), 95 (5), 82 (27), 69 (100), 55 (32). High resolution mass spectrum for $C_7H_{12}O_2$ requires 128.08373; measured 128.0842.

20. 2-Iodo-6-heptenoic acid 108

Lithium diisopropylamide (30.1 mmol) was prepared by adding n-butyllithium (12.19 ml of 2.47 M solution in hexanes, 30.1 mmol) to diisopropylamine (3.06 g, 30.2 mmol) in THF (30 ml) at -78°C. HMPA (2 ml), and then a solution of 107 (1.92 g, 15.0 mmol) in THF (15 ml) were added to this mixture and stirred at -78°C for 15 min. The contents were then warmed to room temperature for 30 min and subsequently transferred very slowly via syringe into a -78°C solution of iodine (4.6 g, 18.1 mmol) in THF (30 ml). After stirring for 10 min, the contents were diluted with 100 ml diethyl

ether and aqueous 1N HCl solution until the pH was 3. A pinch of sodium thiosulfate was added to remove the red color and the ether layer was then dried and concentrated *in vacuo* to afford 2.12 g (67%) of a 3:7 mixture of 107 and 108 as a pale yellow liquid. NMR, 300 MHz ($CDCl_3$) δ 4.25-4.5 (t, integration 11), 4.8-6.2 (m, integration 47), thus 3:7 mixture. IR (neat) 3600-2840 (br), 1720-1710, 1640 $cm^{-1}$.

21. Tri-n-butylstannyl 2-iodo-6-heptenoate 110

The 3:7 mixture of 107 and 108 (2.12 g, 10.0 mmol) was heated with hexa-n-butyldistannoxane (2.98 g, 5.0 mmole) in an open 25 ml round bottom flask at 130°C for 30 min to give 4.93 g (98%) of a 3:7 mixture of 109 and 110 as a pale brown liquid. NMR ($CDCl_3$) δ 4.25-4.5 (t, integration 8), 4.8-6.0 (m, integration 11), thus a 3:7 mixture. IR (neat) 2960-2920 (br), 2860, 1640, 1570, 1450, 1350 $cm^{-1}$. High resolution mass spectrum for $C_{15}H_{28}O_2SnI(M^+-C_4H_9)$ requires 487.01561; measured 487.01555.

22. 3-Oxabicyclo[3.3.0]octan-2-one 111

The 3:7 mixture of 109 and 110 (2.51 g, 5.0 mmol) was refluxed for 8 hrs in benzene (10 ml) in the presence of AIBN (0.04 g, 0.24 mmol), cooled to room temperature, and stirred for an additional 8 hrs. The mixture was diluted with 50 ml

acetonitrile and washed six times with 50 ml portions of hexanes. The acetonitrile layer was concentrated in vacuo and purified by flash chromatography using hexane and then dichloromethane as solvents to afford 0.18 g (41%) of 111 as a clear liquid. NMR, 300 MHz ($CDCl_3$) δ 1.45-2.2 (br m, 6 H), 2.95-3.1 (m, 2 H), 4.0-4.08 (dd, 1 H, J = 2.5 Hz), 4.45-4.55 (dd, 1 H, J = 7.5 Hz). C-13 NMR ($CDCl_3$) 25.437, 30.624, 33.686, 38.937, 44.423, 73.474, 180.868 ppm. IR (neat) 2960, 2920, 2880, 1770-1760, 1450, 1370, 1180-1170, 1090, 1010 $cm^{-1}$. MS, m/e (%) 126 (4), 79 (4), 68 (18), 67 (100), 54 (14). High resolution mass spectrum for $C_7H_{10}O_2$ requires 126.06808; measured 126.0684. Elemental analysis calculated for $C_7H_{10}O_2$: C, 66.65, H, 7.99. Found: C, 66.52, H, 8.20.

