THE DEVELOPMENT OF HETEROATOM-SUBSTITUTED FURYL SYNTHONS IN A GENERAL METHODOLOGY TOWARD THE SYNTHESIS OF TERPENOIDS

I.

THE PREPARATION OF (±)-LACTARAL

II.

SYNTHESIS AND REACTIONS OF HETEROATOM-SUBSTITUTED FURYLMETHYL ORGANOMETALLICS

III.

AN APPROACH TO THE SYNTHESIS OF (±)-APHIDICOLIN

By

David Brent Head

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ABSTRACT

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Many syntheses of bio-active natural products containing five-membered oxygen-substituted heterocycles have been approached by construction of a parent carbocycle to which the heteroaromatic ring is then appended. This study is directed toward the development of a general methodology in which the heterocyclic component is incorporated as an integral part of the molecule. An additional consideration is that access to all possible mono- or di-substitution

patterns of furan-, butenolide-, butyrolactone- and tetrahydrofuran-containing structures (Figure 1) must be possible from common intermediates.

We envisioned employing highly functionalized furyl synthons as the operational equivalents of furan, butenolide, butyrolactone and tetrahydrofuran mono- and di-anions in alkylative and annulative processes, respectively. To demonstrate the viability of such an approach, the Grignard reagent of 3-chloromethyl-4-tetrahydropyranyloxymethylfuran **24** was produced and coupled with chloride **26** in the total synthesis of the mushroom metabolite (±)-lactaral **15**. A variety of alpha heteroatom substituted, beta furylmethyl organometallic reagents (Figure 6) were investigated in a previously established alkylation-cyclization sequence (Figure 4). The furyl substituents were selected to regiospecifically direct the cyclization sequence as well as to facilitate the placement of oxygen on the five-membered heterocycle in conversions to other oxidation states (Figure 5). These groups included -OTMS, -OTBDMS, -SME, -SPh and -TMS. Precursors to the -SMe (**46**), -SPh (**54**) and -TMS (**64**, **72**) substituted organometallic reagents were successfully produced and alkylated; however, none of these groups proved to be useful in the annulation sequences studied. However, the -TMS variant provided an efficient means for the production of various 3- and 4-alkyl-2(5H)-furanones (Figure 9).

A synthetic approach to the antiviral substance (±)-aphidicolin was also undertaken. Furyl-Grignard coupling product **91** was converted to the tricyclic aphidicolin precursor **92** via a Lewis acid catalyzed biomimetic cyclization. Completion of a formal total synthesis of (±)-aphidicolin requires the conversion of **92** to the McMurry intermediate cyclopentenone.

For my parents, Harvey and Naomi Head,

whose love and support made this endeavor possible.

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Dr. Steven P. Tanis for his guidance, encouragement and advice throughout the course of this work. The unique learning opportunity which was provided is also appreciated.

Thanks are extended to my colleagues, the faculty and staff of the Michigan State University Chemistry Department who all contributed to a memorable experience.

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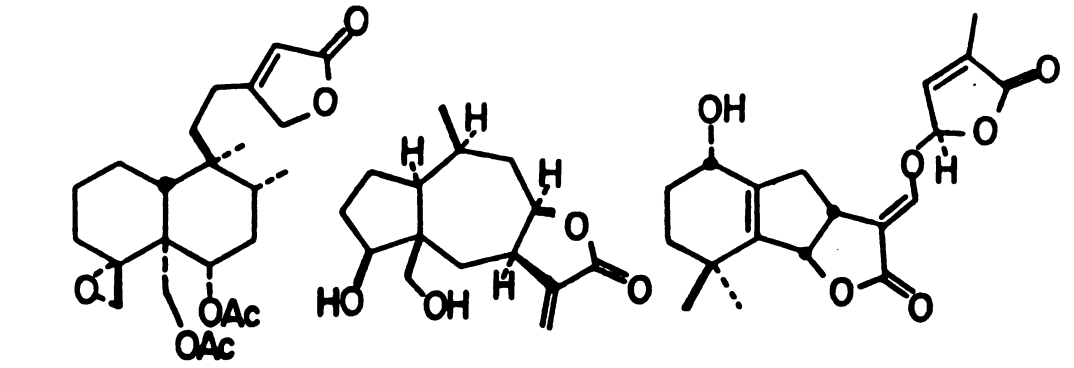
INTRODUCTION

INTRODUCTION

In recent years, a major emphasis of synthetic organic chemistry has been placed on the synthesis of naturally occurring compounds, particularly those with unusual or medicinally useful biological activities. These activities include antibiotic, antifungal, antileukemic, cytotoxic and antitumor properties. The diversity of the structural features that are associated with these compounds is fascinating as well as bewildering; however, upon closer inspection, a number of recurring themes appear. Many biologically active terpenoids incorporate five-membered oxygen-containing heterocyclic rings within their structures.[1] This feature is an integral part of such molecules as the insect antifeedant ent-neo-clerodane ajugarin I **1**,[2] the antileukemic pseudoguaianolide rudmollin **2**,[3] the witchweed germination promotor strigol **3**,[4] the fish antifeedant nakafuran-8 **4**,[5] and the cytotoxic confertifolin **5**,[6] which might also be a synthetic intermediate in the synthesis of the cytotoxic and insect antifeedant drimane sesquiterpene warburganal **6**.[7]



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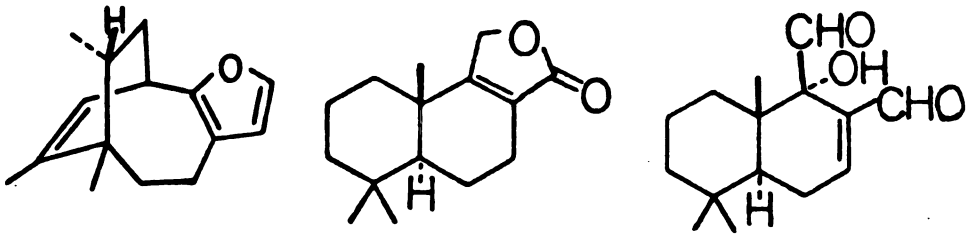
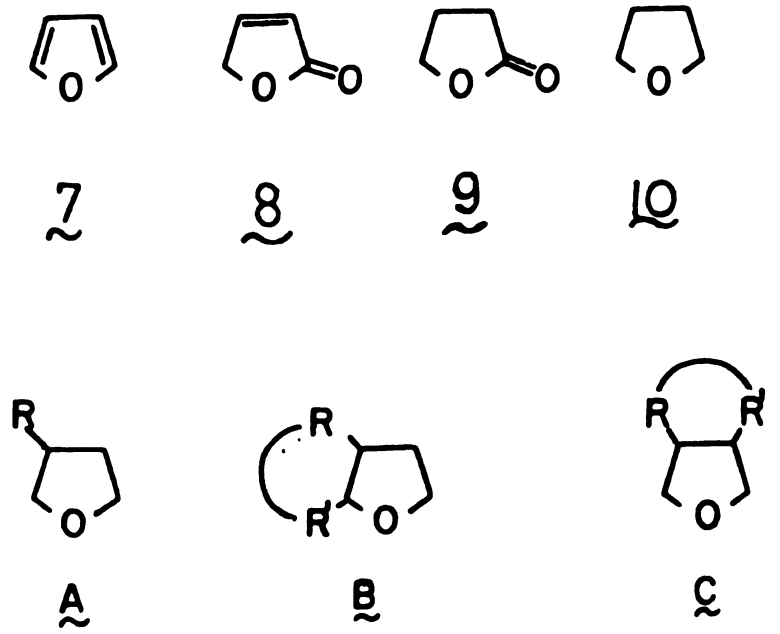


4 5 6

Terpenoids **1-5** exhibit two of the four common oxidation states of the five-membered oxygen containing heterocyclic system. These range from the fully aromatic furan **7** to tetrahydrofuran **10** (Figure 1). The terpenoids **1-5** also display the three (**A-C**) substitution patterns commonly observed about this ring system. Ajugarin I **1** incorporates

the 3-substituted substructure **A**, while rudmollin **2**, strigol **3**, and nakafuran-8 **4** provide examples of the 2,3-fused substructure **B** and confertifolin **5**, the 3,4-fused substructure C.



7 8 9 10

A B C

Figure 1.
Oxidation states 7-10 and substitution patterns A-C of five-membered oxygen containing heterocyclic ring systems.

Structural classification of these terpenoids according to the ring systems displayed in Figure 1 suggests that a synthetic methodology centered around the incorporation of the heterocyclic component into a cyclic or acyclic framework would be a powerful and versatile technique in the synthesis of various terpenoids. The relative similarities of **5** and the non-heterocyclic **6** also suggests

that this methodology could be applied to the synthesis of non-heterocycle containing terpenoids as well.

As a result of the interesting biological activities associated with compounds such as **1-5**, this class of molecules has attracted considerable attention as targets for total synthesis. Most of the reported syntheses of such compounds have centered upon the preparation of a parent carbocycle upon which the five-membered heterocycle is then appended. These schemes have generally not considered the utilization of the five-membered ring nucleus as a unit upon which the remainder of the molecule might be assembled. A truly general approach to the synthesis of molecules **1-5** should provide access to the various states of oxidation (**7-10**) as well as the different patterns of substitution (**A-C**) about the heterocyclic nucleus.

A synthetic program which has the potential to meet these requirements has been under investigation in our laboratories. This strategy revolves around the preparation of ring systems **A-C** from common intermediates. If one considers that **A-C**, in the various oxidation states shown by **7-10**, can be obtained from furanoid precursors via standard oxidation or reduction techniques[11], a common intermediate becomes evident. Thus, the fully aromatic furan **7** can function as the precursor to oxidation states **8-10**. This suggests that a common furanoid intermediate might provide access to all structural combinations implied

by Figure 1 if substitution patterns **A**-C could also be readily established.

It is well known that furan suffers electrophilic aromatic substitution at unsubstituted positions alpha to the ring oxygen.[10] Therefore, this predisposition can be utilized to introduce various substitution patterns around a furyl nucleus in an annulation sequence. This could be accomplished if, for example, a simple 3-substituted furan (**7A**, Figure 1) contains a benign electrophilic center in its side chain. Unmasking of the electron-poor center and subsequent electrophilic substitution would provide **7B** (Figure 1). In order to prepare the substitution pattern represented in C (Figure 1) by this protocol, the favored cyclization at the alpha-position of **7A** must be blocked. Therefore, a functional group X must be introduced at the alpha-furyl position which will prevent the electronically favored closure, directing ring formation to the unsubstituted beta-position. Oishi[12] has examined the furan-terminated cyclization of such an X-group blocked substrate and has observed the formation of type **7C** (Figure 1) products as shown in Figure 2. Unfortunately, the difficulties associated with the manipulation of the α-CO_2Me group render this approach less useful.

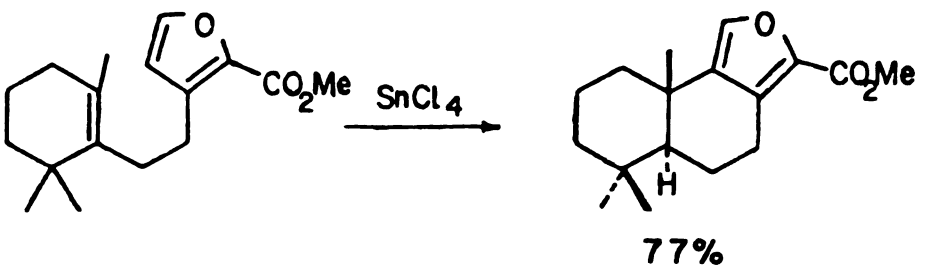


Figure 2.
Alpha-position carbomethoxy blocked, beta furyl cyclization.

The analysis presented above suggests that the more complicated **B** and **C** substitution patterns (Figure 1) should be readily constructed from the much less complex 3-substituted furans **7A** as shown in Figure 3.

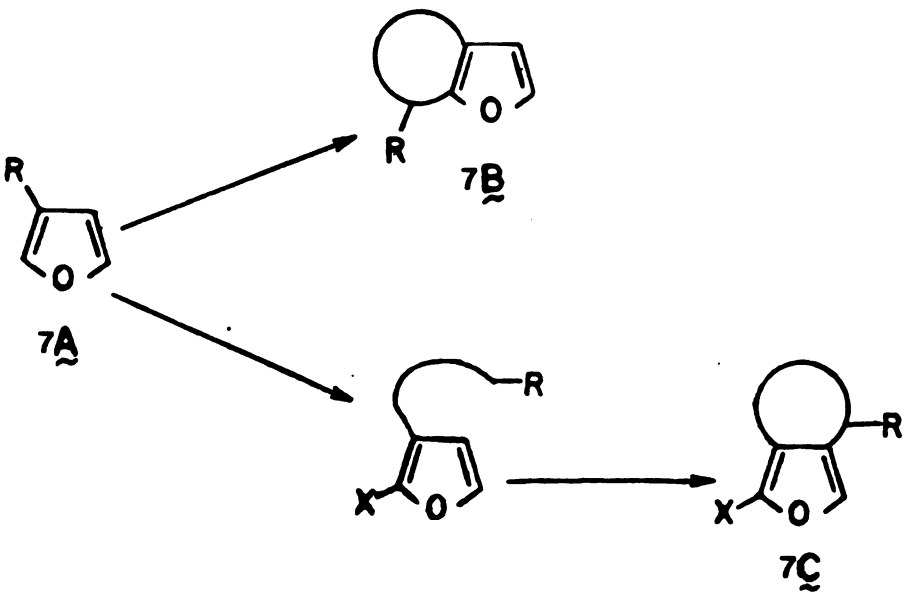


Figure 3.
Conversion of furans 7A to 7B and 7C.

We have previously described a simple route for the preparation of 3-substituted furans[8] as well as their cyclizations[9] to compounds of type **7B** (Figure 1) as illustrated in Figure 4. The readily available isoprenoid

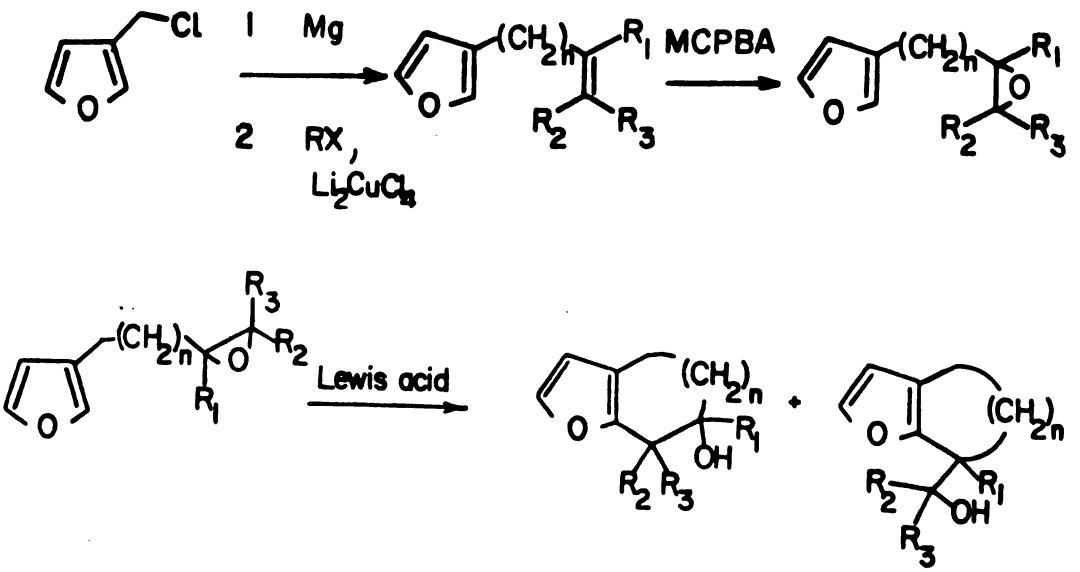


Figure 4.
3-Furylmethyl Grignard reagent formation, alkylation and cyclization.

3-chloromethyl furan is smoothly converted to the corresponding Grignard reagent which, in the presence of Li_2CuCl_4,[42] readily couples with a wide variety of primary and secondary alkyl halides as well as allylic halides. In this process, remote electrophilic centers, such as epoxides can be incorporated without destruction. Alternatively, as shown in Figure 4, these centers can be introduced after the Grignard coupling step.

With an efficient route to a variety of 3-substituted furans available, the cyclization sequences (Figure 4) leading to bicyclic products were examined.[9] In the initial studies, the epoxide function was selected as the initiator for the ring forming sequence. This selection was based upon the ease of epoxide preparation and the relative mildness of the Lewis acidic conditions previously utilized in polyolefin cyclizations. However, the success of these studies was complicated by the poorly nucleophilic character of the furyl terminator coupled with the acid lability of the starting materials and products. These problems were manifested in poor material balance or in the production of unwanted, uncyclized epoxide-opening products.

To address these concerns, several Lewis acids were investigated to determine their ability to promote epoxy-furan cyclization. The choice of Lewis acids selected was dictated by the following factors: (i) the ability to readily modify the potency of a group of Lewis acids with a common metal center; (ii) the possibility of moderating the Brønsted acidity of the medium through the choice of Lewis acid, i.e. adventitious protic acid might be scavenged by a Lewis acid possessing a carbon-metal bond releasing an alkane; and (iii) moderation of the Lewis acid-product alcohol complex acidity.

Although considerable success was enjoyed in these cyclization studies, the reactions tended to be quite substrate dependent. Exact experimental conditions often

had to be worked out carefully with regard to substrate functionality and Lewis acid. These studies have shown, however, that a variety of fused, spirocyclic and bridged furan-containing molecules can be readily obtained.

Although these experimental techniques have proven to be quite useful, they cannot provide access to all of the substructures of Figure 1. As shown in Figure 4, only compounds of type **7A** and **7B** have been produced; however, in principle, oxidation states **8-10** should be accessible from them. In order to produce compounds of the type **7C**, utilizing the experimental techniques above, it becomes necessary to consider a fundamental modification of the reaction substrates. This modification would consist of the attachment of some group X to the 2-position of furans **7A** to direct the cyclization step (Figures 2 and 3).

In addition to cyclization direction, attachment of a group X to a furan **7A** would also facilitate the transformation of it into the desired oxidation states **8** and **9**. This is particularly appealing in light of the lack of regioselectivity in the oxidation of furans to butenolides. The group X could be converted to oxygen which would regiospecifically produce the desired butenolide **8** which could furthermore be reduced to butyrolactone **9**. If **10** was desired, the X-group could simply be removed to provide the parent **C** followed by reduction.

A scheme which illustrates this proposed reaction sequence utilizing X-group appended furyl intermediates

is shown in Figure 5. Cases I and II illustrate the two possibilities for 2-position, X-group appended furans of type **7A**. In both cases, the reaction sequence is identical to that established previously (Figure 4), i.e., formation of a 3-furylmethyl Grignard reagent followed by alkylation to attach a side chain containing a latent electrophile and cyclization. However, we must now consider the nature and preparation of suitable precursors to X-group appended furylmethyl Grignard reagents.

In Case I, the X-group would not exert control over the cyclization but would facilitate conversion of the cyclization products to butenolides of type **8B** (Figure 1). In Case II, the X-group serves to block the electronically favored cyclization process, affording the 3,4-disubstitution pattern of furans of type **7C**. In addition, the X-group can serve to direct the introduction of oxygen in an otherwise relatively symmetrical molecule to afford butenolides of type **8C**.

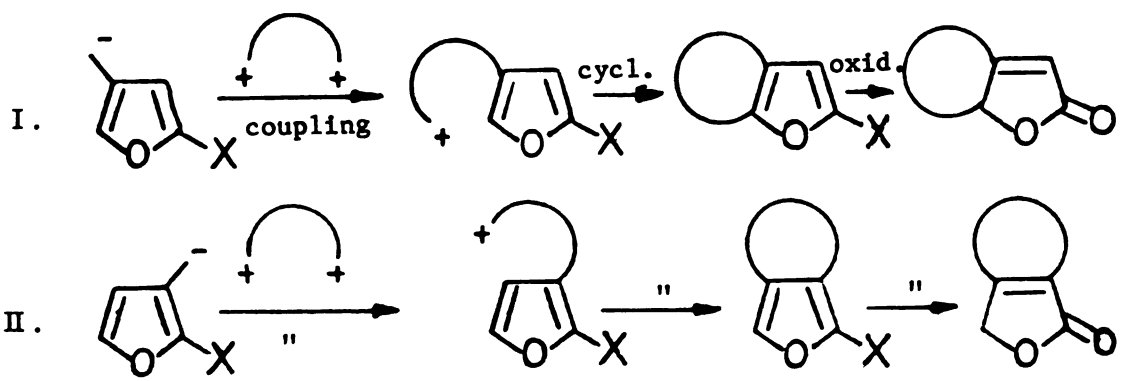


Figure 5.
X-Group blocked 3-furylmethyl synthons in alkylation, cyclization sequence.

The goal of the research efforts described herein was to develop new synthetic methods which might allow the transformations illustrated above (Figure 5) to be realized in the laboratory.

I. The Preparation of (±)-Lactaral[13]

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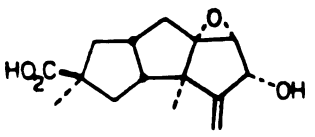
The Basidiomycotina subdivision of fungi have provided a myriad of terpenoid metabolites. Notable among these structurally diverse natural products are the hirsutane sesquiterpenoids such as hirsutic acid **11**,[14] the marasmanes illustrated by marasmic acid **12**,[15] the fomannosanes such as fomannosin **13**,[16] the lactaranes represented by lactarorufin A **14**,[17] and the secolactarane lactaral **15**.[13a,18] As a result of the unique structures and the promising antibacterial and antitumor activities exhibited by several compounds of these types, there has been considerable effort directed toward their total synthesis. These efforts have culminated in elegant syntheses of **11**, **12**, **13**, and related compounds. However, the lactaranes and seco-lactaranes have not been as thoroughly studied.



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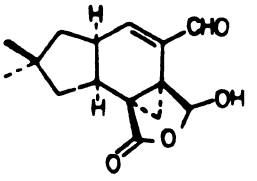

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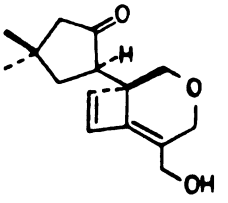

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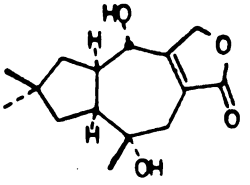

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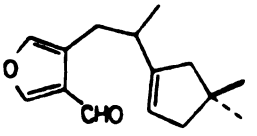
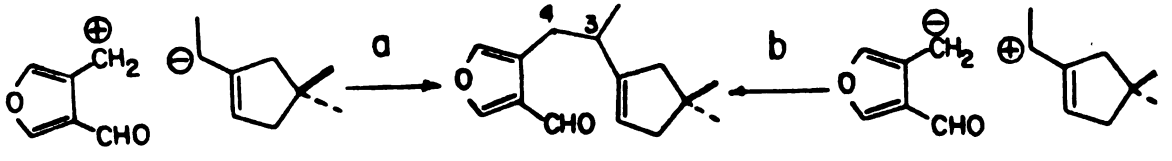


15

As part of our program directed toward the total synthesis of furan containing natural products, the synthesis of (±)-lactaral **15** was undertaken. Central to this program is the development of highly functionalized furans as viable synthons.