23. Di-t-butyl bromomalonate 113

To malonic acid (5.2 g, 50 mmol) and glacial acetic acid (15 ml) at room temperature was added bromine (8.0 g, 50 mmol) dropwise over 30 min. The mixture was connected to a water aspirator and heated to 80°C for 1 h to allow for removal of hydrogen bromide. Removal of acetic acid by distillation afforded 9.8 g of a white solid which was dissolved in diethyl ether (20 ml) in a sealable pyrex tube. Isobutylene (14 ml) was condensed into this mixture at -78°C,

sulfuric acid (0.6 ml) was added, and the tube was sealed and allowed to stir at room temperature for 15 hrs. The sealed tube was then cooled to -78°C, opened, and the contents poured into 100 ml ice cold aqueous 6N NaOH solution. This mixture was extracted twice with 100 ml portions of diethyl ether. The combined ether layers were dried and evaporated in vacuo. Flash chromatography using 1:1 dichloromethane/hexanes as solvent system afforded 4.31 g (29%) of 113 as a clear liquid. NMR ($CDCl_3$) δ 1.5 (s, 18 H), 4.7 (s, 1 H). IR (neat) 2970, 2920, 1730, 1450, 1360, 1290, 1245, 1120 $cm^{-1}$. High resolution mass spectrum for $C_{10}H_{16}O_4Br(M^+-CH_3)$ requires 279.02319; measured 279.02250.

24. Allyl chloromethyl ether 114

Gaseous hydrogen chloride (3.6 g, 100 mmol) was passed through a drying tube containing calcium chloride into allyl alcohol (11.6 g, 200 mmol) at 0°C. After 10 min, paraformaldehyde (3.0 g, 100 mmol) was added to this mixture and stirring was continued for an additional 10 min. Then another 3.6 g hydrogen chloride and finally, after 10 min, another 3.0 g gaseous hydrogen chloride were added. The mixture was stirred for another 20 min period of time during which more gaseous hydrogen chloride was added to dissolve any solid material. The mixture was transferred to a separatory funnel and the top layer was dried for 12 hrs

over calcium chloride. A simple distillation afforded 8.71 g (41%) of pure 114 (bp 110-111°C/760 mm Hg). NMR, 300 MHz ($CDCl_3$) δ 4.2 (d, 2 H), 5.2-6.0 (m, 5 H). The large single peak at 5.5 was presumed to be due to the nonallylic methylene hydrogens. IR (neat) 3100, 3040, 2960, 2890, 1640, 1460, 1420, 1320, 1250, 1150-1090 (br) $cm^{-1}$.

25. Di-t-butyl allyloxymethyl(bromo)malonate 115

Diester 113 (4.0 g, 13.56 mmol) was added neat to sodium hydride (0.34 g, 14.17 mmol) suspended in THF (15 ml) at 0°C and was stirred at that temperature for 20 min. (The sodium hydride had been previously washed three times with 10 ml volumes of hexanes.) To this solution was slowly added 114 (1.44 g, 13.56 mmol) as a solution in THF (10 ml). After 15 min of stirring at 0°C, the mixture was warmed to room temperature, stirred for 1 h, diluted with 100 ml diethyl ether, and acidified to pH 6 with aqueous 1N HCl solution. The aqueous layer was removed and the ether layer washed twice with 50 ml portions of aqueous saturated sodium chloride solution. The ether layer was dried and then concentrated in vacuo to give 4.3 g (87%) of 115 as a pale yellow liquid. NMR, 300 MHz ($CDCl_3$) δ 1.5 (s, 18 H), 4.0 (s, 2 H), 4.1 (br d, 2 H), 5.2-6.0 (m, 3 H). C-13 NMR ($CDCl_3$) 27.620, 63.541, 72.568, 73.996, 83.439, 117.277,

133.975, 164.195 ppm. IR (neat) 2970, 2920, 2860, 1730-1720, 1640-1630, 1470, 1450, 1360, 1260, 1130 $cm^{-1}$. High resolution mass spectrum for $C_{11}H_{17}O_5Br(M^+-C_4H_8)$ requires 308.02594; measured 308.02543.