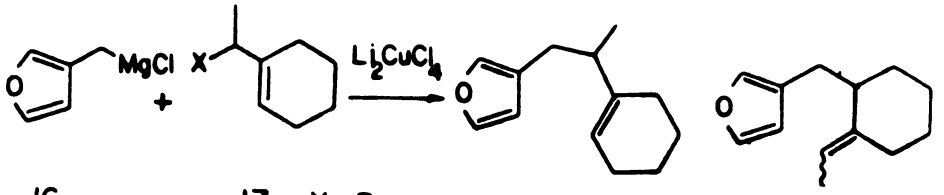


15 (1)

Initially, attention was focused upon the formation of the C(3)-C(4) bond (lactarane numbering) as the crucial step in the synthesis of (±)-**15** (eq. 1). This bond can be constructed in either of two polar senses. Path a utilizes an allylic nucleophile while path b employs a benzylic-type nucleophile in the bond-forming process. Based upon earlier work by Tanis,[8] the reverse polarity (relative to the normal use of substituted furylmethyl derivatives) path b route was chosen as the method of choice. This approach has a distinct regiochemical advantage over the path a construction in which an allylic carbanion is added to an electrophilic furylmethyl residue. Whereas an allyl organometallic may undergo rearrangement, the furylmethyl carbanion approach illustrated in eq. 1 allows the regiochemical integrity of the trisubstituted double bond to be retained.

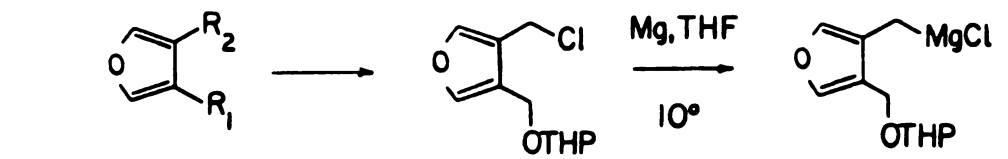
The synthesis of (±)-lactaral **15** via a path b approach requires that the displacement by the furylmethyl carbanion upon the requisite allylic halide proceed in an S_N2 fashion and not S_N2'. Previously, the tendency of related furyl organometallics to yield mixtures of products resulting from S_N2 and S_N2' displacement has been noted[8] when the halogen-bearing carbon and the terminal olefinic carbon are sterically similar. To determine if mixtures of products might be obtained in the preparation of **15**, the model system illustrated in eq. 2 was examined.

The readily available bromide **17**, prepared from the precursor alcohol[20,21] (CBr_4, Bu_3P)[19] and chloride **18** (CCl_4, Ph_3P),[19] were selected as coupling partners for Grignard reagent **16**.[8] The reaction of Grignard reagent **16** with allylic bromide **17**, in the presence of Li_2CuCl_4,



16 **17** X = Br; **18** X = Cl **19** (60%, 6:4) (47%, 100:0) **20** (2)

afforded a 60% yield of a mixture **19** and **20** in a ratio of 60:40 as determined by 250 MHz proton NMR.[22a] However, the coupling of **16** with the corresponding chloride **18** provided the desired **19** as the sole product in 47% yield. It was gratifying to observe only the desired S_N2 substitution product from the reaction of **16** and **18** although the reasons for the observed selectivity are not immediately obvious.[22b]



(3)

21 $R_1 = R_2 = CO_2Et$

22 $R_1 = R_2 = CH_2OH$ (77%)

23 $R_1 = CH_2OTHP$, $R_2 = CH_2OH$ (50%)

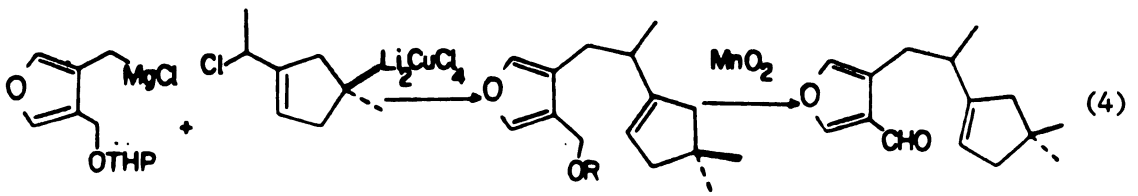
24 77%

25 100%

With this crucial information in hand, a precursor to the nucleophilic furyl residue outlined in path b of eq. 1 was prepared (eq. 3). The formerly inexpensive diethyl-furan-3,4-dicarboxylate **21** was reduced with lithium aluminum hydride to provide alcohol **22** in 77% yield. Protection as a mono-THP ether was accomplished by the procedure of Grieco[23] affording a statistical mixture of un-, mono-, and bis-protected diol from which **23** was isolated in 50% yield after chromatography. Numerous attempts to perform the chlorination of **23** by previously used methods[24] afforded only trace quantities of **24**. However, when the procedure of Meyers[25] was employed, chloride **24** was obtained in 77% yield.

Initial attempts to convert **24** to Grignard reagent **25** at room temperature provided only low yields of **25** as

determined by titration.[26] Earlier work[27] investigating the formation of Grignard reagents in the presence of acetalic functions suggested attempting the conversion at a lower temperature. At 10°C (internal), **25** was formed over a period of 2 h in quantitative yield as determined by titration.[26]



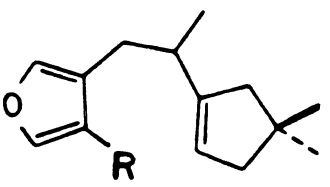
(4)

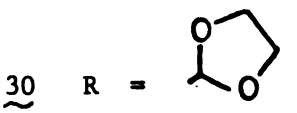
25 26 27 R = THP(75%) 15(96%)
28 R = H(100%)

The reaction of **25** with chloride **26** (prepared from the corresponding alcohol;[18c] CCl_4, Bu_3P[19]) afforded lactarol-THP ether **27** in 75% yield as the sole product. Deprotection[23] of **27** gave lactarol **28** in quantitative yield. Alcohol **28** was then oxidized with activated manganese dioxide[28] to (±)-lactaral **15**[18] in 96% yield. Synthetic

15 was identical in all respects to a sample of authentic lactaral kindly provided by Professor G. Magnusson.

With the successful completion of the synthesis of lactaral accomplished, studies were undertaken toward its cyclization into the lactarane skeletal system (see **14**). A cyclization might occur if the cyclopentene double bond could be induced to act in a nucleophilic sense and attack the Lewis acid complexed aldehyde of lactaral or other functional groups such as the corresponding cyclic acetal **30** alcohol **28**, or acid chloride **33**.[29,30]





30 R =

31 R = CH_2OCHO

32 R = COOH

33 R = COCl

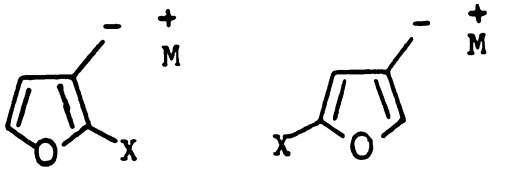
Initially, the direct cyclization of lactaral **15** was examined. A variety of Lewis acids and reaction conditions were employed including $SnCl_4$, ZnI_2, $BF_3 \cdot OEt_2$. Et_2AlCl, and TFA/TFAA; however, none of these techniques provided cyclized product. The cyclization of lactarol **28** was also attempted with trifluoroacetic acid (TFA) and with formic acid. In the latter case, only the formate **31** was isolated.

Finally, lactaral **15** was oxidized via the Corey procedure (MnO_2, NaCN, MeOH)[31] to the corresponding methyl ester, followed by hydrolysis to afford lactaroic acid **32** (72% yield overall). Acid **32** was converted to the corresponding acid chloride **33** (oxalyl chloride, benzene) in 80% yield. Treatment of **33** with aluminum chloride afforded only trace amounts of cyclized products. It is likely that the fragility of the system results in destruction under the relatively harsh conditions required for closure.

II. Synthesis and Reactions of Heteroatom-substituted Furylmethyl Organometallics

II. Synthesis and Reactions of Heteroatom-substituted Furylmethyl Organometallics

In order to evaluate the strategies discussed in the introduction which were designed to provide access to 3,4-disubstituted furans as well as to control regioselectivity in butenolide preparation, it was necessary to prepare a variety of X-group substituted furylmethyl organometallic intermediates. In the course of the study, a number of novel and previously unknown furyl compounds were prepared. For those cases in which the desired organometallic was obtained, alkylation and cyclization studies were carried out. Additionally, the ease with which these products could be converted to the corresponding butenolides was examined. In order to ensure facile conversion of the furyl precursors into their corresponding butenolides, only heteroatom containing X-groups were considered.



2,3-substitution 2,4-substitution

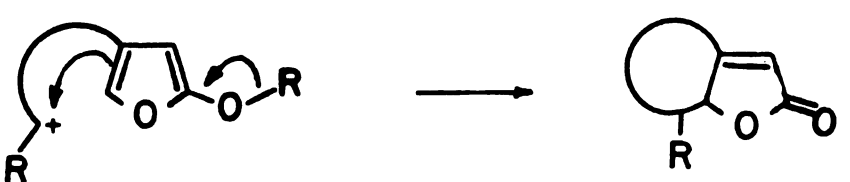
X = -OTMS, -OTBDMS, -SMe, -SPh, -TMS

Figure 6.
Heteroatom containing X-group substituted
3-furylmethyl organometallic reagents.

As shown in Figure 6, the X-groups investigated were: O-trimethylsilyl; O-t-butyl-dimethylsilyl; methylsulfenyl; phenylsulfenyl; and trimethylsilyl. In all of these cases, the target organometallic was the Grignard reagent due to the convenience of formation and previously demonstrated[8,9] utility in alkylation sequences.

II. A. Alkoxy- and Siloxy-substituted Furans

Since butenolide- and butyrolactone-containing molecules are the ultimate targets of this methodology, the first X-groups to be examined were those in which the heteroatom was oxygen, i.e., X = OR where R = alkyl or trialkylsilyl. The ease of hydrolysis of alkoxy and siloxyfurans[32a,33a,b] and their reactivity when treated with exogenous electrophiles[33b] suggested that X = OR, $OSiR_3$ would be an excellent first choice. One additional benefit of this approach is the possible direct production of a butenolide from the cyclization of a 3-alkyl-5-OR-substituted furan (Figure 7) in a manner analogous to the work done with exogenous electrophiles.[33]

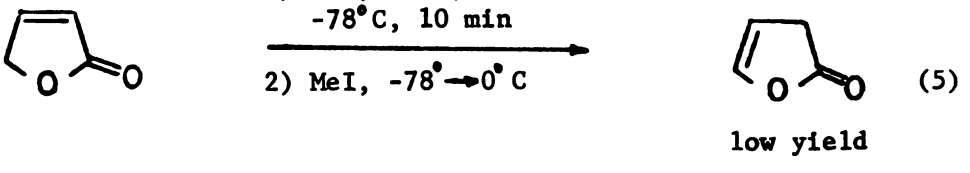


R = alkyl, trialkylsilyl

Figure 7.
Proposed cyclization of 3-alkyl-5-alkoxy substituted furans.

Initially, X = OR for R = alkyl was considered. Unfortunately, only a few members of this class of compounds are known, i.e., X = methoxy,[32a] t-butoxy,[32b] and acyloxy.[32c] Of these compounds, a methoxy-substituted derivative appeared to be the most suitable for this study since it should be less inclined to R-O bond cleavage than the t-butoxy analog; however, the preparation of the methoxy-substituted derivative is tedious. Therefore, an attempt was made to prepare it via the procedure of Kraus[32c] which was successfully used to prepare 2-acyloxy- and 2-t-butyldimethylsiloxy-furans.

As shown in eq. 5, the attempted O-alkylation of the enolate anion of 2-(5H)-furanone with methyl iodide led to a low yield of only double-bond shifted product. More reactive methylating reagents (Me_3OBF_4, $MeOSO_2CF_3$) were not investigated due to their expense and difficulty in handling.

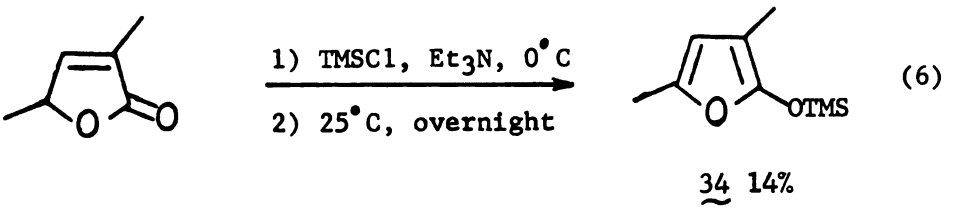


low yield (5)

Attention was then directed to the silicon analogs of the alkoxyfurans, which have been more thoroughly investigated. To date, siloxyfurans have been prepared via O-silylation of the corresponding butenolides with trimethylsilyl chloride or t-butyldimethylsilyl chloride by two general methods. Kraus[32c] has accomplished this conversion via the lithium enolate of a butenolide; however, in this study, the milder silylation conditions of Asaoka,[33a] Cazeau,[34] and Wiesner[35] have been found to be more useful. Typically, a weak base such as triethylamine, often in the presence of a coordinating metal cation, was used to catalyze the silylation, analogous to the manner in which silyl enol ethers of ketones have been formed.[36]

3,5-Dimethyl-2(5H)-furanone[37] was converted to the corresponding siloxy derivative, 2-trimethylsiloxy-3,5-dimethylfuran **34**[33a] via the two methods shown[33a,34] (eqs. 6 and 7) to afford 14% and 56% yields of 34, respectively.

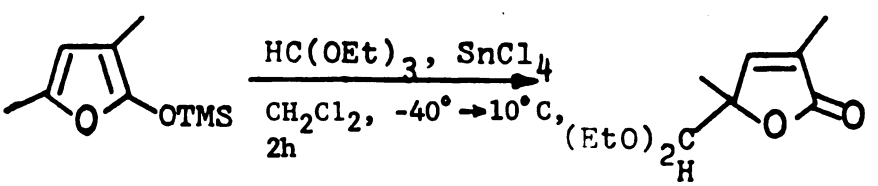
With siloxyfuran **34** in hand, a reaction designed to give an indication of the ability of O-trimethylsilyl to function as a cyclization blocking group was carried out. Compound **34** was subjected to electrophilic attack via the procedure of Asaoka[33b] to afford a high yield of alkylated product **35** (eq. 8). Although Asaoka[33b] has observed beta(3)-position electrophilic attack in reactions of alpha(2)-trimethylsiloxy-alpha'(5)-alkyl furans, the analogous reactions of alpha(2)-trimethylsiloxy-beta(3),



(6)

34 14%

" TMSCl, Et_3N, NaI, CH_3CN, 25°C, 2.5 h → 34 56% (7)



(8)

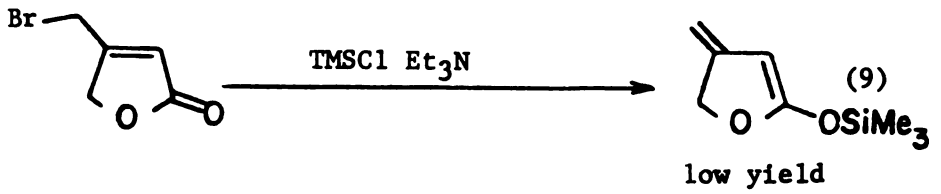
34 35 93%

alpha'(5)-dialkyl furans (such as **34**) have not until now been examined. Treatment of compound **34** with an electrophile resulted in exclusive alpha(5)-position attack even though this position was already methyl substituted. Although these results suggest that electrophilic attack at the beta'(4)-position is not electronically favorable, the possibility of intramolecular cyclization to this position is not ruled out. In the event of an intramolecular cyclization, steric constraints would make attack at the remote

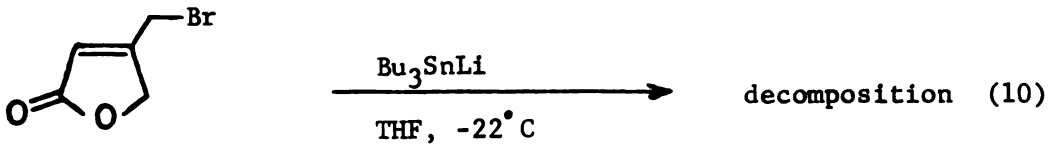
alpha'-position to form a 3,5-bridged bicycle very unfavorable.

After having examined the properties of simple siloxyfurans, it was necessary to consider the introduction of a functionality which would facilitate the appendage of a side chain. The placement and nature of the reactive site must be reconciled with the chemistry required to develop the siloxy furans.

One of the most direct and obvious solutions to this problem is illustrated in eq. 9. Using the methodology



of Asaoka[33] to establish a siloxy X-group, the 3-bromomethyl-butenolide shown[34] was successfully silylated. Unfortunately, the only product obtained, which was isolated in low yield, resulted from the expected halide elimination. In an attempt to overcome problems associated with the halide, an effort was made to transform it into the corresponding organotin compound via the procedure of Still;[38] however, as expected, only decomposition resulted (eq. 10).



The difficulty in the preparation of a halomethylsiloxy-furan presumably arises due to the relative sensitivity of both functionalities as well as the furan itself. An alternative which addresses the problem of functional compatability is illustrated in Figure 8.

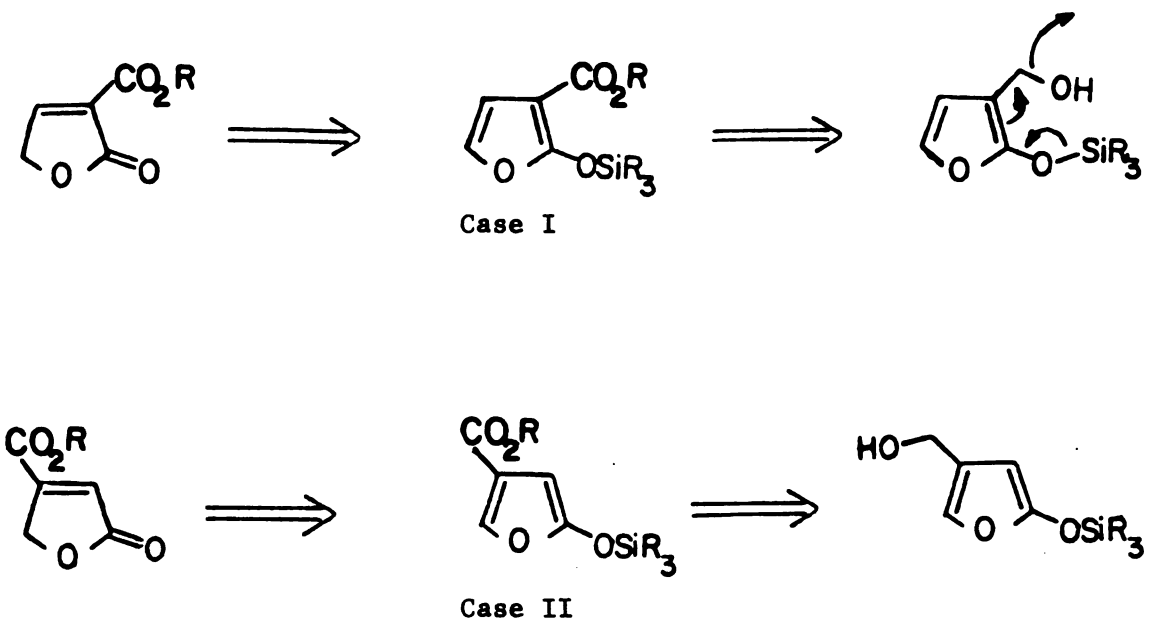


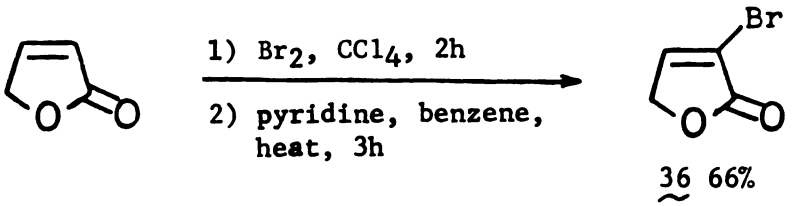
Figure 8.
Proposed synthetic pathway to alpha-siloxy, beta-hydroxymethyl furans.

In this scheme, the organometallic precursor is left in the relatively insensitive carboxylic acid oxidation state in order to establish the sensitive siloxy functionality. However, in path I, the final structure is perfectly set up for decomposition and probably would not survive the relatively acidic conditions required to convert it to the corresponding halide. In path II, the regioisomeric 2-siloxy-4-hydroxymethyl furan has an electronic structure that promises greater stability. However, the lack of availability of the appropriate precursors to these materials prompted us to abandon this approach in favor of the following one.

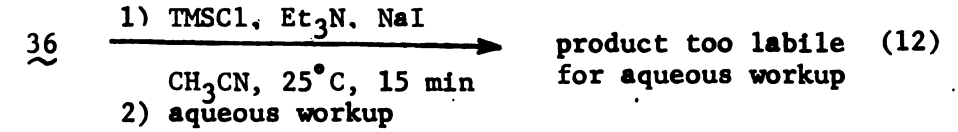
Utilizing the "umpolung"[39] capabilities afforded by organotin compounds, a one carbon extension of a carbanion can be performed via its alkylation with iodomethy-tri-n-butylstannane and subsequent tin-lithium exchange (nBuLi).[38]

The two requisite, regioisomeric siloxy-furylmethyl organometallic reagents (see Figure 5) should, in principle, be obtainable by alkylation of the corresponding siloxy-furylanions with Bu_3SnCH_2I. The carbanionic nature of this mode of functional elaboration should be compatable with the siloxy group whereas the carbocationic nature of the halogenation discussed previously is not.

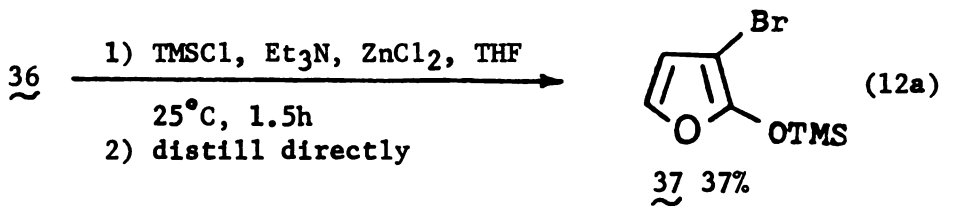
To regioselectively produce a beta-furylanion, it is necessary to perform a halogen-lithium exchange on the corresponding furyl halide since the most acidic proton



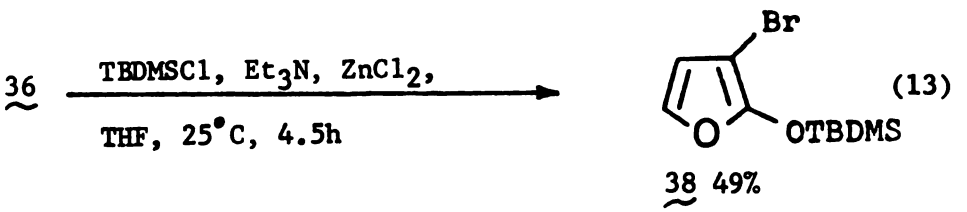
36 66% (11)



(12)



37 37% (12a)

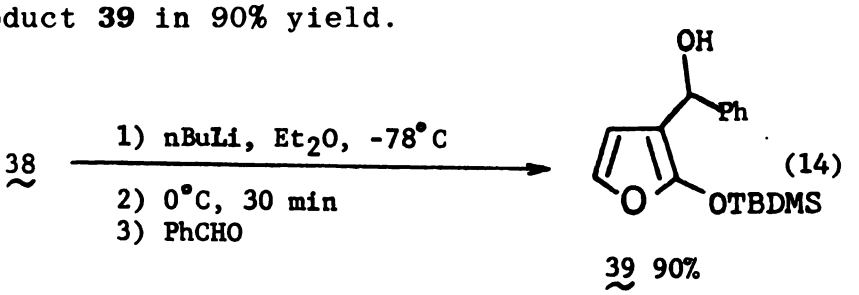


38 49% (13)

resides at the alpha position. Although there are far fewer reports of the additions of beta-furylanions to electrophiles than of the alpha counterparts,[46] Wiesner has reported the high yield addition of the lithium derivatives of 3-bromo- and 4-bromo-2-trimethylsilyloxyfuran to steroidal ketones.[32] These results suggest that the alkylation of these anions with ICH_2SnBu_3 would provide access to the desired organometallic reagents of Figure 5. Therefore, it became necessary to prepare the precursor halo-butenolides. A simple procedure[40] for the preparation of the 2-bromobutenolide **36** from 2-(5H)-furanone[41] is illustrated in eq. 11.

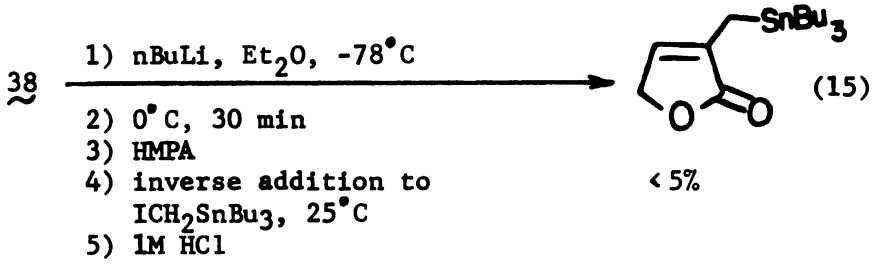
Compound **36** was then subjected to the silylation conditions illustrated in eq. 12, 12a, and 13. The trimethylsilyl derivative, 2-trimethylsilyl-3-bromofuran **37** was successfully prepared; however, it was found to be extremely labile. The t-butyldimethylsiloxy derivative **38** was successfully prepared (eq. 14) and found to be reasonably stable.

With compound **38** in hand, its conversion to the corresponding halogen-lithium exchange product and reaction with electrophiles was examined. Treatment of **38** with nBuLi followed by the addition of benzaldehyde provided the addition product **39** in 90% yield.



(14)

Several methods were then examined in an attempt to alkylate the anion derived from **38** with ICH_2SnBu_3. Direct alkylation of the corresponding organolithium was unsuccessful as was alkylation of the Grignard reagent, produced by treatment of the organolithium derivative with $MgBr_2$. Introduction of Copper I and II catlysts[42] was also unsuccessful in promoting alkylation as was the mixed cyano-cuprate. A very low yield of the stannylmethylated butenolide was obtained, however, by alkylation of the organolithium reagent in the presence of HMPA, followed by desilylation as shown in eq. 15. It was concluded that the anion of **38** was not sufficiently nucleophilic to react with ICH_2SnBu_3 in good yield.



Due to our inability to prepare precursors to the siloxy-furylmethyl organometallics in acceptable yield, this approach to butenolide equivalents was abandoned in favor of sulfur-substituted furans as described in Section II.B.

II. B. Sulfur-substituted Furans

At this point, our attention was directed toward furans substituted at the 2-position with sulfur-containing X-groups, e.g., X = SR, R = alkyl as potential butenolide dianion equivalents. This functional group appeared to have several advantages over the oxygen-containing analog. First, it was assumed that the poorer pi-system overlap of the sulfur containing group would result in lower furyl electron density imparting more stability to the alkylthio-furans than was observed for the labile siloxy and alkoxy-furans. Additionally, since sulfides in general are more easily prepared than ethers, it was assumed that unlike the siloxyfuryl analogs, the appropriate precursors to the desired sulfenyl furyl organometallic reagents would be more readily accessible. Another positive aspect concerning the use of sulfur is the variety of oxidation states in which it can exist. This property might be useful in subsequent cyclization studies especially in light of the electron-withdrawing nature of the furyl substituent employed by Oishi in Figure 4.

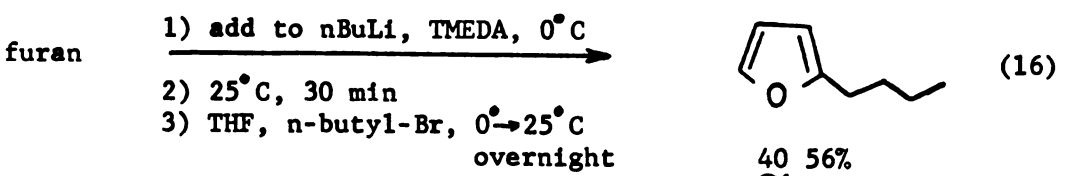
Along with the greater stability of the sulfenylfurans, however, comes the added complication of removing sulfur with conversion of the furan to the corresponding butenolide. This, of course, should in principle be achievable via the appropriate hydrolytic conditions similar to the hydrolyses of dithiane alkylation products in the well-known

aldehyde and ketone synthetic methodologies reported by Corey,[43] Seebach,[44] Schlessinger,[45] and others. Although alkylthio-furans are known compounds,[46] there have been few literature reports of their hydrolyses.[47a,b]

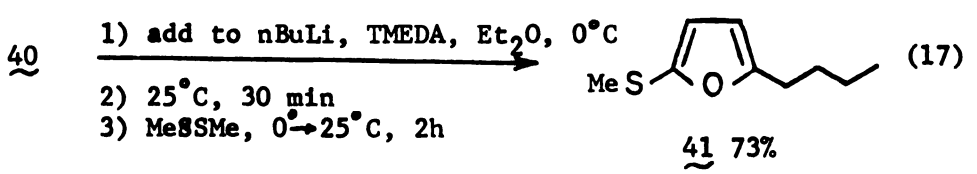
II. B. 1. Methylsulfenyl as X-group

The first sulfur containing X-group to be investigated was methylsulfenyl, X = SMe. Our initial studies, which examined the introduction of $-S-CH_3$ and its removal by hydrolysis, are described below.

The volatile furan was first converted to 2-n-butyl-furan **40** (eq. 16) by a modification of the procedures of Chadwick[48] and Levine[49]. In a similar sequence, **40** was metalated and treated with dimethyl disulfide yielding **41**.



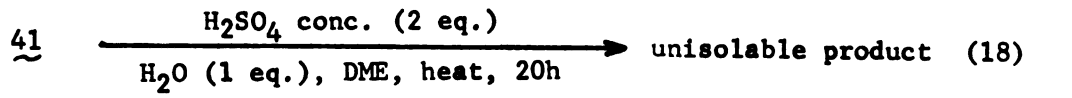
40 56% (16)

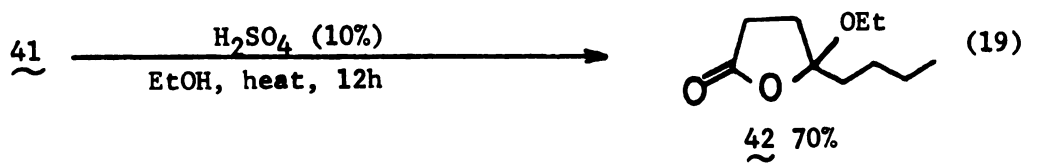


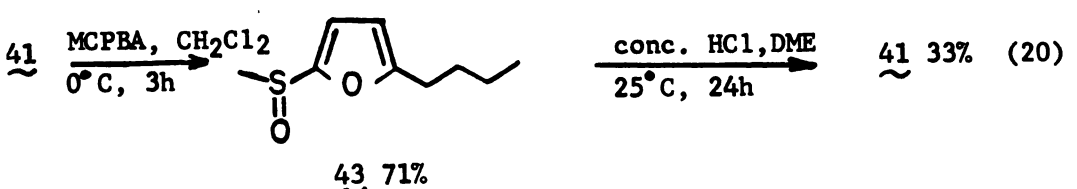
41 73% (17)

With methylthio-furan **41** in hand, hydrolysis studies were carried out. A variety of conditions were explored including some of the milder variants which have been used successfully for the hydrolysis of various hemithio- and dithio-acetals and ketals. These include: $HgCl_2$, H_2O;[44] $HgCl_2$, HCl, H_2O, MeOH,[47b] and HgO, HBF_4, THF.[50] Unfortunately, these attempts provided unreacted starting material.

The high stability of the methylthio-furans to hydrolysis requires the use of a strong acid such as H_2SO_4. However, it is necessary to carefully adjust conditions in order to avoid complete decomposition of the furan. These

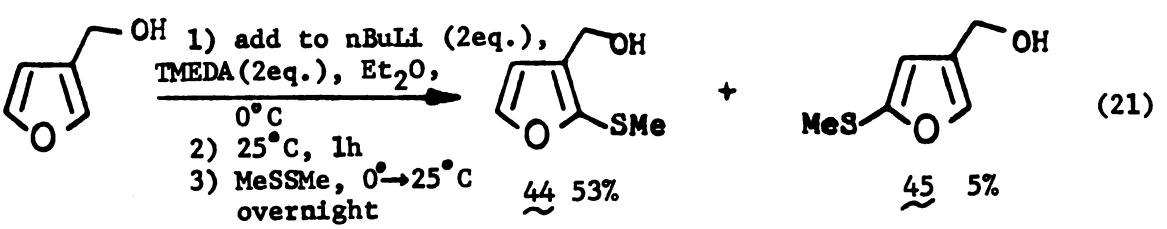






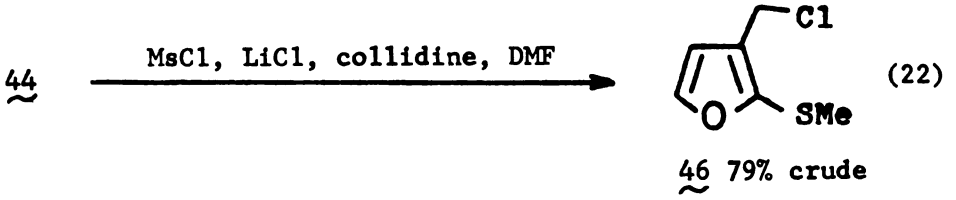
conditions were examined as described in eqs. 18 and 19. Although the conditions of eq. 18 did not provide unreacted starting material, we were unable to isolate or purify the product. However, the milder conditions of eq. 19 did afford a good yield of hydrolyzed material **42** as the ethanol addition product. This observation may explain the enhanced stability of the product of eq. 19 relative to that of eq. 18. In light of the difficulties encountered in these hydrolysis attempts, we next examined the hydrolysis of the derived sulfoxide **43**. Using milder hydrolysis conditions than before, **43**, unfortunately, gave only a low yield of reduction product.

During the course of the hydrolysis studies, a synthetic sequence to the methylsulfenyl-substituted organometallic precursor was begun. As shown in eq. 21, 3-hydroxymethyl-furan was metalated in a fashion similar to that of eqs. 16 and 17 (2 eq. nBuLi). The dianion was then reacted with dimethyldisulfide to give a mixture of two regioisomeric sulfenylated 3-hydroxymethyl-furans **44** and **45** in 53% and ca. 5% yields, respectively. The major regioisomer was



(21)

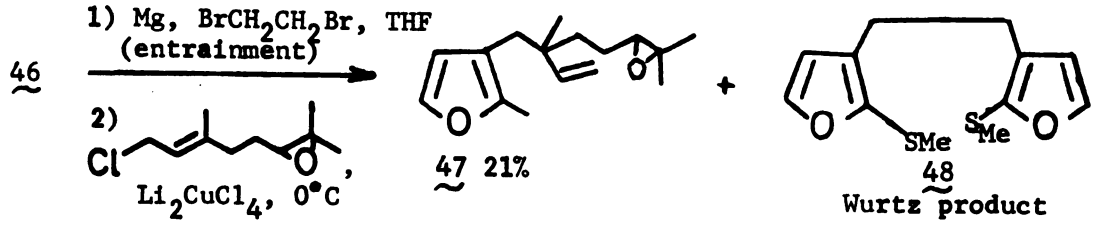
purified and halogenated in the usual way[25] to afford **46** in 79% crude yield (eq. 22).



44 → **46** 79% crude (22)

The chloride **46** was not thermally stable and could not be purified; however, the crude material was clean enough to allow the alkylation studies described below to be carried out.

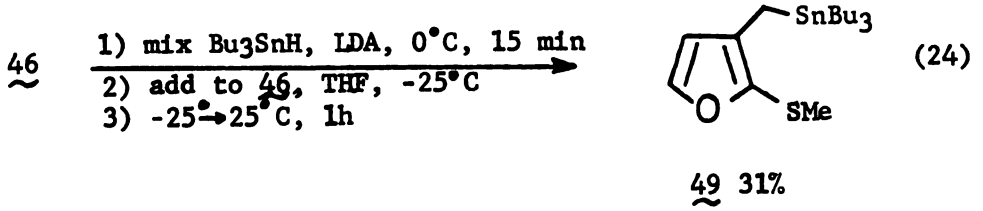
When Grignard formation with chloride **46** could not be induced by conventional methods, an "entrainment" tech-



(23)

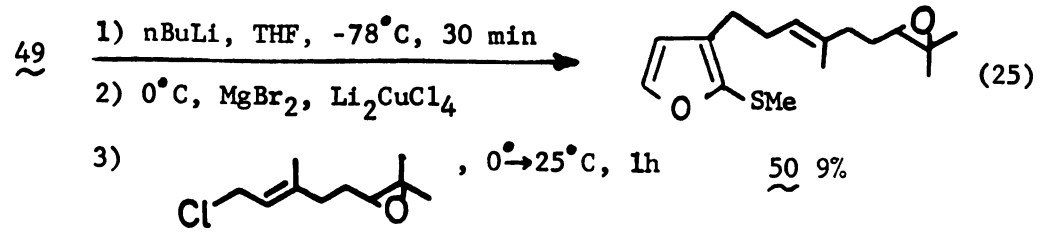
nique was successfully utilized (eq. 23). The Grignard reagent thus prepared was coupled with epoxygeranyl chloride[51,52] in the presence of Li_2CuCl_4 catalyst[42] to provide a mixture of products from which the S_N2' product **47** could be isolated in disappointingly low yield (21%). A 64% yield of the furan dimer **48** was also isolated. It was hoped that the formation of the Grignard by a different method might reduce the amount of dimerization and also produce more of the desired S_N2 displacement product rather than the S_N2' product **47** observed. Unfortunately, when the coupling was attempted after Grignard formation by the Rieke[53] technique, only the furan dimer **48** was observed.

It is thought that the dimerization products are produced during the Grignard formation. In an attempt to circumvent this problem, the chloride **46** was converted into the corresponding tri-n-butylstannane **49**[38] followed by tin-lithium exchange and treatment with magnesium bromide to form the Grignard reagent (eqs. 24 and 25). Although the stannane **49** was not produced in very high yield (31%, eq. 24), a sufficient quantity was obtained to allow the alkylation of the corresponding Grignard reagent with epoxygeranyl chloride[51,52] (eq. 25).

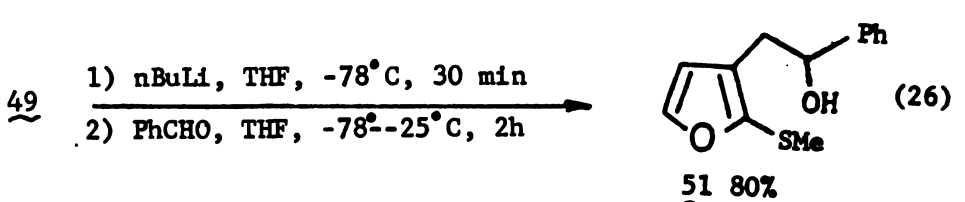


(24)

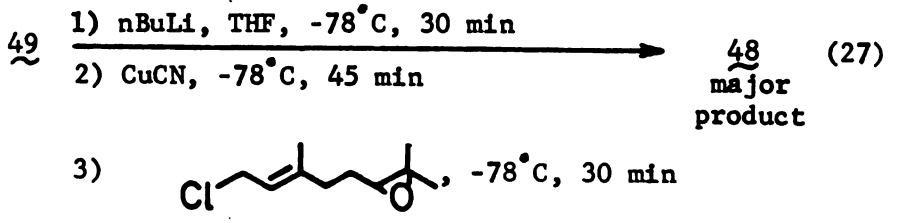
49 31%



The alkylation product **50** was produced in quite low yield (9%); however, no dimerized material was produced and no recovered stannane or its proton exchange product were observed. This suggested that the low yield of the reaction was not due to problems in the anion formation or its alkylation but in the stability of the anion itself. To verify this assumption, the stannane **49** was subjected to tin-lithium exchange at low temperature (-78°C) as before, then reacted directly with benzaldehyde at -78°C (eq. 26). A high yield of addition product was produced suggesting that the anion was stable at low temperature.



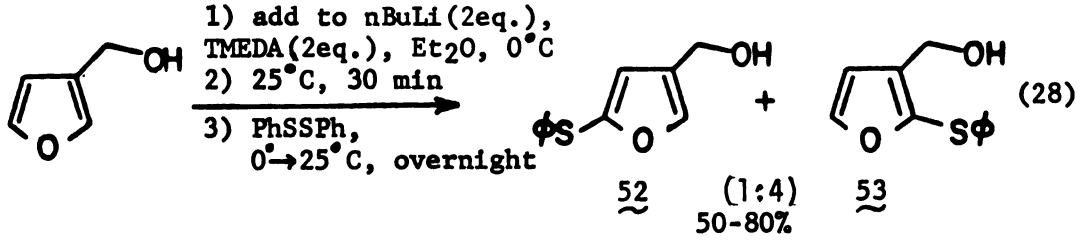
Since the Cu(II) catalyzed Grignard coupling process, which is the usual method for alkylation of furylmethyl anions,[8] does not work well with alkyl halides at low temperature, a mixed organo-cuprate was utilized (eq. 27). Unfortunately, only the furan dimer **48** was again obtained.

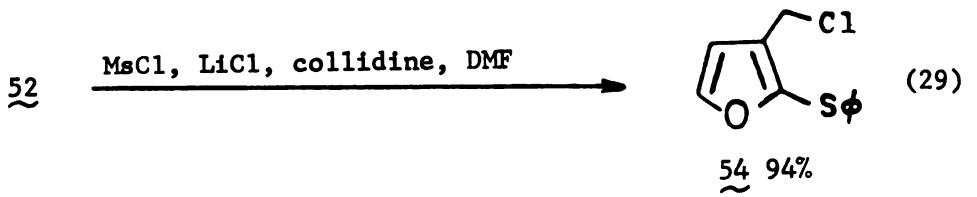


Concurrent with these investigations into methylsulfenyl as X-group, a similar effort was directed toward phenylsulfenyl as X-group.

II. B. 2. Phenylsulfenyl as X-group

In a reaction sequence identical to that for the methylsulfenyl analog, 3-hydroxymethyl-furan was elaborated into the chloro-precursor of the corresponding phenylsulfenyl

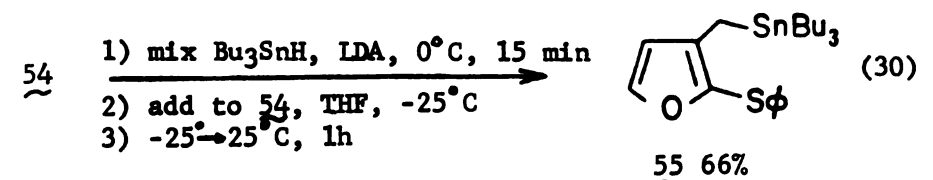




organometallic reagent (eqs. 28 and 29). Unlike the methylsulfenyl derivative **46**, phenylthio-furylmethyl-chloride **54** is quite stable and can be purified by distillation.

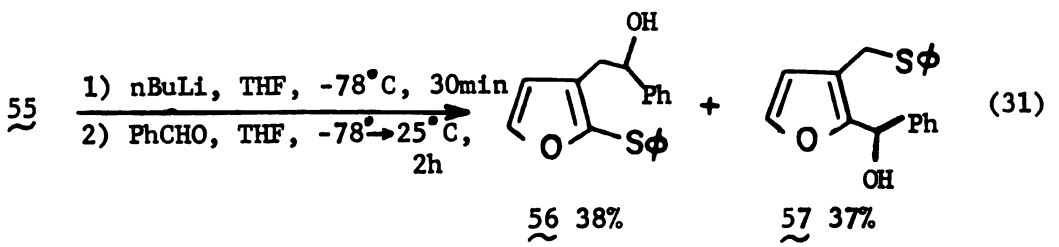
Although the Grignard reagent from chloride **54** could be directly formed by standard methods, several alkylation attempts provided the same results as those for the methylsulfenyl analog.