26. 2-Bromo-3-allyloxypropanoic acid 116

An 88% aqueous solution of formic acid (0.74 g, 14.2 mmol) and 115 (2.55 g, 6.99 mmol) were combined and heated to reflux for 90 min. The mixture was diluted with 50 ml diethyl ether and extracted three times with 50 ml portions of aqueous saturated sodium bicarbonate solution. The aqueous layers were combined, acidified to pH 2 with aqueous 1N HCl, and then extracted three times with 50 ml portions of diethyl ether. The combined ether layers were dried and concentrated in vacuo. The material was then heated neat for 1 h at 100°C to ensure that decarboxylation had been completed. Compounds 116 and 117 were provided as a 67:33 mixture in 70% yield (0.93 g). NMR, 300 MHz ($CDCl_3$) $\delta$ 5.1-6.2 (m, integration 20), 6.4 (d), 7.2 (d), 10.3 (br s, integration 10), thus a 67:33 mixture. IR (neat) 3650-2850 (br), 1740-1720, 1620, 1460, 1420, 1350, 1290, 1250, 1120 $cm^{-1}$.

27. 2-Iodo-3-allyloxypropanoic acid 118

Tetra-n-butylammonium iodide (6.42 g, 17.38 mmol) and the mixture of 116 and 117 (1.21 g, 5.79 mmol) were combined

with DMF (40 ml) and stirred at room temperature for 48 hrs. The solution was diluted with 100 ml diethyl ether and washed twice with 25 ml portions of aqueous saturated sodium thiosulfate solution. The aqueous layer was drained off and the organic layer was washed once with 100 ml water, twice with 50 ml portions of aqueous saturated sodium chloride solution, and then dried and concentrated in vacuo to give 0.75 g (51%) of 118 as a pale brown liquid. NMR ($CDCl_3$) δ 3.4-4.1 (m, 4 H), 4.3-4.6 (t, 1 H), 5.1-6.2 (m, 3 H), 11.2 (s, 1 H). IR (neat) 3600-2900 (br), 1730-1720, 1630, 1450, 1350, 1280, 1250, 1110 $cm^{-1}$.

b. Tri-n-butylstannyl 2-iodo-3-allyloxypropionate 119

Hexa-n-butyldistannoxane (0.88 g, 1.48 mmol) and 118 (0.75 g, 2.93 mmol) were refluxed for 3 hrs in benzene (10 ml). A Dean-Stark apparatus containing anhydrous sodium sulfate (about 1 g) was used to remove the water formed during the reaction. The solution was cooled to room temperature and concentrated in vacuo to afford 1.62 g (100%) of 119 as a pale brown liquid. NMR, 300 MHz ($CDCl_3$) δ 0.9-1.8 (m, 27 H), 3.7-4.6 (m, 5 H), 5.1-6.2 (m, 3 H). IR (neat) 2940, 2900, 2840, 1640, 1590-1570, 1440, 1360, 1280, 1240, 1080 $cm^{-1}$. High resolution mass spectrum for $C_{14}H_{26}O_3SnI(M^+-C_4H_9)$ requires 484.99486; measured 484.99393.

29. 3,7-Dioxabicyclo[3.3.0]octan-2-one 120

AIBN (0.02 g, 0.12 mmol) and 119 (1.62 g, 2.97 mmol) were refluxed in benzene (5 ml) for 8 hrs, cooled to room temperature, and stirred for an additional 8 hrs. This solution was diluted with 50 ml acetonitrile and washed six times with 25 ml portions of hexanes. The acetonitrile layer was concentrated in vacuo and subjected to flash chromatography using dichloromethane and then 1:20 ethyl acetate/dichloromethane as the solvent systems. The bicyclic lactone 120 (0.14 g) was afforded in 37% yield as a colorless liquid. NMR, 300 MHz ($CDCl_3$) δ 3.21-3.29 (m, 2 H), 3.78-3.96 (m, 4 H), 4.11-4.16 (dd, 1 H, J = 3.9 Hz), 4.51-4.57 (dd, 1 H, J = 9 Hz). C-13 NMR ($CDCl_3$) 39.455, 45.326, 71.438, 72.733, 74.707, 178.373 ppm. IR (neat) 2980, 2920, 2880, 1780-1760, 1480, 1390, 1360, 1280, 1240, 1200, 1170, 1080 $cm^{-1}$. High resolution mass spectrum for $C_6H_8O_3$ requires 128.0473; measured 128.0472.

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