As with chloride **46**, the phenylthio-furylmethyl-chloride **54** was transformed into the corresponding tri-n-butyl stannane **55** as shown in eq. 30. Initial alkylation studies



of the tin-lithium exchange product of **55** gave the same results as those observed for the

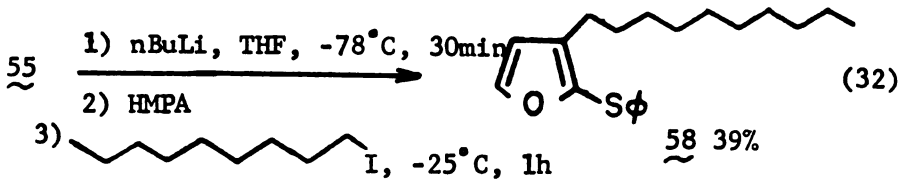
methylthio-furylmethyl-stannane **49**. Therefore, a similar low-temperature reaction with benzaldehyde was attempted



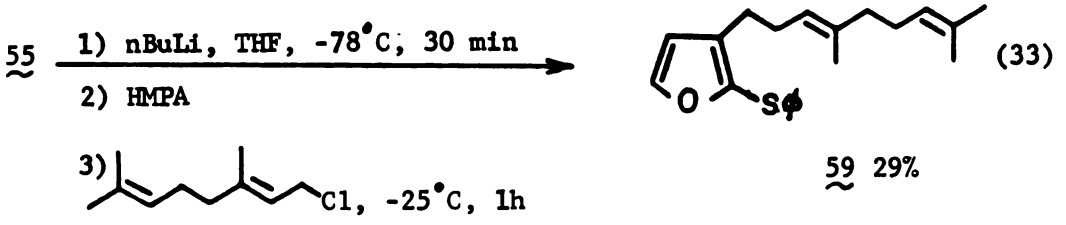
(31)

(eq. 31). The anion of **55** was successfully produced and added at low temperature to PhCHO. However, in this case, along with the expected product **56**, an unusual rearranged product **57** was obtained.

However, as is shown in eq. 32 and 33, we found that the phenylthio-substituted organolithium reagent could be successfully alkylated by some of the more reactive alkyl halides in the presence of HMPA at temperatures no higher than -25°C. If the temperature was raised above this, decomposition resulted; and if lowered much below -25°C, the rate of alkylation slowed to an unacceptable level.

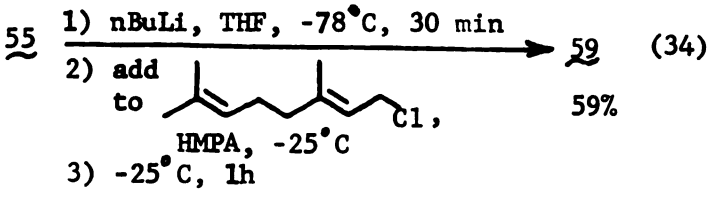


(32)



(33)

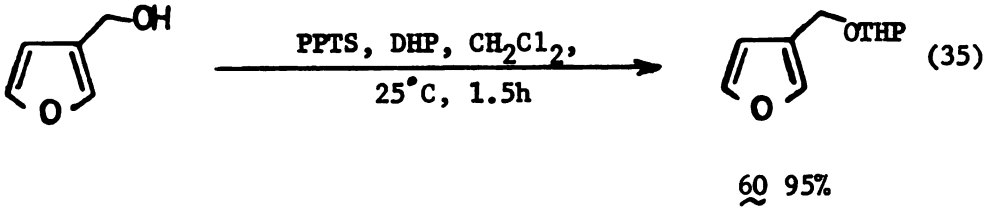
This process was improved further by adding the preformed-organolithium reagent, via a dry ice jacketed syringe, to a solution of the alkyl halide in THF and HMPA at -25°C (eq. 34) giving **59** in a more acceptable yield (59%).



(34)

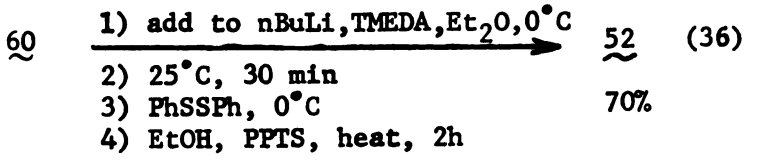
Upon successful preparation of 2-phenylthio-3-alkyl furans, the problem of efficiently constructing an organometallic precursor of the 2,4-substitution pattern

was addressed. Both the 2,3-substituted methylthio and phenylthio organometallic precursors were prepared via an oxygen-directed metalation of 3-hydroxymethyl furan. However, in both cases, small amounts of the 2,4-substituted regioisomers were produced. We, therefore, assumed that blocking of the directing oxygen, for example, as an ether, might lessen the directing effect and result in a greater proportion of the 2,4-substituted regioisomer. Additionally, it was thought that if this ether was particularly large and bulky, a steric preference for metalation leading to the 2,4-substituted regioisomer might be observed. This hypothesis was tested as shown in eq. 35 and 36.



(35)

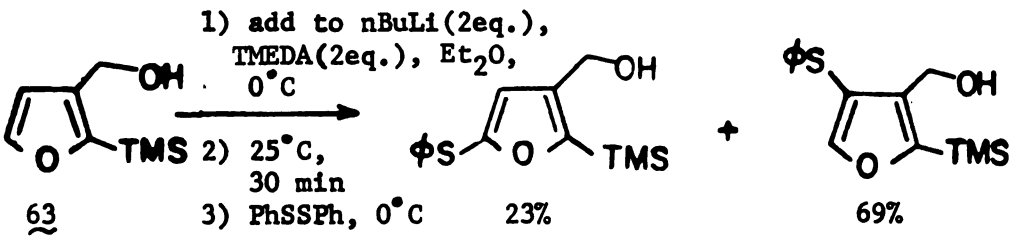
60 95%

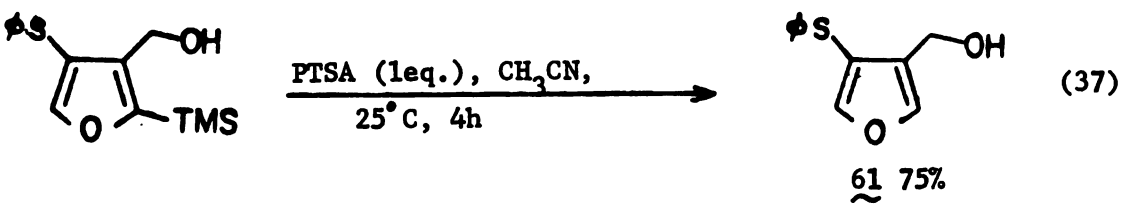


(36)

In the event, blockage of the hydroxylic oxygen of 3-hydroxymethyl furan as its THP ether **60** did not provide a sufficient barrier to metalation at the 2-position as the subsequent sulfenylation reaction (eq. 36) afforded only the 2,3-substituted regioisomer **52**.

In a further attempt to prepare the 2,4-substituted regioisomer, a different strategy was adopted. Instead of blocking the directing hydroxylic oxygen, a substituent which could be selectively removed at a later time was placed at the favored alpha metalation position. As shown in eq. 37, 2-trimethylsilyl-3-hydroxymethyl furan **63** (prepared from 3-hydroxymethyl furan) was subjected to sulfenylation conditions as before.

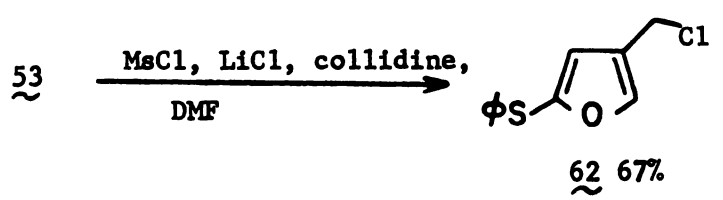




Surprisingly, the major product was not the desired 2-phenylthio-5-trimethylsilyl-4-hydroxymethyl furan (23%) but an unexpected isomer resulting from beta-position metalation (69%). Apparently, the directing effect of the hydroxylic oxygen is strong enough to override the furyl ring electronic factors that favor alpha-position metalation. The beta-position metalation product was subjected to desilylation conditions to provide the novel 3-phenylthio-4-furan methanol **61**.

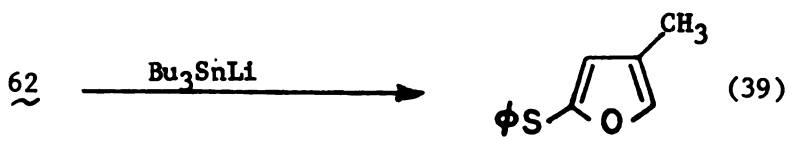
Although the major product of this procedure did not give the desired 2,4-substitution pattern, these results suggest a possible solution to this problem. If, in addition to placing a substituent at the favored metalation position, the directing oxygen was also blocked, one would predict that the desired substitution pattern would be produced. However, this was not pursued further.

The minor product of eq. 37 was subjected to desilylation conditions and through this procedure an adequate amount of the 2,4-substituted regioisomer **53** was produced for subsequent alkylation studies. The alcohol **53** was submitted to the usual chlorination conditions to produce the corresponding chloride **62** (eq. 38). As with



(38)

compounds **46** and **54**, when the conversion of the chloride **62** to the Grignard reagent was attempted, the predominant product was found to be the furan dimer. Unfortunately, we were unable to convert chloride **62** to the corresponding tri-n-butylstannane in greater than 13% yield. A variety of techniques were examined in attempts to overcome this problem (see eqs. 24 and 30); however, the major isolated species was the reduction product shown in eq. 39.



(39)

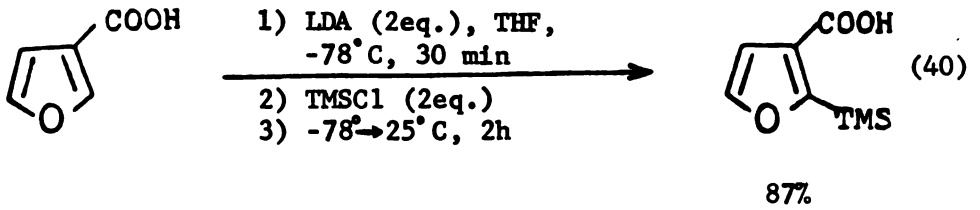
Despite the fact that we had some success in the alkylation of the sulfenyl organometallics, it became apparent that this X-group would not be satisfactory. The methylthio-furans were hydrolyzed only under extremely vigorous conditions and in similar studies, the phenylsulfenyl analog was found to be even more resistant to hydrolysis.

II. C. Silicon-substituted Furans

At the outset, a silyl-substituted furyl organometallic appeared to have a good chance for success because of the

precedent for the preparation of silyl furans and their conversion into butenolides.[59]

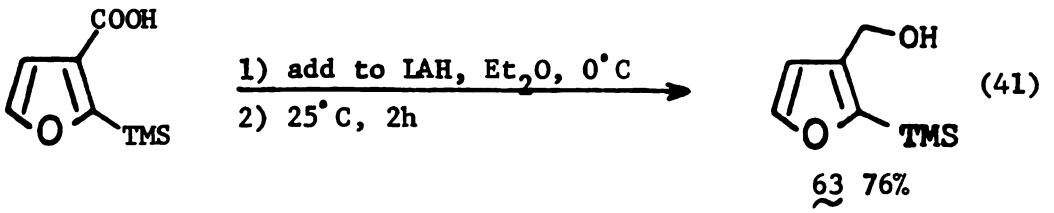
Although silyl furans have been prepared from furan or alkyl furans via standard metalation techniques,[46] a newer procedure allows direct preparation of a precursor to the 2,3-substituted silyl-furylmethyl organometallic. This was accomplished via the procedure of Knight[54] in the preparation of 2-trimethylsilyl-3-furan carboxylic acid in 87% yield (eq. 40). The initially formed



(40)

carboxylate oxyanion directs abstraction of the adjacent alpha furyl proton by coordination to a second equivalent of base. The dianion is quenched with trimethylsilyl chloride to give, exclusively, the 2,3-substituted regioisomer after hydrolysis of the silyl ester.

The trimethylsilyl-furancarboxylic acid was reduced to the corresponding alcohol **63** (76%), followed by conversion to the chloride **64**, (77%) (eq. 41 and 42).



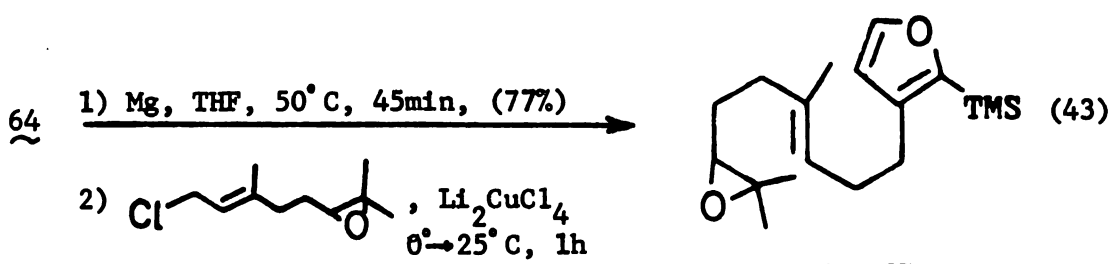
(41)

63 76%

(42)

64 77%

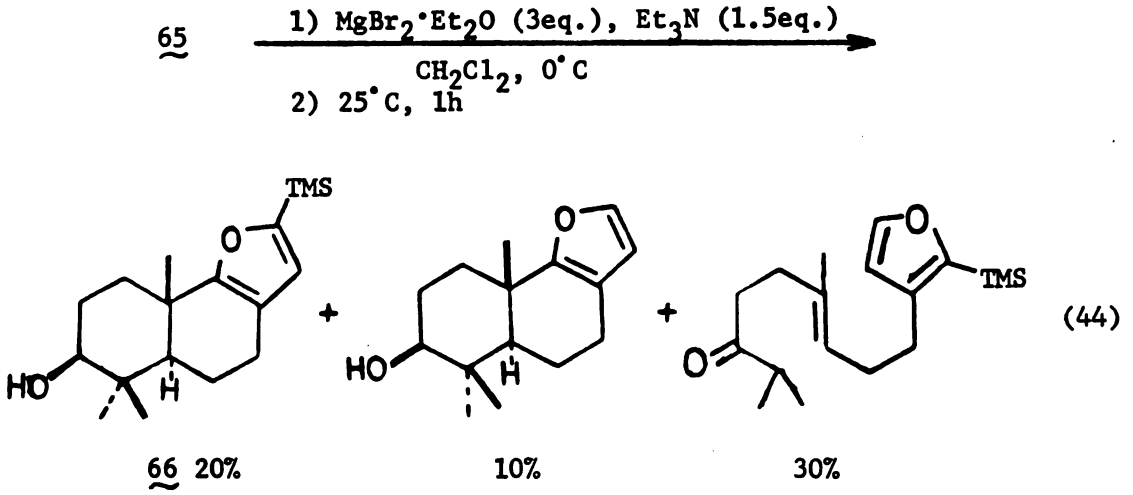
Unlike the sulfur-substituted analogs, silyl chloride **64**, was readily transformed into the corresponding Grignard reagent and alkylated in high yield with epoxygeranyl chloride[51,52] to afford **65** in 93% yield (eq. 43).



(43)

65 93%

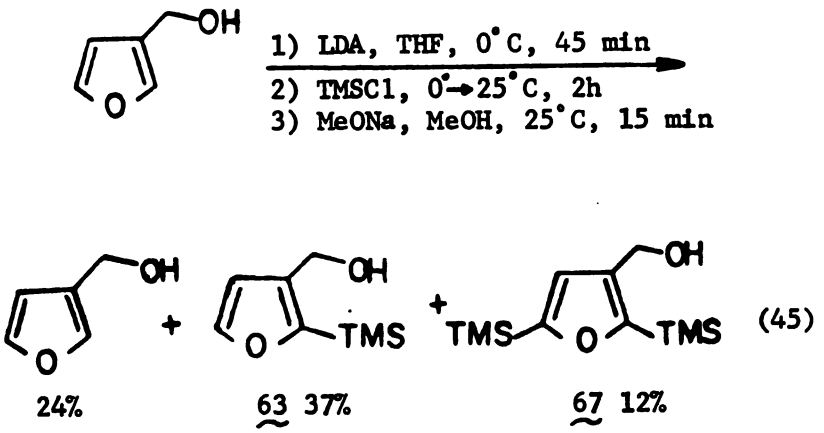
The cyclization of **65** was examined with several different Lewis acids including ZnI_2 Et_2O, $Ti(O\text{-}ipr)_3Cl$, $BF_3\text{-}Et_2O$, and $MgBr_2$ Et_2O, Et_3N. In all cases the solvent used was methylene chloride. Unfortunately, for all the Lewis acids employed, the predominant products were those of silicon loss. However, the magnesium bromide catalyst gave the best results as shown in eq. 44.



The majority of the cyclization product was accounted for by cyclized, desilylated product (10%) and uncyclized ketone (30%). The silicon-containing cyclization product **66**, isolated in 20% yield, is not the expected regioisomer however. By some as yet undetermined pathway, cyclization to the initially silicon-bearing position of the furyl ring, along with migration of the trimethylsilyl group to the remote alpha position, has occurred.

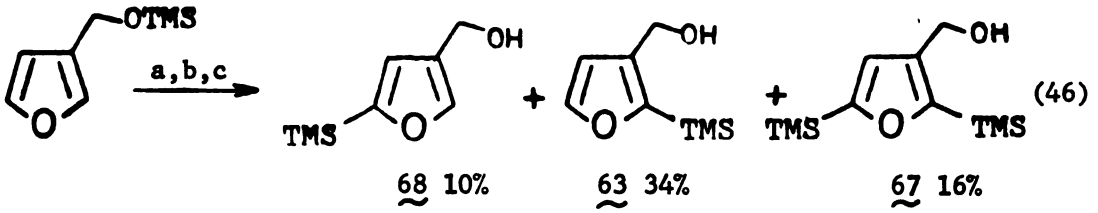
While these studies were underway, some potential pathways to a precursor of the regioisomeric 2,4-substituted silyl-furylmethyl organometallic were also being investigated. The most direct way of preparing beta-position functionalized silyl-furans is via silylation of the corresponding alpha-furylanions as shown in eq. 40. Hence, the major obstacle in the establishment of the 2,4-substitution pattern lies in the placement of the silyl moiety at a position remote from the strongly directing beta-position functionality.

As shown in eq. 40, the directing strength of the carboxylic acid group is such that none of the remote alpha silylated product is produced. Submission of 3-hydroxymethyl-furan to these reaction conditions led to the production of a mixture of products (eq. 45) including a bis-silyl furan **67**, but none of the desired 2-trimethylsilyl-4-hydroxymethyl-furan was observed.



(45)

To further reduce this directing effect, 3-hydroxymethyl-furan was protected as its trimethylsilyl ether and then submitted to the same silylation conditions. As is shown in eq. 46, the desired 2,4-disubstituted furan



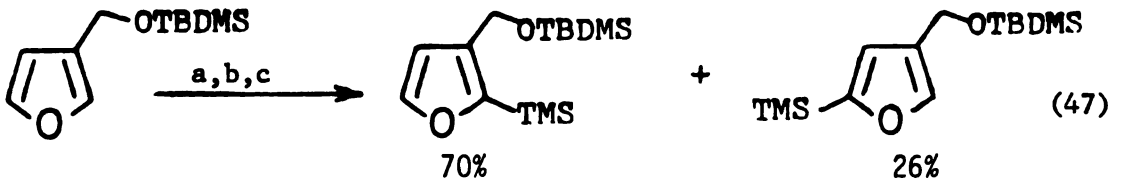
68 ~ 10% 63 ~ 34% 67 ~ 16%

a) LDA, THF, 0°C, 10 min b) TMSCl, 0°→25°C, overnight
c) MeONa, MeOH, 25°C, 15 min

68 was produced in low yield but in sufficient quantities to allow further experimentation.

To further decrease the coordinating effect of the 3-hydroxymethyl group beyond that of the trimethylsilyl ether above, the t-butyldimethylsilyl ether was prepared. Additionally, different metalation conditions were utilized in an attempt to decrease the amount of bis-silylated material produced.

As shown in eq. 47, silylation[48] of the t-butyldimethylsilyl ether afforded twice as much of the desired 2,4-substituted regioisomer as before (eq. 46) and none of the bis-silylated material.

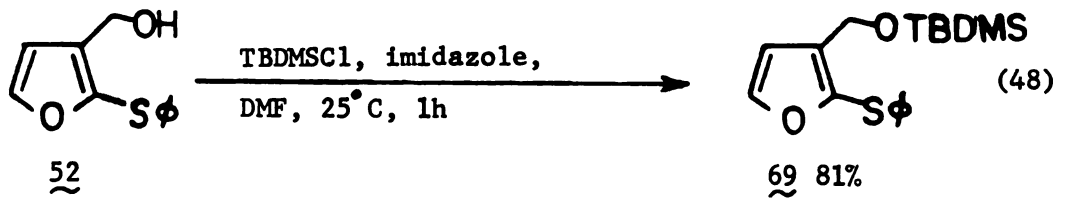


(47)

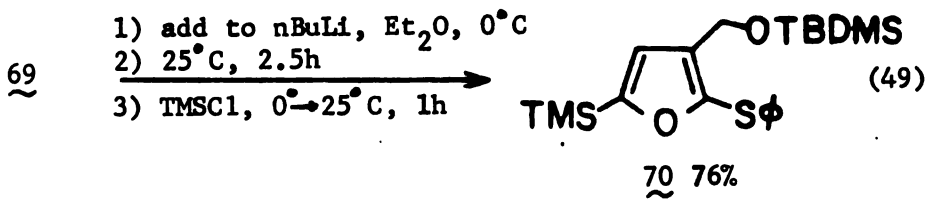
a) add to nBuLi, TMEDA, 0°C b) 25°C, 30 min
c) TMSCl, 0°→25°C, 1h

The measures taken above afforded the desired 2,4-substituted regioisomer only as a minor product. To overcome this problem, a previously discussed strategy (see eq. 37) was adopted in which the favored site of reaction is blocked by a removable group. Therefore, silylation was, at this point, attempted on a furyl substrate in which a substituent is placed at the favored alpha metalation position.

The t-butyldimethylsilyl ether of 2-phenylsulfenyl-3-hydroxymethyl-furan **69**, prepared from **52** as shown in eq. 48, was submitted to standard metalation conditions followed by quenching with trimethylsilyl chloride (eq. 49). A good yield (76%) of the desired silylated material **70** was obtained. The next step toward the 2,4-substituted silyl hydroxymethyl furan is removal of the phenylsulfenyl substituent by desulfurization with Rancy Nickel. However, in practice, it was found necessary to

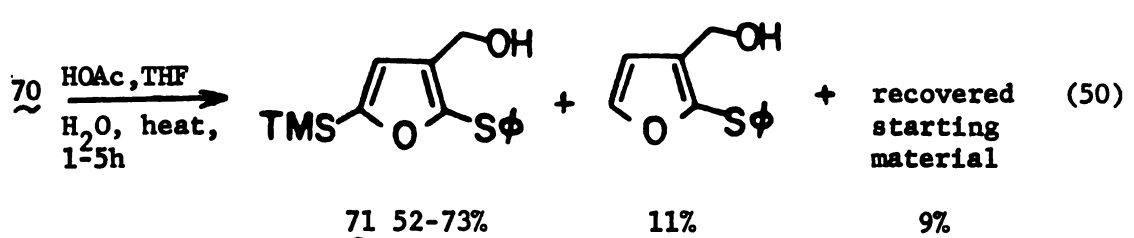


52 69 81% (48)



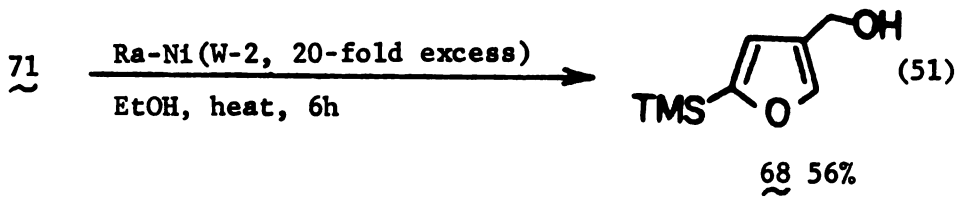
69 70 76% (49)

cleave the t-butyldimethylsilyl ether before the desulfurization could efficiently be carried out. Carefully controlled conditions were required to avoid concurrent C-desilylation. Attempted fluoride desilylation was unsuccessful; however, cleavage with aqueous HOAc in THF did provide **71** in reasonable (52-73%) yield (eq. 50).



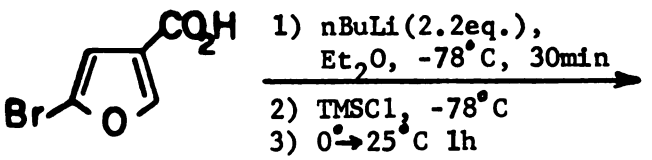
71 52-73% 11% 9% (50)

The silyl ether cleavage product **71** was then subjected to Raney Nickel[55] desulfurization (eq. 51) to afford a 56% yield of the desired 2-trimethylsilyl-4-hydroxymethyl furan **68**. This reaction also suffered some reproducibility problems and was extremely sensitive with regard to the time of exposure to Raney-Nickel.

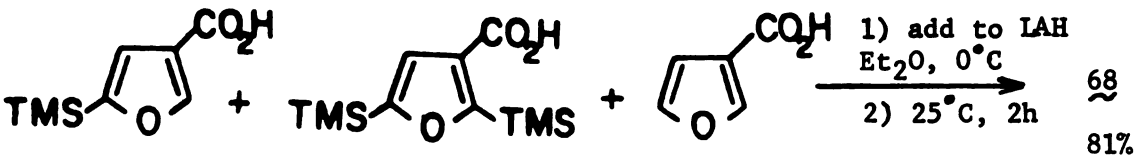


Although this procedure does provide the desired 2,4-substituted organometallic precursor **68**, the reaction sequence is relatively long (5 steps from 3-hydroxymethyl-furan) and the overall yield is low (16%). This strategy is essentially identical to that reported by Goldsmith and Liotta; however, in our hands, the yields were lower than reported.[56]

A more efficient process for the preparation of **68** was devised as shown in eq. 52. 2-Bromo-4-furoic acid, prepared by the direct bromination of furoic acid with



(52)

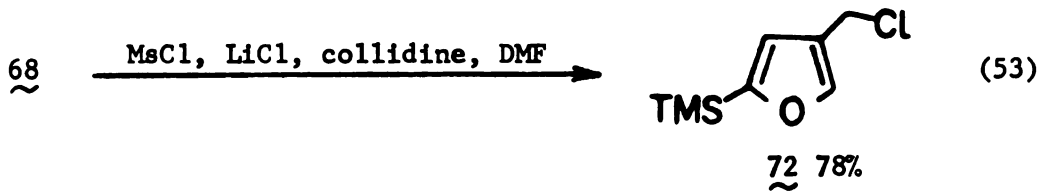


63% 15% 15%

pyridinium hydro-perbromide in 60% yield,[57] was submitted to lithium-halogen exchange conditions followed by quenching with trimethylsilyl chloride. A 63% yield of the corresponding trimethylsilyl furoic acid was obtained along with some bis-silylated and reduction products. This crude mixture was directly reduced (LAH) to afford an 81% yield of the desired 2,4-substituted furan **68**; 31% overall yield (3 steps from furoic acid).

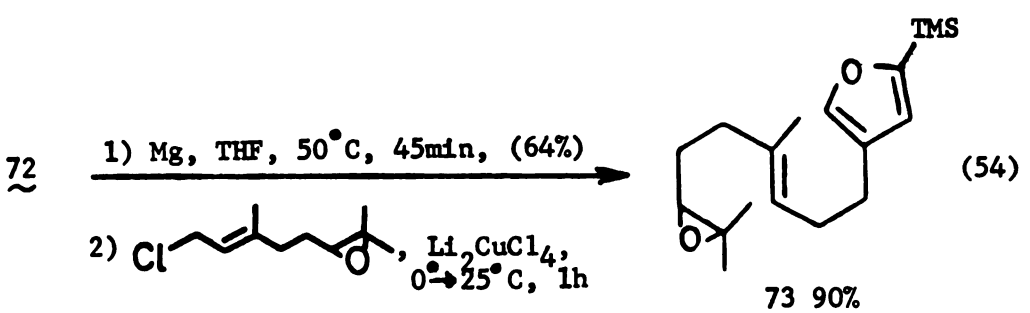
With a precursor to the silyl-appended 2,4-substituted organometallic reagent readily available, alkylation and cyclization studies were undertaken. 2-Trimethylsilyl-4-hydroxymethyl-furan **68** was smoothly

transformed to the corresponding chloride as shown in eq. 53. Like its regioisomer **64**, chloride **72** was readily converted into the Grignard reagent and alkylated in high



(53)

yield with epoxygeranyl chloride[51] as shown in eq. 54.



(54)

As before (see eq. 44), similar cyclization studies were undertaken with **73**, and as previously noted, the same cyclization conditions ($MgBr_2 \bullet Et_2O$ (3 eq.)), Et_3N (1.5 eq.) gave the best results. Analysis of the cyclization products demonstrated that the materials isolated were identical to those previously obtained (eq. 44) and the overall yield was similar. The desired cyclization product **66**, which previously was the unexpected regioisomer, was also produced here, albeit in only 20% yield.

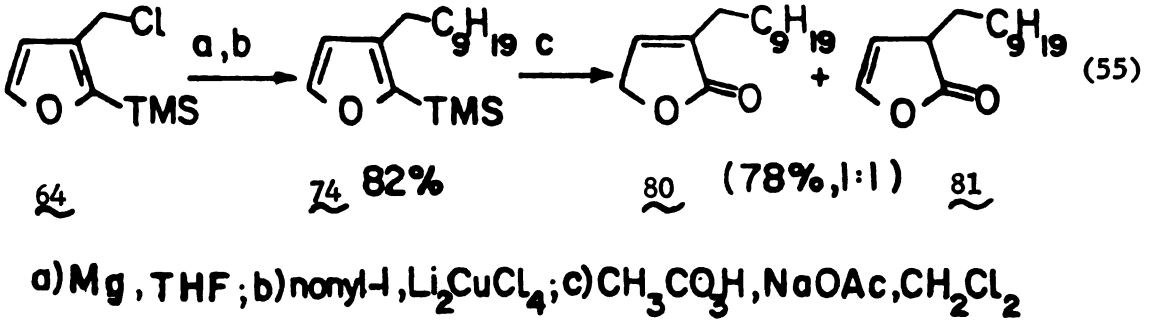
We must conclude that the trimethylsilyl-furans are too acid labile to be efficiently utilized in Lewis acid catalyzed cyclization reactions. As an alternative, some variants on trialkylsilyl, such as triethylsilyl or methyldiisopropylsilyl, which should be less acid sensitive, have been considered and may be investigated in the future.

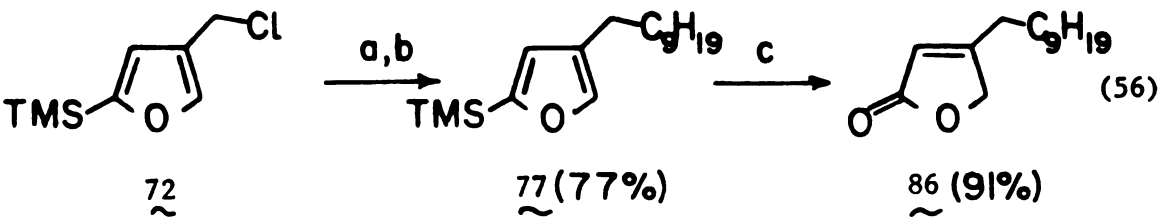
Although considerable success was enjoyed in alkylation reactions of silyl-appended organometallics, it is apparent that the trimethylsilyl variant will not meet all of the requirements for a general methodology as set forth in the introduction. However, these silyl-substituted furans should serve admirably as precursors to 3- and 4-alkyl-2-(5H)-furanones.

As shown in eqs. 55 and 56, the chlorides **64** and **72** were converted to the corresponding Grignard reagents and coupled in high yield with nonyl-iodide to afford the alkylation products **74** and **77**, respectively.

In principle, the direct oxidation of a 3-substituted furan will provide the corresponding butenolide;[58a,b] however, regio-chemical ambiguities usually render this approach impractical for general synthetic applications. A more suitable solution to this problem is afforded via oxidation of the corresponding 2- or 5-silylated, 3-alkylfurans. As has been demonstrated by Kuwajima[59] and recently employed by Schultz,[60] Goldsmith and Liotta,[56] a trimethylsilyl group can serve to regio-specifically direct the introduction of oxygen providing the corresponding 3- or 4-alkyl-2(5H)-furanones.

Utilizing the procedure reported by Kuwajima,[59] the alkylation products **74** and **77** were smoothly converted into their corresponding butenolides **80**, **81** and **86**.





(56)

72 77 (77%) 86 (91%)

a-c) as in equation 55

Other representative examples designed to examine the relative rate of furan vs. remote olefin oxidation as a function of the degree of alkene substitutions are presented in Figure 9. As shown, good to excellent yields of coupled silyl-furans are realized in all cases; and if the alkene is less than trisubstituted, the major or exclusive oxidation product is the result of attack at the furyl residue.

These methods provide access to a wide variety of 2- and 3-substituted butenolides depending on the alkyl halide used. According to the organizational scheme presented in the introduction, these products can be considered as type **A** (Figure 1) furans with access to all of the oxidation states **7-10**.

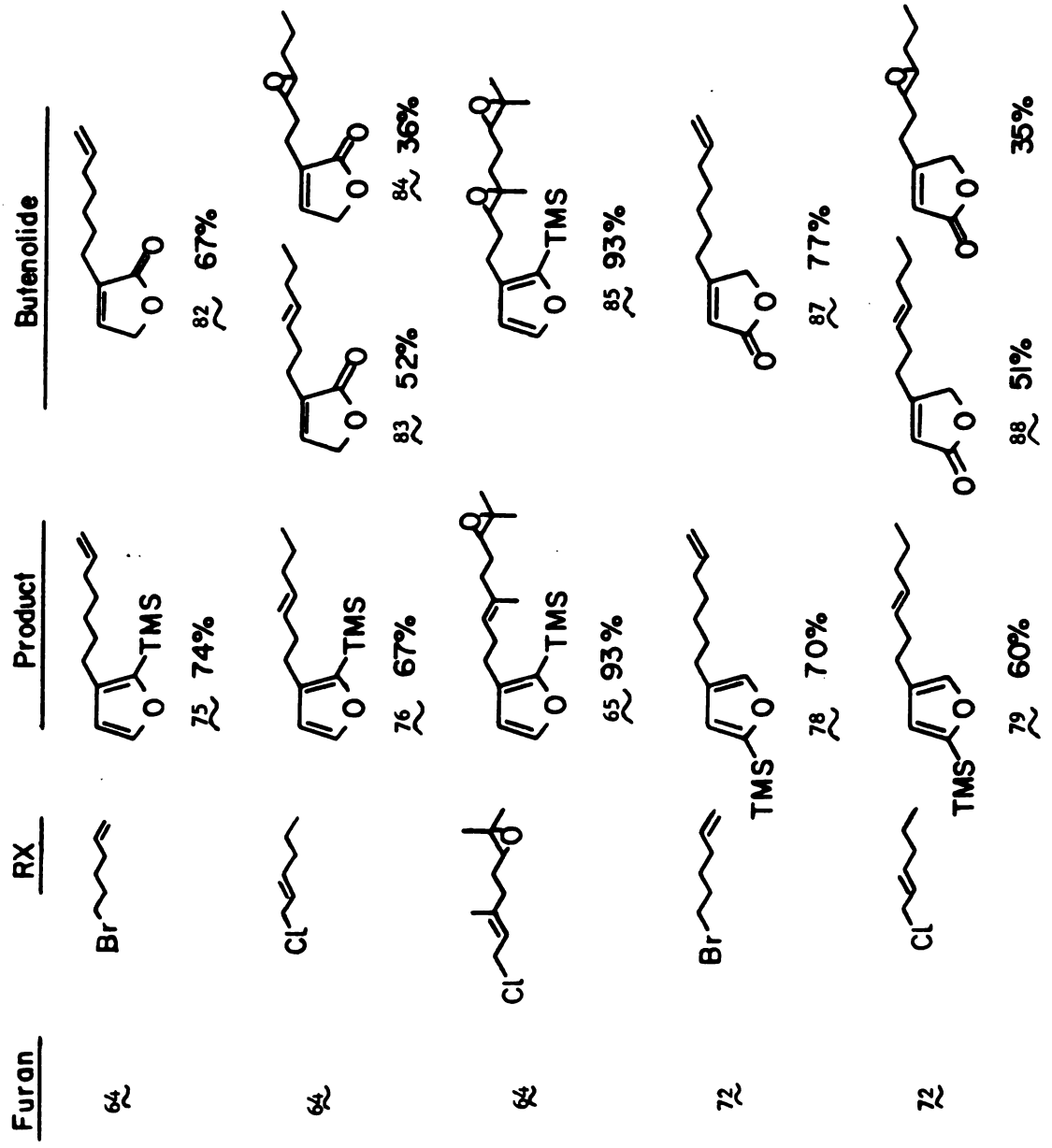


Figure 9.
2-Trimethylsilyl-3- and 4-alkyl furans and their 2(5H)-furanone oxidation products.

III. An Approach to the Synthesis of (±)-Aphidicolin

III. An Approach to the Synthesis of (±)-Aphidicolin

The novel, tetracyclic diterpenoid aphidicolin (see Figure 10) was isolated[61] in 1972 from cultures of the fungus **cephalosporium aphidicola** (Petch). Subsequently, intensive biological activity studies were undertaken[62] when it was discovered that aphidicolin was an antibiotic that possessed strong in vitro activity against Herpes simplex type 1 and 2 viruses.

Because relatively few antiviral substances are known and due to the novel structure of the molecule, there has been intense interest among synthetic organic chemists in aphidicolin. As a result, several total syntheses of aphidicolin have been reported.[63a,b,c,d]

The Corey synthesis[63c] utilizes a polyene cyclization to establish the A and B rings of aphidicolin with the appropriate stereochemistry. This strategy very efficiently affords access to the basic carbocyclic skeleton upon which most of the published approaches then work to append the sterically congested spirocycle. The construction of the D-ring is very neatly accomplished by McMurry.[63a] He efficiently attacks the problem via an intermediate cyclopentenone (see Figure 10). With this in mind, a study directed towards a formal, total synthesis of aphidicolin, utilizing

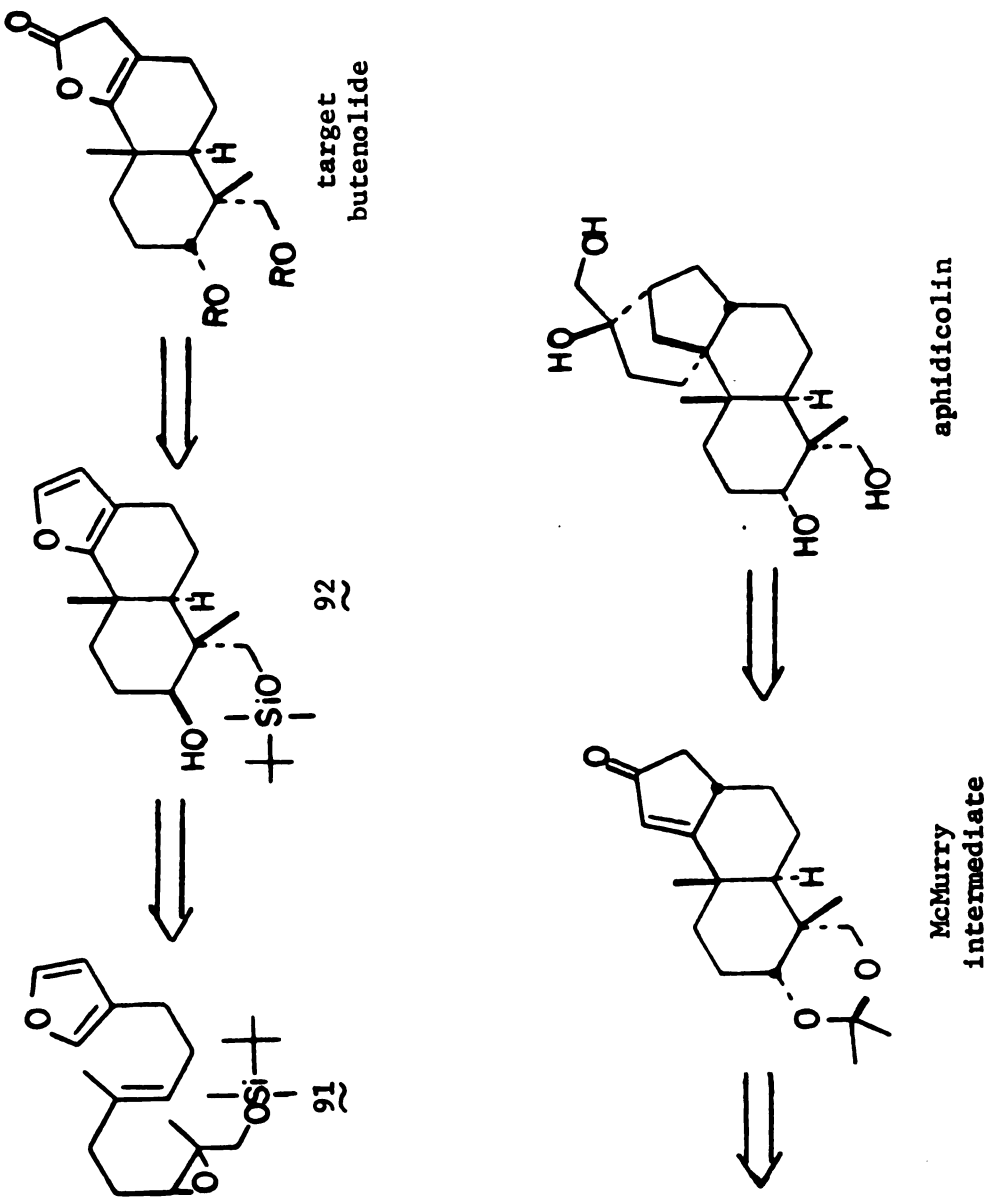


Figure 10.
Proposed retrosynthetic scheme to (±)-aphidicolin.

the methodology explored in this thesis, was undertaken. This study would exploit; i) a furan-terminated polyolefin cyclization to rapidly establish the carbocyclic nucleus of aphidicolin, followed by ii) a furan to butenolide to cyclopentenone conversion yielding the McMurry intermediate. A retrosynthetic scheme of this strategy is shown in Figure 10. Cyclization of **91** would afford **92** in which the A and B rings of the target have been established. With a furyl moiety integrated into the cyclization product, an efficient transformation of it into the McMurry intermediate should be possible via the target butenolide.

As discussed in the introduction, it would have been desirable to have a substituent appended to the furyl ring which could be carried through the cyclization to enable facile conversion to a butenolide. Unfortunately, a suitable substituent which could survive cyclization conditions has not yet been found. However, since in this case, the desired orientation of the cyclization is produced without a directing furyl substituent, it should be possible to append the substituent after the cyclization has occurred. Although less efficient than introduction as part of an X-substituted alkyl furan, this strategy should serve well in the present case.

An analysis of the substituents located at C(3) and C(4) of aphidicolin suggests, as in the Corey synthesis, that an ω-oxygenated geranyl halide, after alkylation and

cyclization would yield the proper relative stereochemistry at C(4). In addition, should the cyclization substrate possess a 6,7-epoxide, then the cyclized product would have an oxygen at C(3), however opposite in stereochemistry to that desired (see Figure 11). Another desirable feature of this construction is the potential for an asymmetric synthesis should an optically pure geranyl synthon be employed.[64]

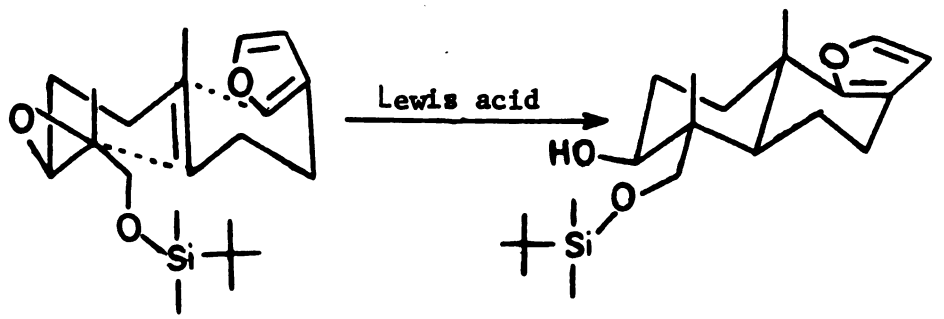
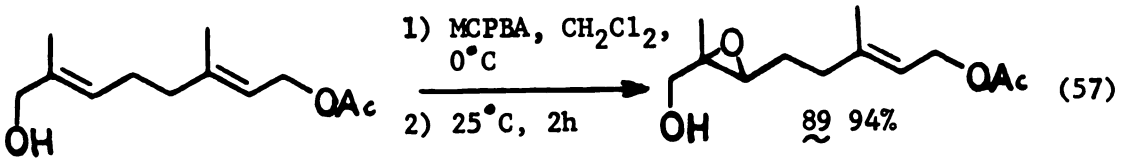


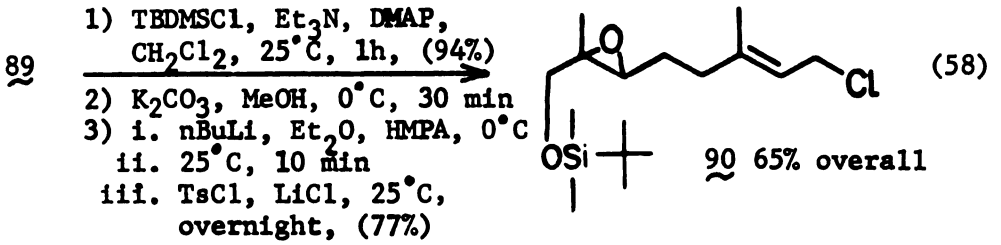
Figure 11.
Furan terminated, epoxide initiated olefin cyclization.

(E)-8-Hydroxygeranylacetate, prepared from geranyl acetate[65] when submitted to Henbest epoxidation, afforded **89** in 94% yield. After protection of the hydroxyl as a TBDMS ether, the acetate functionality was cleaved with

potassium carbonate in methanol followed directly by chlorination via the procedure of Stork[52] to afford chloride **90** in 65% yield overall from **89**.

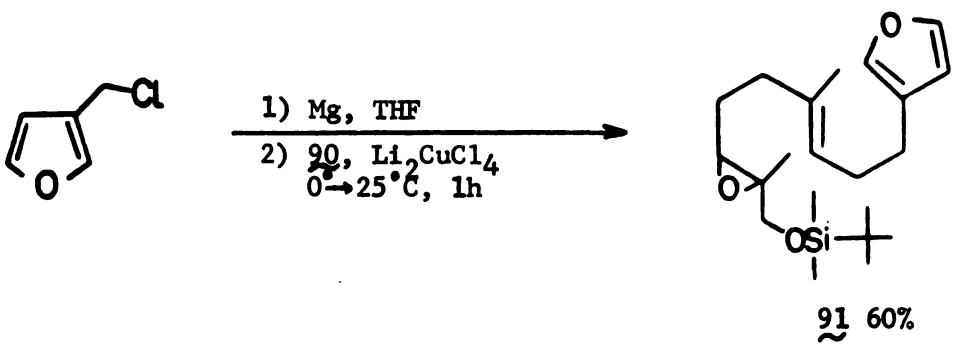


89 94% (57)



89 **90** 65% overall (58)

The modified epoxygeranyl chloride **90** was coupled with the Grignard reagent produced from 3-furylmethyl chloride in the usual way[8] to afford a 60% yield of coupling product **91** (eq. 59). Several Lewis acids were examined



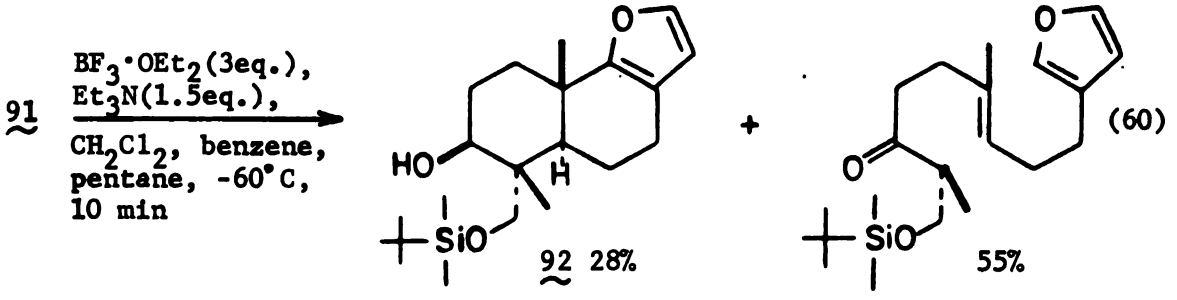
91 60%

(59)

(see eq. 44) in the attempted cyclization of **91**, but only two were found to give a significant amount of desired product **92**. As is shown in eq. 60, boron trifluoride etherate catalyst in the presence of triethylamine gave the best results as a 28% yield of desired cyclization product **92**. Although related cyclizations are usually conducted solely in methylene chloride solvent, in this case, it was discovered that the addition of benzene and pentane to the reaction solvent almost completely inhibited the formation of a mono-cyclic side product which created difficulties in the purification of **92**.

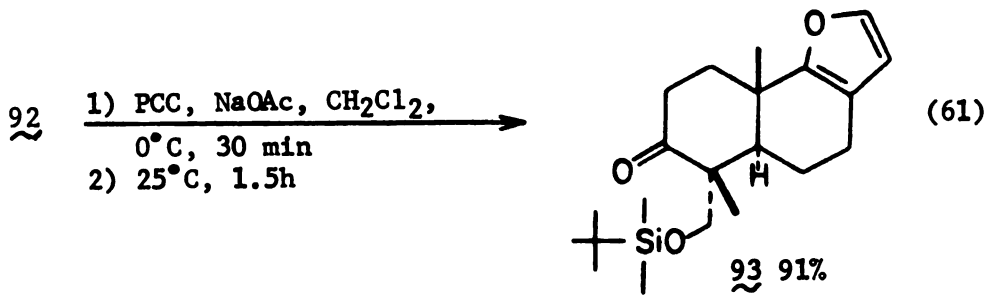
Unfortunately, the major product of this reaction appeared to be an uncyclized, epoxide-opened ketone as shown in eq. 60. Although considerable effort was expended

in an attempt to increase the yield, we were unable to obtain greater than a 30% yield of **92**. Titanium tri-isopropoxy chloride was the only other Lewis acid tried that afforded a significant amount of **92**. However, the yield was only about half of that obtained with $BF_3 \bullet OEt_2$ and much more of the troublesome monocyclic product was produced.

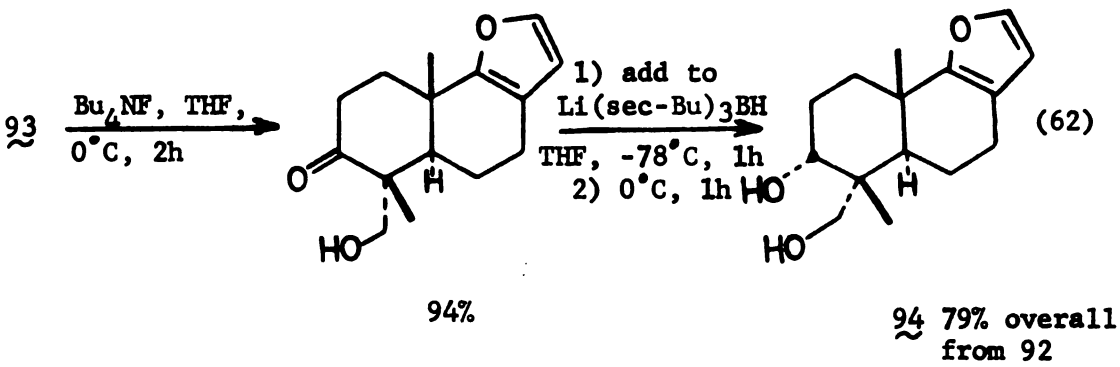


As shown in Figure 10, the configuration of the hydroxyl at C(3) of the cyclization product **92** is opposite to that of aphidicolin. Several techniques for the direct inversion of the hydroxyl in **92** were examined at this stage of the synthesis including the Mitsunobu reaction [66] and nitrite displacement[67] of the mesylate of **92**. Unfortunately, the highly hindered nature of the C(3) hydroxyl precluded any success with these measures.

The inversion was accomplished in a manner identical to that utilized in the Corey[63c] and McMurry[63a] syntheses of aphidicolin as illustrated in eqs. 61 and 62. The C(3) hydroxyl of **92** was oxidized to the corresponding ketone



(61)

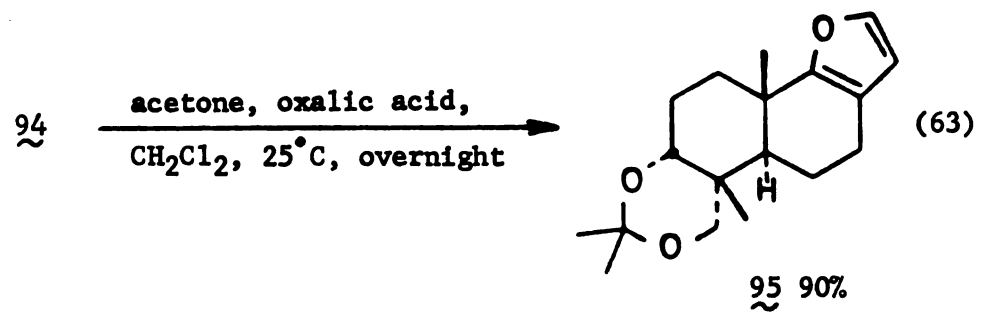


(62)

93 in 91% yield (eq. 61). Desilylation of **93** with tetra-n-butyl ammonium fluoride (94%) and immediate reduction with L-selectride, to avoid decomposition of the intermediate aldol, afforded the diol **94** in a 79% overall yield from **92**.

With the desired A-ring functionality of aphidicolin now intact, the conversion of **94** to the McMurry intermediate was undertaken. As discussed above, this was to be approached via the appendage of a substituent to the furyl moiety and subsequent elaboration of the target (see Figure 10).

With diol **94** in hand, the most direct route to the McMurry intermediate appeared to lie in protection of the diol system as the acetonide followed by metalation and silylation of the furyl moiety. As shown in eq. 63, the acetonide **95** was smoothly produced in 90% yield.



(63)

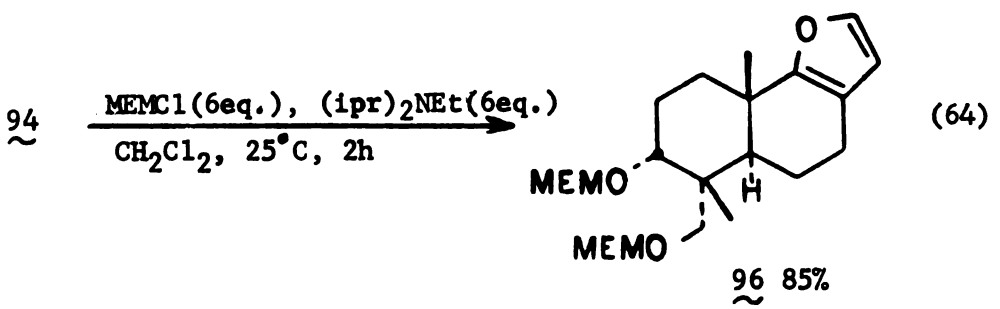
However, the metalation and silylation of **95** turned out to be quite problematic. Initially, the procedure of Schultz[60] was applied to the problem. The metalation was carried out by adding 1 equivalent of nBuLi to a solution of **95** in THF at 0°C. The solution was stirred for 2h at 0°C followed by addition of TMSCl and gradual warming to

25°C overnight. Upon workup and analysis, only recovered starting material was obtained. The reasons for the failure of this procedure are not clear inasmuch as the substrate Schultz successfully silylated is rather closely related to **95**. Additionally, these reaction conditions have worked in this lab when applied to a different substrate.

It was assumed that the problem was not in the alkylation step, but in difficulty with the metalation. Attempting to overcome this, a series of progressively more vigorous metalation procedures were examined. When metalation was attempted by stirring of **95** with 2 equivalents of n-BuLi in THF at 25°C for 1 h, solvent decomposition became a problem. The same conditions were then applied with Et_2O as the solvent with added TMEDA but attempted silylation yielded none of the desired silylated product. The material that was recovered was slightly different from the starting material and spectral analysis suggested that the acetonide moiety had been altered.

Some simple studies of the silylation of furyl-lithium derivatives revealed that alkylation with TMSCl is considerably slower in Et_2O than in THF. Hence, metalation of **95** was attempted as before with 2 equivalents of n-BuLi and added TMEDA but with only hexane solvent. After stirring for 2 h at 25°C, the reaction was cooled to 0°C and THF was added. After the addition of TMSCl, the reaction was analyzed indicating that much decomposition had occurred.

At this point, it was concluded that the acetonide moiety was consuming base. We hoped that a different protecting group here might circumvent the above difficulties and so the bis-methoxyethoxymethyl ether[68] **96** was prepared from the diol **94** (eq. 64). Our initial attempts to metalate **96** again indicated that the protecting group was not stable to the reaction conditions.



(64)

As a last resort, silylation of the diol **94** was attempted. This was carried out by stirring **94** with 4 equivalents of nBuLi and TMEDA in hexane at 25°C for 30 min. Subsequently, the solution was cooled to 0°C and THF was added followed by TMSCl. Analysis of the reaction mixture showed no furyl silylation; however, O-silylation at the A-ring hydroxyls was observed.

In conclusion, we have observed that the furyl moiety of this molecule is unusually difficult to metalate. A solution to this problem might lie in the proper selection of the A-ring diol protecting functionality. Alternatively, the furyl nucleus might be selectively and carefully brominated. A simple metal-halogen exchange would lead to the silylated equivalent of **96** after treatment with TMSCl. These possibilities are currently being examined in our laboratories.

EXPERIMENTAL

EXPERIMENTAL

General: Tetrahydrofuran (THF) was dried by distillation under nitrogen from sodium benzophenone ketyl; methylene chloride was dried by distillation under nitrogen from calcium hydride; N-N dimethylformamide (DMF) was dried by distillation at reduced pressure from phosphorous tentoxide; hexamethylphosphoramide (HMPA) was dried by distillation at reduced pressure from calcium hydride; pyridine was dried by distillation under nitrogen from calcium hydride; diisopropyl amine was dried by distillation under nitrogen from calcium hydride. Petroleum ether refers to the 30-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Mallinkrodt, Inc., St. Louis, Missouri, and used as received. n-Butyl lithium in hexane was purchased from Aldrich Chemical Company , Milwaukee, Wisconsin and titrated by the method of Watson and Eastham.[26] All reagents were used as received unless otherwise stated; all reactions were performed under argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrometer or a Perkin-Elmer Model 167 spectrometer with polystyrene

as standard. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian T-60 at 60 MHz, a Varian CFT-20 at 80 MHz, or a Bruker WM-250 spectrometer at 250 MHz as mentioned in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (δ scale) from internal standard tetramethylsilane. Data are reported as follows: chemical shifts (multiplicity: s = singlet, brs = broad singlet, d = doublet, t = triplet, m = multiplet, coupling constant (Hz), integration). Electron impact (EI/MS, 70eV) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system.

Flash chromatography was performed according to the procedure of Still et.al.[69] using Whatman silica gel and eluted with the solvents mentioned. Analytical thin-layer chromatography was run on either Macherey-Nagel Polygram SIL G/UV_{254} pre-coated plastic sheets or Brinkman Instruments SIL G/UV pre-coated glass plates. Spots were visualized by either dipping into a solution of Vanillin (1.5g) in absolute ethanol (100 mL) and concentrated sulfuric acid (0.5 mL) and heating with a heat gun or spraying with a 5% solution of molybdophosphoric acid in absolute ethanol and heating to 120°C.

1-(1-Bromoethyl)-cyclohexene 17. To a mechanically stirred solution of cyclohexenyl ethanol[20,21] (3.0g, 24mmol) in dry Et_2O (100 mL) was added carbon tetrabromide (19.9g, 60 mmol) followed by triphenylphosphine (14.8g, 60 mmol).[19] After 30 minutes, the solution became bright yellow and warm. Upon termination of exothermicity, the solution was refluxed for 8h. After cooling to room temperature, pentane (50 mL) was

added, followed by stirring for 10 minutes. The solution was then cooled to 0°C and the resulting precipitate was removed by filtration through celite. After removal of solvent *in vacuo*, the crude product was purified by chromatography on a column of silica gel (60-230 mesh, 25g, hexane-Et_2O, 2:1) followed by distillation through a 20 cm vigreux column, $BP_{2.0mm}$ = 67°C to provide 4.07g (90%) of bromide **17** as a water white liquid. ^1H NMR (60 MHz) δ 5.75 (brs, 1H), 4.60 (q, J=7Hz, 1H) 2.10 (brm, 4H), 1.75 (d, J=7Hz, 3H), 1.60 (brm, 4H); IR (neat) 2960, 2880, 1660, 1450, 1185, 915, 740 cm^{-1}; CI-MS (CH_4) 189 (M^++1, 50.6), 187 (M^++1, 46.4), 145 (7.5), 125 (17.6), 109 (base).

1-(-chloroethyl)-cyclohexene 18. To a magnetically stirred solution of cyclohexenyl ethanol[20,21] (1.26g, 10 mmol) in dry carbon tetrachloride (20 mL) cooled to 0° (ice water) was added tri-n-butyl phosphine (3.04g, 15 mmol).[19] After addition, the reaction mixture was reluxed for 2.5h then pentane (20 mL) was added and stirring was continued for 5 minutes. A heavy bottom layer separated out from which the top layer was decanted. Removal of solvent and distillation of the residue through a vigreux column, BP_{5mm} = 60°C, afforded 0.68g (47%) of **18** as a viscous liquid. ^1H NMR (250 MHz) δ 5.77 (brs, 1H), 4.54 (q, J=7Hz, 1H), 2.05 (m, 4H), 1.60 (m, 4H), 1.59 (d, J=7Hz, 3H); IR (neat) 2960, 2890, 1670, 1445, 1380, 1230, 1040, 675 cm^{-1}; CI-MS (CH_4) 145 (M^++1, 3.2), 119 (9.9), 109 (base), 63 (19.8).

Coupling of Grignard Reagent 16 with Bromide 17. To a solution of the furyl-methyl Grignard reagent **16** (3.9 mmol) (titer determined by titration[26]) in dry THF (5 mL) at 0°C (ice water) was added bromide **17** (0.57g, 3.0 mmol) in dry THF (1 mL) dropwise followed by Li_2CuCl_4 catalyst (0.1M in THF, 0.12 mL, 0.012 mmol). The solution was stirred at 0°C for 10 minutes then quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was cast into Et_2O/hexane 1:1 (50 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL) and saturated aqueous NaCl (50 mL). The organic phase was dried (Na_2SO_4). Concentration <u>in vacuo</u> provided the crude product as a pale yellow liquid which was purified by chromatography on a column of silica gel (60-230 mesh, 50g, Et_2O-hexane, 1:99) to provide 0.34g (60%) of coupling product R_f 0.6 (Et_2O-hexane, 5:95). Spectral analysis (integration of vinyl protons in proton NMR below) showed this to be an approximately 3:2 mixture of S_N2 vs. S_N2' like products, respectively. ^1H NMR (250 MHz) δ 7.30 (s, 2H), 7.18 (s, 2H), 6.37 (s, 1H), 6.23 (s, 1H), 5.40 (brs, 0.6H, S_N2), 5.18 (dq, J=2,7Hz, 0.4H, S_N2'), 1.43 (dd, J=2,7Hz, 1.2H, S_N2'), 1.00 (d, J=7Hz, 1.8H, S_N2); IR (neat) 2940, 2885, 1505, 1455, 1385, 1030, 785 cm^{-1}; EI/MS (70eV) 190 (M^+, 35.8), 175 (8.9), 109 (base).

Coupling of Grignard Reagent 16 with Chloride 18. As in the coupling of **16** and **17**, **16** (3.9 mmol) and **18** (0.43g, 3.0 mmol) provided 0.27g (47%) of **19** after purification as the sole product, with the following spectral data. ^1H NMR (60

MHz) δ 7.15 (d, J=2Hz, 1H), 7.00 (s, 1H), 6.05 (d, J=2Hz, 1H), 5.15 (brs, 1H), 2.35 (m, 2H), 1.85 (m, 4H), 1.50 (m, 4H), 1.00 (d, J=6Hz, 3H); IR (neat) 2940, 2860, 1670, 1505, 1455, 1385, 1030, 880 cm^{-1}; EI-MS (70eV) 190 (M^+, 37.0), 175 (8.1), 109 (base).

Furan-3,4-dimethanol 22.[18c] A solution of diethyl-furan-3,4-dicarboxylate **21** (18.0g, 0.085 mmol) in dry Et_2O (150 mL) was added dropwise to $LiAlH_4$ (7.60g, 0.20 mmol) in dry Et_2O (300 mL) at 0°C (ice water) over 1h. After addition, the solution was refluxed for 1h and allowed to stand at 25°C overnight. The reaction was carefully quenched with 20% aqueous Rochelle Salt (200 mL). The ether layer was separated, the aqueous phase saturated with NaCl, and then extracted with Et_2O/EtOAc, 9:1 (3 x 150 mL). The conbined organic phases were dried (Na_2SO_4), concentrated <u>in vacuo</u> and distilled ($BP_{0.15mm}$ = 110°C, lit.[18c] BP_{2mm} = 130°C) to afford 8.16g (77%) of **22** as a viscous water white fluid. Spectral data was consistent with the literature.[18c]

Furan-3,4-dimethanol,mono-THP-ether 23.[18c] Furan-3,4-dimethanol **22** (6.10g, 47 mmol) was added to a solution of dihydropyran (3.95g, 47 mmol) and pyridinium paratoluenesulfonate[23] (1.18g, 4.7 mmol) in dry CH_2Cl_2 (200 mL) and stirred for 4h at 25°C. The solution was then diluted with Et_2O (200 mL) and washed with half saturated aqueous NaCl (100 mL). The organic phase was dried (Na_2SO_4) and concentrated <u>in vacuo</u> to afford 10.86g of crude product which contained three components by TLC. The desired mono-THP ether was separated from

the bis-THP ether side product and unreacted diol by flash chromatography on a column of silica gel (60-230 mesh, 300g, CH_2Cl_2/EtOAc, 6:1) as the second compound to be eluted. This was performed in two runs on the same bed of silica gel providing 4.90g (50%) of mono-THP ether **23**, $BP_{0.15mm}$ = 125°C (no literature value was reported[18c]), 3.40g (25%) of bis-THP ether and 1.50g (25%) of unreacted furan dimethanol. Spectral data of the mono-THP ether was consistent with the literature.[18c]

3-Chloromethyl-4-tetrahydropyranyloxymethylfuran 24. To the mono-THP-ether **23** (1.0g, 4.8 mmol) was added collidine (0.70 mL, 5.3 mmol) followed by a solution of dry LiCl (0.41g, 9.6 mmol) in dry DMF (10 mL). The solution was cooled to 0°C (ice water) and methanesulfonyl chloride (0.41 mL), 5.3 mmol) was added over 15 minutes.[25] The resulting solution became a bright yellow suspension which was stirred for 2h at 0°C, and at 25°C for 1h. The reaction mixture was diluted with Et_2O-pentane, 1:1 (150 mL) and washed with saturated aqueous $NaHCO_3$ (150 mL) and saturated aqueous $Cu(NO_3)_2$ (150 mL). The organic phase was dried (Na_2SO_4), concentrated <u>in vacuo</u> and purified by bulb-to-bulb (Kugelrohr) distillation, oven 140°C (0.02 mm) to provide 0.85g (77%) of chloride **24** as a slightly yellow fluid. ^1H NMR (250 MHz) δ 7.46 (d, J=Hz, 1H), 7.40 (d, J=2Hz, 1H), 4.72 (t, J=4Hz, 2H), 4.64 (s, 1H), 4.58 (s, 1H), 4.56 (s, 2H), 3.92 (m, 1H), 3.56 (m, 1H), 1.60 (brs, 6H); IR (neat) 2940, 2860, 1560, 1450, 1270, 1140, 1035 cm^{-1}; EI-MS (70eV) 230 (M^+, 1.7), 146 (9.4), 129 (98.4), 85 (base).

Lactarol-THP-ether 27. A solution of 3,-chloromethyl-4-tetrahydropyranyloxymethyl furan **24** (0.50g, 2.2 mmol) and dibromoethane (2 drops) in dry THF (1 mL) was added over 5 minutes to activated magnesium turnings (0.060g, 2.5 mmol) covered with dry THF (4 mL) at 25°C. After addition was complete, the internally measured temperature of the reaction began to rise and at 30°C a cooling bath was introduced so that the temperature was maintained at 10°-15°C as the magnesium was consumed. This occurred over 2h at which time titration[26] of an aliquot of the Grignard solution showed formation to be quantitative. A portion of the Grignard solution (0.38 M, 3 mL), 1.1 mmol) was cooled to 0°C (ice water) and 4,4-dimethyl-1-(1-chloroethyl)-cyclopentene[18c] (0.16g, 1.0 mmol) in dry THF (1 mL) was added via syringe followed immediately by Li_2CuCl_4 catalyst (0.1 M in THF, .04 mL, .004 mmol). The solution was stirred at 0°C for 30 minutes then allowed to warm to 25°C and worked up as before (see coupling of **16** and **17**) to afford 0.48g crude product. Purification was accomplished by flash chromatography on a column of silica gel (230-400 mesh, 100g, Et_2O-PE, 5:95) to afford 0.24g (75%) of lactarol-THP-ether **27**, R_f 0.46 (Et_2O-PE, 1:9). ^1H NMR (250 MHz) δ 7.36 (s, 1H), 7.17 (s, 1H), 5.22 (brs, 1H), 4.64 (s, 1H), 4.59 (s, 1H), 4.33 (dd, J=12,4Hz, 1H), 3.90 (m, 1H), 3.55 (m, 1H), 2.62 (dd, J=14,6Hz, 1H), 2.47 (ddt, J=6,7,7Hz, 1H), 2.33 (dd, J=14,7Hz, 1H), 2.09 (brs, 4H), 1.60 (brm, 6H), 1.06 (s, 3H), 1.05 (s, 3H), 1.00 (d, J=7Hz, 3H); IR (neat) 2970, 2890, 1550, 1465, 1368, 1125, 1030 cm^{-1}; EI-MS (70eV)

318 (M^+, 1.7), 300 (1.2), 233 (5.0), 216 (19.0), 123 (18.8), 85 (base).

Lactarol 28. A solution of lactarol-THP-ether **27** (2.68g, 8.4 mmol) in absolute ethanol (800 mL) and pyridinium toluenesulfonate[23] (2.68g, 10.6 mmol) was heated to 55°C for 3h. After cooling to 25°C, the ethanol was removed in vacuo and the residue diluted with Et_2O (200 mL). After washing with half saturated brine (200 mL), the organic phase was separated and dried (Na_2SO_4). Removal of solvent afforded 1.87g (95%) of lactarol **28** which required no further purification. ^1H NMR (250 MHz) δ 7.35 (s, 1H), 7.16 (s, 1H), 5.22 (brs, 1H), 4.51 (s, 2H), 2.62 (dd, J=14,6Hz, 1H), 2.47 (ddt, J=6,7,7Hz, 1H), 2.33 (dd, J=14,7Hz, 1H), 2.09 (brs, 4H), 1.57 (brs, 1H), 1.06 (s, 3H), 1.04 (s, 3H), 1.00 (d, J=7Hz, 3H); IR (neat) 3380, 2970, 2890, 1545, 1465, 1365, 1150, 1055, 805 cm^{-1}; EI-MS (70eV) 234 (M^+, 11.1), 216 (14.8), 201 (17.1), 160 (15.0), 123 (base).

Lactaral 15. To a solution of lactarol **28** (1.0g, 4.3 mmol) in methylene chloride-pentane, 1:1 (100 mL), was added "activated" MnO_2[28] (23g). The suspension was stirred overnight and the solid was removed by filtration through celite. Concentration in vacuo provided the crude product which was purified by flash chromatography on silica gel (60-230 mesh, 70g, Et_2O-PE, 1:4) to afford 0.96g (96%) of lactaral **15**, R_f 0.62 (Et_2O-PE, 1:4), as a slightly yellow liquid. Spectral data was identical to that kindly provided by Dr. G. Magnusson.[18c] ^1H NMR (60 MHz) δ 9.76 (s, 1H), 7.80 (d, J=2Hz, 1H), 7.07 (brs,

1H), 5.10 (brs, 1H), 2.60 (m, 2H), 2.40 (m, 1H), 2.02 (brs, 4H), 1.06 (s, 3H), 1.04 (s, 3H), 1.00 (d, J=7Hz, 3H); IR (neat) 2990, 2870, 2770, 1700, 1545, 1480, 1155, 1055, 825, 762 cm^{-1}; EI-MS (70eV) 232 (M^+, 9.1), 214 (12.8), 199 (19.1), 123 (base), 81 (84.5).

Lactaral ethylene acetal 30. To a biphasic mixture of anhydrous ethylene glycol (0.80g, 12.9 mmol) and lactaral **15** (0.30g, 1.3 mmol) in dry benzene (10 mL) was added para-toluenesulfonic acid (0.02g, 0.1 mmol). The mixture was warmed to 60°C for 3h, then after cooling the 25°C, was cast into ether (20 mL), washed with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and dried (Na_2SO_4). Removal of solvent <u>in vacuo</u> afforded 0.30g (84%) of lactaral ethylene acetal **30**, (R_f identical to **29**) which required no further purification. ^1H NMR (60 MHz) δ 7.32 (d, J=2Hz, 1H), 7.05 (brs, 1H), 5.72 (s, 1H), 5.13 (brs, 1H), 3.92 (m, 4H), 2.50 (m, 3H), 2.09 (brs, 4H), 1.06 (s, 3H), 1.04 (s, 3H), 1.00 (d, J=7Hz, 3H); IR (neat) 2970, 2890, 1550, 1465, 1368, 1125, 1030 cm^{-1}; EI-MS (70eV) 276 (M^+, 1.5), 258 (1.3), 214 (15.3), 123 (base).

Attempted cyclization of Lactaral 28. A solution of lactarol **28** (0.09g, 0.43 mmol), formic acid (99%, 4.3 mL) and cyclohexane (4.3 mL) was stirred at 25°C for 1h. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), and dried (Na_2SO_4). Removal of solvent afforded 0.08g (71%) of lactarol formate **31**. ^1H NMR (60 MHz) δ 7.95 (s, 1H), 7.31 (s, 1H), 7.10 (s, 1H), 5.15 (brs, 1H), 3.98 (s, 2H), 2.39 (m, 3H), 2.05 (brs, 4H), 1.05 (brs, 9H); IR

(neat) 2980, 2865, 1735, 1555, 1470, 1373, 1170, 1060 cm^{-1}; EI-MS (70eV) 262 (M^+, 6.6), 247 (0.7), 216 (23.8), 201 (13.4), 123 (base).

Lactaroic Acid 32. Lactaral **15** (0.18g, 0.8 mmol) was stirred for 12h in a solution containing sodium cyanide (0.25g, 5.0 mmol), "activated" manganese dioxide[28] (5.0g), acetic acid (0.1 mL), 1.5 mmol) and methanol (10 mL). The methanol was then removed in vacuo and the residue diluted with Et_2O (50 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 0.16g of crude methyl lactarate. The ester was hydrolyzed by refluxing for 12h in a solution of THF (10 mL) containing 5 equivalents of 20% aqueous NaOH solution. Acidification of the reaction medium followed by extraction with Et_2O (50 mL) provided an organic phase which was dried (Na_2SO_4). Removal of solvent afforded 0.14g lactaroic acid **32** (71% overall) which was not purified further. ^1H NMR (60 MHz) δ 12.34 (brs, 1H), 7.99 (s, 1H), 7.16 (s, 1H), 5.16 (brs, 1H), 2.61 (m, 3H), 2.02 (brs, 4H), 1.06 (s, 3H), 1.04 (s, 3H), 1.00 (d, J=7Hz, 3H); IR (neat) 3100, 2980, 2640, 1695, 1540, 1435, 1310, 1245, 1150 cm^{-1}; EI-MS (70eV) 248 (M^+, 26.4), 233 (21.4), 215 (3.6), 149 (5.2), 123 (base).

Lactaroyl Chloride 33. A solution of lactaroic acid **32** (0.38g, 1.5 mmol) and oxalyl chloride (0.30g, 3.5 mmol) in dry benzene (10 mL) was stirred at 25°C for 12h. Removal of solvent in vacuo afforded 0.32g (80%) of lactaroyl chloride **33** as a brown oil which was not purified further. ^1H NMR (60 MHz) δ 7.99 (s, 1H), 7.16 (s, 1H), 5.16 (brs, 1H), 2.61

(m, 3H), 2.02 (brs, 4H), 1.06 (s, 3H), 1.04 (s, 3H), 1.00 (d, J=7Hz, 3H); IR (neat) 2980, 2890, 1775, 1535, 1470, 1390, 1160, 818, 687 cm^{-1}; EI-MS (70eV) 266 (M^+, 5.1), 251 (4.5), 231 (4.7), 215 (2.6), 123 (base).

Reaction of 34 with $(EtO)_3CH/SnCl_4$. Preparation of 35. To a solution of 2-trimethylsiloxy-3,5-dimethyl-furan **34** (0.20g, 1.1 mmol) and triethyl orthoformate (0.16g, 1.1 mmol) in dry methylene chloride (2 mL) cooled to -40°C was added a catalytic amount of stannic chloride (four drops). The reaction temperature was gradually raised to 10°C over a period of 2h. The mixture was cast into Et_2O (25 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 25 mL) and brine (25 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 0.22g (93%) of **35**. ^1H NMR (60 MHz) δ 6.99 (q, J=2Hz, 1H), 4.30 (s, 1H), 3.65 (m, 4H), 1.90 (d, J=2Hz, 3H), 1.41 (s, 3H), 1.23 (m, 6H); IR (neat) 2985, 2900, 1765, 1665, 1455, 1375, 1125, 1080 cm^{-1}; CI-MS (CH_4) 215 (M^++1, 1.0), 169 (8.6), 141 (4.9), 103 (base).

3-Bromo-2(5H)-furanone 36. To a solution of 2-(5H)-furanone (11.2g, 0.13 mol) in dry carbon tetrachloride (40 mL) was added bromine (21.9g, 0.137 mol) at 25°C. The solution was stirred until most of the bromine had been consumed and became light orange in color (2h). The solvent and excess bromine were then removed <u>in vacuo</u> to afford 32.4g (100%) crude yield of the 2,3-dibromobutyrolactone as a red fluid. The material was subjected to dehydrohalogenation without further purification. To a solution of the dibromide (32.4g, 0.134 mol) in

dry benzene (250 mL) was added pyridine (51.8 mL, 0.64 mol). The solution was heated under reflux for 3h, then after removal of most of the solvent in vacuo, the residue was diluted with methylene chloride (200 mL). After washing with 1N HCl (2 x 200 mL), the organic phase was dried (Na_2SO_4) and removal of solvent afforded 20g of an orange solid. The crude product was purified by filtration through a column of silica gel (60-230 mesh, 100g, methylene chloride-hexanes, 1:1) followed by recrystallization from CCl_4-CH_2Cl_2 to give 13.9g (66%) of **36** as yellow-green flakes (MP = 59°C). ^1H NMR (60 MHz) δ 7.76 (s, 1H), 4.97 (s, 2H); IR ($CHCl_3$) 3065, 1785, 1620, 1360, 1230, 1170, 1068, 1003 cm^{-1}; EI-MS (70eV) 164 (M^+, 30.0), 162 (M^+, 33.6), 135 (70.0), 133 (77.6), 107 (40.9), 105 (42.0), 39 (base).

2-Trimethylsiloxy-3-bromofuran 37. To the 2-bromobutenolide **36** (1.50g, 9.3 mmol) in dry THF (70 mL) was added a catalytic amount of zinc chloride (10 mg) followed by triethylamine (1.6 mL, 11.0 mmol). The solution was stirred at 25°C for 1.5h. After the suspended solids had settled, the solution was transferred via syringe to a dry flask, and the solvent was removed by distillation. Continued distillation under reduced pressure afforded 0.82g (37%) of **37** as a cloudy liquid (BP_{10mm} = 65°C). ^1H NMR (60 MHz) δ 6.78 (d, J=3Hz, 1H), 6.23 (d, J=3Hz, 1H), 0.33 (s, 9H); IR (neat) 2980, 1645, 1522, 1380, 1260, 1065, 865 cm^{-1}; EI-MS (70eV) 164 (M^+, 15.4), 162 (M^+, 15.9), 135 (41.9), 133 (42.2), 107 (21.2), 105 (23.9), 85 (base).

2-tButyldimethylsiloxy-3-bromo-furan 38. To a solution of the 2-bromobutenolide **36** (3.0g, 18.5 mmol) in dry THF (14 mL), under argon was added a catalytic amount of zinc chloride (10 mg) followed by tbutyldimethylsilyl chloride (2.88g, 19.1 mmol) and triethylamine (2.76 mL, 19.1 mmol). The solution was stirred at 25°C for 4.5h. After removal of most of the solvent in vacuo, the residue was diluted with Et_2O-pentane, 1:1 (150 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 150 mL). The discolored organic phase was shaken with a generous amount of activated charcoal followed by filtration through celite. The solution was dried (Na_2SO_4) and removal of solvent gave a red fluid which was purified by bulb-to-bulb (Kugelrohr) distillation, oven temp. = 100°C (1 mm), to afford 2.5g (49%) of **38**. ^1H NMR (60 MHz) δ 6.76 (d, J=3Hz, 1H), 6.23 (d, J=3Hz, 1H), 1.00 (m, 9H), 0.27 (s, 3H), 0.50 (s, 3H); IR (neat) 2990, 2950, 2890, 1640, 1520, 1480, 1380, 1255, 1065, 1010, 860 cm^{-1}; EI-MS (70eV) 278 (M^+, 6.7), 276 (M^+, 7.9), 193 (3.5), 191 (3.9), 139 (5.1), 137 (5.0), 73 (base).

Reaction of Lithiated 38 with Benzaldehyde. Preparation of 39. To a solution of 2-tbutyldimethylsiloxy-3-bromo-furan **38** (0.28g, 1.0 mmol) in dry Et_2O (4 mL) was added n-butyl lithium (1.3 M in hexane, 0.77 mL, 1.0 mmol) dropwise at -78°C. The solution was warmed to 0°C and stirred for 30 minutes, then benzaldehyde (0.1 mL, 1.0 mm) in dry Et_2O (1 mL) was added over 5 minutes. The reaction was stirred for 1h at 0°C then quenched with saturated aqueous $NaHCO_3$ (1 mL). The solution was diluted with Et_2O-pentane, 1:1 (50 mL) and washed

with saturated aqueous $NaHCO_3$ (2 x 50 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo afforded 0.27g (90%) of **39** as an orange-yellow liquid. ^1H NMR (60 MHz) δ 7.26 (m, 5H), 6.69 (d, J=2Hz, 1H), 6.09 (d, J=2Hz, 1H), 5.68 (s, 1H), 2.10 (m, 1H), 0.98 (m, 9H), 0.24 (m, 6H); IR (neat) 3410, 2950, 2890, 1645, 1530, 1420, 1260, 1010, 912, 860, 796, 707 cm^{-1}; EI-MS (70eV) 304 (M^+, 4.5), 287 (1.1), 247 (11.4), 189 (0.4), 172 (26.1), 75 (base).

2-Methylthio-5-nbutyl-furan 41. To a solution of n-butyl lithium (2.6 M in hexane, 15.3 mL, 40 mmol) and tetramethyl-ethylene diamine (6.03 mL, 40 mmol) in dry Et_2O (50 mL) at 0°C (ice water) was added 2-n-butyl furan · **40** (5.0g, 40 mmol) via syringe. The resulting solution was warmed to 25°C and stirred for 30 minutes followed by cooling to 0°C (ice water) and addition of dimethyl disulfide (3.6 mL, 40 mmol) via syringe. The resulting solution was allowed to warm to 25°C with stirring overnight. The reaction was then diluted with Et_2O (300 mL) and washed with water (300 mL), 5% aqueous NaOH (300 mL), and saturated aqueous NH_4Cl (300 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo followed by distillation, BP_{5mm} = 90°C, afforded 5.0g (73%) of **41** as a yellow liquid. ^1H NMR (60 MHz) δ 6.25 (d, J=3Hz, 1H), 5.85 (m, 1H), 2.55 (t, J=7Hz, 2H), 2.29 (s, 3H), 1.44 (m, 4H), 0.90 (m, 3H); IR (neat) 2980, 2910, 1600, 1510, 1465, 1130, 1020, 985, 805 cm^{-1}; EI-MS (70eV) 170 (M^+, 27.5), 127 (base), 113 (5.0), 99 (12.0).

Attempted Hydrolysis of 41. Preparation of 42. A solution of 10% sulfuric acid (5 mL), 95% ethanol (5 mL), and 2-methylthio-5-nbutyl-furan **41** (0.5g, 2.9 mmol) was heated under reflux overnight, cooled to 25°C, then diluted with Et_2O (50 mL) and washed with water (50 mL). After drying, the organic phase (Na_2SO_4) and removal of solvent provided 0.44g of crude product. Purification by chromatography on a column of silica gel (60-230 mesh, 50g, Et_2O-hexane, 1:9) provided 0.40g (75%) of **42** as a colorless liquid. ^1H NMR (60 MHz) δ 4.11 (q, J=6Hz, 2H), 2.50 (m, 2H), 1.40 (m, 8H), 1.00 (m, 6H); IR (neat) 3000, 2910, 1750, 1380, 1200, 1040, 830 cm^{-1}; EI-MS (70eV) 186 (M^+, 2.8), 171 (0.35), 156 (2.6), 141 (26.6), 101 (52.2), 85 (61.5), 57 (base).

2-Methylthio-3-hydroxymethyl-furan 44 and 2-Methylthio-4-hydroxymethyl-furan 45. To a solution of n-butyl lithium (2.6 M in hexane, 48.0 mL, 125 mmol) and tetramethylene diamine (18.9 mL, 125 mmol) in dry Et_2O (150 mL) at 0°C (ice water) was added 3-hydroxymethyl-furan (5.9g, 60 mmol) in dry Et_2O (5 mL) via syringe. The solution was warmed to 25°C and stirred for 1h, during which time a white precipitate formed. The mixture was cooled to 0°C and dimethyl disulfide (5.37 mL, 60 mmol) was added dropwise via syringe. The solution was slowly warmed to 25°C while stirring overnight. The reaction mixture was diluted with Et_2O (150 mL) and washed with water (250 mL), 10% aqueous NaOH (250 mL), 1 N aqueous HCl (250 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded 6.0g crude product which was purified

by distillation through a vigreux column, $BP_{0.2mm}$ = 75°C, to yield 4.64g (53%) of 2-methylthio-3-hydroxymethyl-furan **44** as a colorless liquid. A second fraction from the distillation, $BP_{0.2mm}$ = 85°C yielded less than 5% of the regioisomeric 2-methylthio-4-hydroxymethyl-furan **45**. The following is spectroscopic data for **44**. ^1H NMR (60 MHz) δ 7.35 (d, J=2Hz, 1H), 6.40 (d, J=2Hz, 1H), 4.50 (bds, 2H), 2.55 (m, 1H), 2.35 (s, 3H); IR (neat) 3400, 2955, 2910, 1495, 1435, 1320, 1150, 1055, 1010, 900, 775, 745 cm^{-1}; EI-MS (70eV) 144 (M^+, 50.1), 128 (base).

2-Methylthio-3-chlormethyl-furan 46. On the same scale and utilizing a procedure identical to that used in the preparation of chloride **24**, **46** was prepared from alcohol **44** in 79% crude yield as a slightly yellow liquid. The chloride could not be purified by distillation due to its thermal instability; however, the crude material was found to be sufficiently pure to be utilized in subsequent reactions. ^1H NMR (60 MHz) δ 7.34 (d, J=2Hz, 1H), 6.42 (d, J=2Hz, 1H), 4.50 (s, 2H), 2.33 (s, 3H); IR (neat) 3000, 2970, 2920, 1500, 1450, 1290, 1155, 1065, 730 cm^{-1}; EI-MS (70eV) 164 (M^+, 20.7), 162 (M^+, 44.0), 149 (4.6), 127 (base).

Reaction of Grignard Reagent of 46 with Epoxygeranyl chloride;[51,52] Preparation of 2,6-Dimethyl-6-vinyl-7-(2-methylthio-3-furyl)-hept-2-ene-2,3-epoxide 47. In a Grignard entrainment procedure, to magnesium powder (0.15g, 6.2 mmol) in dry THF (10 mL) was added a solution of 2-methylthio-3-chloromethyl-furan **46** (0.50g, 3.1 mmol) and ethylene dibromide (0.27

mL, 3.1 mmol) in dry THF (20 mL) over 1h so that reflux was maintained. After the addition was complete, the solution was stirred at 60°C until most of the magnesium had been consumed (30 min.). The solution was then cooled to 0°C (ice water) and Li_2CuCl_4 catalyst (0.1 M in THF, 0.3 mL, 0.03 mmol) was added followed by epoxygeranyl chloride[51,52] (0.58g, 3.1 mmol) in dry THF (2 mL). The resulting solution was warmed to 25°C over the course of 1h. After most of the solvent was removed in vacuo, the residue was diluted with Et_2O/pentane, 1:1 (100 mL) and washed with water (100 mL), saturated aqueous NH_4Cl (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 0.90g of crude product. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 100g, Et_2O-hexane, 2.5:7.5) to provide 0.18g (21%) of **47**, R_f 0.51 (Et_2O-hexane, 1:9). Isolation of a lower-lying component provided 0.50g (64%) of dimerized **46**, the Wurtz product **48**. ^1H NMR (60 MHz) δ 7.36 (m, 1H), 6.36 (m, 1H), 5.81 (dd, J=18,10Hz, 1H), 5.14 (dd, J=14,2Hz, 1H), 4.92 (dd, J=8,2Hz, 1H), 2.71 (bdt, J=8Hz, 1H), 2.33 (m, 3H); IR (neat) 2990, 2950, 1615, 1495, 1450, 1390, 1375, 1320, 1250, 1190, 1150, 1120, 1080, 1030, 1005, 980, 925, 900, 710 cm^{-1}; EI-MS (70eV) 264 (M^+-16, 4.1), 127 (97.2).

2-Methylthio-3-tri-n-butylstannylmethyl-furan 49. According to the procedure of Still[38] to LDA prepared in the usual way (3.5 mmol), in dry THF (5 mL) chilled to 0°C (ice water) was added tri-n-butyl stannane (0.82 mL, 3.1 mmol) and the resulting

solution was stirred for 15 minutes at 0°C. The resulting tri-n-butyl stannyl lithium solution was then added via syringe to 2-methylthio-3-chloromethyl-furan **46** (0.50g, 3.1 mmol) in dry THF (5 mL) cooled to -25°C (dry ice-isopropanol). The resulting solution was stirred at -25°C for 1h, then warmed to 25°C over the course of 1h. The solution was then diluted with Et_2O-pentane, 1:1 (150 mL) and washed with water (100 mL), saturated aqueous NH_4Cl (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded 1.3g crude product. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 50g, hexanes) to provide 0.38g (31%) of **49**, R_f 0.23 (pentane). ^1H NMR (60 MHz) δ 7.20 (d, J=2Hz, 1H), 6.03 (d, J=2Hz, 1H), 2.25 (s, 3H), 2.03 (s, 2H), 1.33 (m, 18H), 0.91 (m, 9H); EI-MS (70eV) 363 (5.1), 362 (4.7), 361 (36.8), 360 (12.8), 359 (26.5), 358 (9.8), 357 (14.5), all M^+-Bu; 127 (base, M^+-$SnBu_3$).

2,6-Dimethyl-9-(2-methylthio-3-furyl)-non-6-ene-2,3-oxirane 50. To a solution of 2-methylthio-3-tri-n-butyl-stannylmethyl-furan **49** (0.32g, 0.8 mmol) in dry THF (3 mL) cooled to -78°C (dry ice-isopropanol) was added nBuLi (2.6 M in hexane, 0.31 mL, 0.8 mmol). The solution was stirred for 30 minutes at -78°C and after warming to 0°C (ice water) a solution of anhydrous magnesium bromide (0.18g, 1.0 mmol) in dry THF was added followed by Li_2CuCl_4 catalyst (0.1 M in THF, 0.1 mL, 0.01 mmol). Epoxygeranyl chloride[51,52] (0.15g, 0.8 mmol) in dry THF (1 mL) was then added via syringe and the solution was

warmed to 25°C over the course of 1h. After most of the THF had been removed *in vacuo*, the residue was diluted with Et_2O-pentane, 1:1 (50 mL) and washed with water (50 mL), saturated aqueous NH_4Cl (50 mL) and saturated $NaHCO_3$ (50 mL). Drying of the organic phase (Na_2SO_4) and removal of solvent afforded 0.40g crude product. The crude material was purified by chromatography on a column of silica gel (60-230 mesh, 50g, Et_2O-hexanes, 2.5:97.5) to afford 0.02g (9%) of **50**, R_f 0.31 (Et_2O-hexanes, 1:9). ^1H NMR (60 MHz) δ 7.35 (d, J=2Hz, 1H), 6.24 (d, J=2Hz, 1H), 5.03 (bdm, 1H), 2.66 (m, 1H), 2.20 (m, 3H), 1.97 (m, 2H), 1.60 (m, 9H), 1.24 (m, 6H); IR (neat) 2960, 2890, 1490, 1450, 1385, 1320, 1255, 1150, 1115, 1080, 1060, 980, 900, 755 cm^{-1}; EI-MS (70eV) 264 (M^+-16, 9.9), 207 (17.2), 127 (base).

Reaction of Lithiated 49 with Benzaldehyde. Preparation of 51. To a solution of 2-methylthio-3-tri-n-butylstannylmethyl furan **49** (0.33g, 0.8 mmol) in dry THF (5 mL) was added nBuLi (2.6 M in hexane, 0.31 mL, 0.8 mmol) at -78°C (dry ice-isopropanol). The solution was stirred at -78°C for 30 minutes during which time it became dark orange in color. Benzaldehyde (0.085g, 0.8 mmol) in dry THF (1 mL) was then added via syringe and the solution changed to a light yellow color. Stirring was continued and the temperature was raised to 25°C over the course of 1h. The solution was then diluted with Et_2O-pentane, 1:1 (100 mL) and washed with H_2O (100 mL), saturated aqueous NH_4Cl (100 mL) and brine (100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent *in vacuo* afforded

a two-phase solution. The upper (colorless) phase (tin containing products) was separated from the lower (orange) phase. The lower layer provided 0.15g (80%) of **51** which was not purified further. ^{1}H NMR (60 MHz) δ 7.25 (bds, 6H), 6.15 (m, 1H), 4.80 (m, 1H), 3.40 (m, 1H), 2.80 (m, 2H), 2.20 (s, 3H); EI-MS (70eV) 233 (M^+, 32.4), 217 (12.1), 127 (base).

Preparation of 2-Phenylthio-3-hydroxymethyl-furan 52 and 2-Phenylthio-4-hydroxymethyl-furan 53. To a solution of nBuLi (10.2 M in hexane, 30.3 mL, 0.31 mmol) and tetramethylethylenediamine (47.1 mL, 0.31 mmol) in dry Et_2O (125 mL) at 0°C (ice water) was added 3-hydroxymethyl-furan (14.7g, 0.15 mmol) in dry Et_2O (30 mL) via syringe over a period of 15 minutes. The solution was then warmed to 25°C and stirred for 1h followed by cooling to 0°C. A solution of diphenyl disulfide (34.3g, 0.16 mmol) in dry Et_2O (125 mL) was then added over the course of 1h. The resulting solution was gradually warmed to 25°C and stirred overnight. The reaction was diluted with Et_2O (1000 mL) and washed with water (750 mL), 1N HCl (750 mL), 1N NaOH (750 mL), water (750 mL) and brine (750 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> gave a cloudy, viscous orange oil which was filtered through a column of silica gel (60-230 mesh, 250g, EtOAc-petroleum ether, 3:7) to provide 25.9g of a golden yellow liquid. The product mixture was purified by preparative HPLC (Waters Prep 500, 2-columns, EtOAc-hexanes, 3:7, 250 mL/min.) to afford 20.7g (67%) of 2-phenylthio-3-hydroxymethyl-furan **52** and 4.6g (15%) of 2-phenylthio-4-hydroxymethyl-furan **53**

as colorless liquids. Spectral data for **52**: ^{1}H NMR (60 MHz) δ 7.42 (d, J=2Hz, 1H), 7.06 (s, 5H), 6.48 (d, J=2Hz, 1H), 4.52 (s, 2H), 2.28 (bds, 1H); IR (neat) 3400, 2960, 2900, 1585, 1510, 1480, 1445, 1395, 1165, 1150, 1075, 1055, 1030, 900, 880, 805, 750, 700 cm^{-1}; MS (EI/70eV) 206 (M^+, base), 189 (9.5), 176 (6.6), 160 (22.0), 115 (33.9), 69 (46.2). Spectral data for **53**: ^{1}H NMR (60 MHz) δ 7.37 (s, 1H), 7.12 (s, 5H), 6.63 (s, 1H), 4.42 (s, 2H), 2.65 (bds, 1H); IR (neat) 3400, 2970, 2910, 1585, 1505, 1480, 1445, 1390, 1175, 1130, 1075, 1030, 985, 925, 880, 750, 700 cm^{-1}; EI-MS (70eV) 206 (M^+, base), 188 (11.9), 176 (11.6), 160 (28.1), 115 (49.5), 69 (57.4).

2-Phenylthio-3-chloromethyl-furan 54. On the same scale and utilizing a procedure identical to that used in the preparation of chloride **24**, **54** was prepared from alcohol **52** in 94% yield ($BP_{.007mm}$ = 85°C). ^{1}H NMR (60 MHz) δ 7.43 (d, J=2Hz, 1H), 7.12 (s, 5H), 6.52 (d, J=2Hz, 1H), 4.53 (s, 2H); IR (neat) 3900, 2890, 1590, 1490, 1485, 1445, 1285, 1265, 1150, 1120, 1060, 1035, 892, 770 cm^{-1}; EI-MS (70eV) 226 (M^+, 36.3), 224 (M^+, base), 189 (87.5), 161 (47.3), 128 (63.0).

2-Phenylthio-3-tri-n-butylstannylmethyl-furan 55. On the same scale and utilizing a procedure identical to that used in the preparation of stannane **49**, **55** was prepared from chloride **54** in 66% yield. ^{1}H NMR (60 MHz) δ 7.38 (d, J=2Hz, 1H), 7.06 (m, 5H), 6.19 (d, J=2Hz, 1H), 2.09 (s, 2H), 1.09-1.48 (m, 12H), 0.80-0.96 (m, 15H); IR (neat) 2980, 2950, 2880, 1575, 1480, 1465, 1445, 1380, 1265, 1165, 1100, 1030, 1000, 895,

760, 745, 695 cm^{-1}; EI-MS (70eV) 421 (M^+-Bu, 85.2), 367 (5.1), 309 (6.0), 291 (21.3), 235 (48.2), 179 (base).

Reaction of Lithiated 55 with Benzaldehyde. Preparation of 56 and 57. On the same scale and utilizing a procedure identical to that used in the reaction of stannane **49** with benzaldehyde, 2-phenylthio-3-tri-n-butylstannylmethyl furan **55** was lithiated and alkylated with benzaldehyde to provide the crude product as a pale yellow oil. Purification of the crude produce was accomplished by chromatography on silica gel to provide **56** (38% yield) and **57** (37% yield). Spectral data for **56**: ^{1}H NMR (60 MHz) δ 7.43 (d, J=2Hz, 1H), 7.24 (s, 5H), 7.05 (m, 5H), 6.29 (d, J=2Hz, 1H), 4.77 (t, J=6Hz, Ph-C<u>H</u>-OH), 3.89 (s, -O<u>H</u>), 2.96 (d, J=6Hz, f-<u>C</u>H_2CHOH); EI-MS (70eV) 296 (M^+, 20.2), 190 (base), 161 (21.0), 129 (37.9), 107 (43.2). Spectral data for **57**: ^{1}H NMR (60 MHz) δ 7.23 (m, 11H), 6.27 (d, J=2Hz, 1H), 5.75 (brs, 1H, f-C<u>H</u>(OH)Ph), 3.86 (s, 2H, f-C<u>H_2</u>-SPh), 2.23 (brs, 1H, -O<u>H</u>); EI-MS (70eV) 296 (M^+, 5.8), 278 (2.7), 186 (base), 109 (99.4).

2-Phenylthio-3-decyl-furan 58. To a solution of 2-phenylthio-3-tri-n-butylstannylmethyl-furan **55** (0.96g, 2.0 mmol) in dry THF (5 mL) was added nBuLi (1.8 M in hexane, 1.1 mL, 2.0 mmol) at -78°C (dry ice-isopropanol). The solution was stirred at -78°C for 30 minutes and then HMPA (0.35 mL, 2.0 mmol) was added via syringe. The solution was warmed to -25°C (dry ice-isopropanol) and nonyl-iodide (0.51g, 2.0 mmol) in dry THF (1 mL) was added via syringe. The resulting solution was stirred for 1h at -25°C then diluted with Et_2O (50 mL)

and washed with saturated aqueous NH_4Cl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 1.0g of crude product. The desired product was separated from tin by-products and unreacted nonyl-iodide by chromatography on a column of silica gel (60-230 mesh, 100g, hexane) to provide 0.23g (39%) of **58**. ^1H NMR (60 MHz) δ 7.33 (d, J=2Hz, 1H), 6.98 (m, 5H), 6.23 (d, J=2Hz, 1H), 2.47 (bdt, J=6Hz, 2H), 1.23 (bds, 16H), 0.88 (m, 3H); EI-MS (70eV) 316 (M^+, base), 302 (11.8), 189 (28.5), 161 (30.0), 128 (30.4).

2,6-Dimethyl-9-(2-phenylthio-3-furyl)-2,6-nonadiene

59. To a solution of 2-phenylthio-3-tri-n-butylstannylmethyl-furan **55** (0.96g, 2.0 mmol) in dry THF (3 mL) was added nBuLi (1.8 M in hexane, 1.1 mL, 2.0 mmol) at -78°C (dry ice-isopropanol). The solution was stirred at -78°C for 30 minutes and then was added dropwise via a syringe jacketed with dry ice held in place by aluminum foil to a solution of geranyl chloride (0.35g, 2.0 mmol) and HMPA (0.35 mL, 2.0 mmol) in dry THF (3 mL) at -25°C. The resulting solution was stirred at -25°C for 1h then diluted with Et_2O (50 mL) and washed with saturated aqueous NH_4Cl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded 1.0g of crude product which was purified by flash chromatography on a column of silica gel (230-400 mesh, 100g, hexane) to afford 0.39g (59%) of **59**. ^1H NMR (60 MHz) δ 7.34 (d, J=2Hz, 1H), 7.03 (m, 5H), 6.28 (d, J=2Hz, 1H), 5.04 (bdm, 2H), 1.92-

2.17 (m, 8H), 1.50-1.64 (m, 9H); EI-MS (70eV) 326 (M^+, 29.8), 217 (2.6), 202 (2.9), 189 (base), 161 (30.9), 128 (29.3).

3-Tetrahydropyranyloxymethyl-furan 60. To a solution of 3-hydroxymethyl-furan (2.5g, 25.5 mmol) in dry methylene chloride (100 mL) was added dihydropyran (3.2g, 38.5 mmol) and pyridinium toluenesulfonate (0.64g, 2.55 mmol). The resulting solution was stirred at 25°C for 1.5h. The majority of the solvent was then removed <u>in vacuo</u> and the residue was diluted with Et_2O (150 mL), washed with water (150 mL), brine (150 mL) and dried (Na_2SO_4). Removal of solvent <u>in vacuo</u> afforded a colorless liquid which was purified by distillation, $BP_{0.17mm}$ = 65°C, to yield 4.42g (95%) of **60**. ^1H NMR (60 MHz) δ 7.25 (m, 2H), 6.30 (d, J=2Hz, 1H), 4.64 (m, 1H), 4.59 (d, J=11Hz, 1H, AB), 4.30 (d, J=11Hz, 1H, AB), 3.30-4.00 (bdm, 2H), 1.40-1.70 (bdm, 6H); IR (neat) 2940, 2860, 1560, 1450, 1270, 1140, 1035 cm^{-1}; EI-MS (70eV) 182 (M^+, 0.6), 161 (0.6), 98 (9.6), 85 (38.2), 81 (base).

3-Phenylthio-4-hydroxymethyl-furan 61. On the same scale and utilizing a procedure identical to that used in the preparation of **52**, 2-trimethylsilyl-3-hydroxymethyl-furan **63** was sulfenylated to give a crude product that was purified by chromatography on a column of silica gel (230-400 mesh, Et_2O-petroleum ether, 2:8). Two major components were isolated: 2-trimethylsilyl-4-phenylthio-3-hydroxymethyl-furan (69%), (R_f 0.60, Et_2O-petroleum ether, 1:1) and 2-phenylthio-5-trimethylsilyl-4-hydroxymethyl-furan (23%), (R_f 0.32, Et_2O-petroleum ether, 1:1). The nature of the 2,3,4-substituted

regioisomer was demonstrated upon analysis of material that was desilylated as follows. The major product above was stirred with pTsOH (1 eq.) in dry CH_3CN at 25°C for 4h. After most of the solvent was removed <u>in vacuo</u>, the residue was diluted with Et_2O and washed with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), followed by removal of solvent <u>in vacuo</u> to provide 3-phenylthio-4-hydroxymethyl-furan **61** (75%) with the following spectral data. ^1H NMR (60 MHz) δ 7.53 (m, 1H), 7.42 (m, 1H), 7.11 (s, 5H), 4.34 (brs, 2H), 2.09 (brs, 1H); IR (neat) 3420, 2970, 2910, 1590, 1520, 1484, 1445, 1145, 1095, 1035, 885, 820, 755, 705, 645 cm^{-1}; EI-MS (70eV) 206 (M^+, base), 187 (21.8), 159 (9.8), 147 (8.4), 134 (7.3), 128 (65.8).

2-Phenylthio-4-chloromethyl-furan 62. On the same scale and utilizing a procedure identical to that used in the preparation of chloride **24**, **62** was prepared from alcohol **53** in 67% yield after distillation, $BP_{.005}$ = 115°C. ^1H NMR (60 MHz) δ 7.48 (s, 1H), 7.19 (s, 5H), 6.72 (s, 1H), 4.37 (s, 2H); IR (neat) 3900, 2890, 1580, 1495, 1485, 1450, 1280, 1150, 1050, 890, 760 cm^{-1}; EI-MS (79eV) 226 (M^+, 9.9), 224 (M^+, 32.3), 177 (6.2), 161 (13.3), 149 (18.8), 128 (18.5), 115 (9.5), 40 (base).

2-Trimethylsilyl-3-hydroxymethyl-furan 63. To a suspension of lithium aluminum hydride (0.11g, 3.0 mmol) in dry Et_2O (10 mL) at 0°C (ice water) was added 2-trimethylsilyl-3-furoic acid (0.36g, 2.0 mmol) in dry Et_2O (5 mL) over 15 minutes. The mixture was allowed to warm to 25°C and was

stirred for 2h. The reaction mixture was cooled to 0°C and quenched with water (10 mL), followed by dilution with Et_2O (25 mL) and washing with water (2 x 25 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded a slightly yellow oil which was distilled, BP_{5mm} = 90°C, to afford 0.26g (76%) of **63** as a colorless liquid. ^1H NMR (60 MHz) δ 7.46 (d, J=2Hz, 1H), 6.37 (d, J=2Hz, 1H), 4.51 (s, 2H), 2.28-2.40 (bdm, 1H), 0.29 (bds, 9H); IR (neat) 3390, 2995, 2935, 1580, 1490, 1425, 1265, 1120, 1060, 1010, 860, 775 cm^{-1}; EI-MS (70eV) 170 (M^+, 28.3), 153 (base), 137 (40.2), 77 (86.1).

2-Trimethylsilyl-3-chloromethyl-furan 64. On the same scale and utilizing a procedure identical to that used in the preparation of chloride **24**, **64** was prepared from alcohol **63** in 69% yield after distillation, BP_{8mm} = 75°C. ^1H NMR (60 MHz) δ 7.43 (d, J=2Hz, 1H), 6.34 (d, J=2Hz, 1H), 4.51 (s, 2H), 0.29 (bds, 9H); IR (neat) 2960, 2900, 1565, 1485, 1450, 1380, 1255, 1175, 1105, 1055, 920, 860, 735 cm^{-1}; EI-MS (70eV) 190 (3.4), 188 (9.0), 173 (64.7), 153 (base), 137 (17.2), 95 (39.4).

2,6-Dimethyl-9-(2-trimethylsilyl-3-furyl)-nona-2,6-diene-2,3-epoxide 65. To a solution of dry 2-trimethylsilyl-3-chloromethyl-furan **64** (4.08g, 22.0 mmol) in dry THF (50 mL) was added magnesium powder (0.53g, 22.0 mmol), with stirring at 25°C. The solution was heated to 50°C and Grignard formation soon became initiated. After 45 minutes at 50°C, most of the magnesium had been consumed producing a slightly turbid

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blackish-brown colored solution. Titration[26] of an aliquot showed Grignard formation to be 77%. The solution was cooled to 0°C (ice water) and Li_2CuCl_4 catalyst (0.1 M in THF, 1.0 mL, 0.1 mmol) was added followed by a solution of epoxygeranyl chloride[51,52] (3.14g, 16.7 mmol) in dry THF (10 mL). The resulting solution was slowly warmed to 25°C over the course of 1h. Most of the solvent was removed in vacuo and the residue was diluted with Et_2O-pentane, 1:1 (200 mL) followed by washing with water (200 mL), saturated aqueous NH_4Cl (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 5.5g of an orange oil which was distilled, $BP_{.007mm}$ = 110°C, to afford 4.76g (93%, based on epoxygeranyl chloride) of **65** as a slightly yellow liquid. ^1H NMR (60 MHz) δ 7.44 (d, J=2Hz, 1H), 6.21 (d, J=2Hz, 1H), 5.18 (m, 1H), 2.00-2.80 (bdm, 5H), 1.64 (bds, 7H), 1.27 (s, 6H), 0.27 (m, 9H); IR (neat) 2900, 2890, 1575, 1465, 1390, 1260, 1110, 1065, 860, 770 cm^{-1}; EI-MS (70eV) 306 (M^+, 2.9), 291 (1.4), 233 (3.6), 207 (15.3), 153 (base).

Attempted Cyclization of 65. Preparation of 66. To a solution of **65** (0.10g, 0.33 mmol) and triethylamine (0.07 mL, 0.50 mmol) in dry methylene chloride (10 mL) at 0°C (ice water) was added freshly prepared magnesium bromide etherate (0.23g, 0.99 mmol). The solution was stirred at 0°C for 20 minutes then warmed to 25°C. The solution was then diluted with Et_2O (50 mL), washed with water (50 mL) and saturated aqueous NH_4Cl (50 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo afforded 0.1g crude product

which was purified by chromatography on a column of silica gel (60-230 mesh, 15g, Et_2O-petroleum ether, 3:7) to afford 30 mg (30%) of uncyclized ketone, R_f 0.64 (Et_2O-petroleum ether, 1:1) and a mixture of two unseparated components which were separated by analytical HPLC. The mixture was found to consist of 10 mg (10%) of cyclized desilylated material, R_f 0.17, and 20 mg (20%) of **66**, R_f 0.24, with the following spectral data. ^1H NMR (250 MHz) δ 6.39 (s, 1H), 3.30 (dd, J=11.3,5.0Hz, 1H), 2.47 (dd, J=12.5,16.3Hz), 2.20 (dt, J=12.5,3.8Hz, 1H), 1.50-1.90 (bdm, 7H), 1.19 (s, 3H), 1.05 (s, 3H), 0.87 (s, 3H), 0.21 (s, 9H); IR (neat) 3440, 2990, 2890, 1505, 1465, 1385, 1260, 1100, 1035, 940, 855, 765 cm^{-1}; EI-MS (70eV) 306 (M^+, 21.6), 291 (49.5), 273 (27.5), 219 (13.7), 201 (16.9), 73 (base).

Silylation of 3-Hydroxymethyl-furan. Preparation of 2,5-Bis-trimethylsilyl-3-hydroxymethyl-furan 67. To LDA (52.0 mmol), prepared in the usual way, in dry THF (50 mL) at 0°C (ice water) was added 3-hydroxymethyl-furan (2.5g, 26.0 mmol) in dry THF (10 mL) via syringe. The solution was stirred for 45 minutes at which time the solution became a thick, pale green suspension. Trimethylsilyl chloride (8.0 mL, 63.0 mmol) neat was then added via syringe and the resulting solution was warmed to 25°C over 2h. Most of the solvent was removed <u>in vacuo</u> and the residue was diluted with Et_2O (100 mL), followed by washing with water (100 mL) and saturated aqueous NH_4Cl (100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded

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6.33g of crude product which was directly submitted to desilylation conditions, as follows, without further purification. A solution of the crude product and sodium methoxide (2.80g, 52.0 mmol) in methanol (100 mL) was stirred at 25°C for 15 minutes. After careful removal of most of the solvent <u>in vacuo</u>, the residue was diluted with Et_2O (100 mL) and washed with water (2 x 100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> followed by distillation through a vigreux column afforded 0.61g (24%) of recovered 3-hydroxymethyl-furan, 1.64g (37%) of 2-trimethylsilyl-3-hydroxymethyl-furan **63**, and 0.76g (12%) of **67**, BP_{5mm} = 108°C, with the following spectral data. ^1H NMR (60 MHz) δ 6.58 (s, 1H), 4.52 (s, 2H), 2.07 (bds, 1H), 0.29 (bds, 18H); IR (neat) 3400, 2990, 2890, 1580, 1420, 1255, 1090, 1015, 940, 855, 765, 705 cm^{-1}; EI-MS (70eV) 242 (M^+, 26.4), 227 (73.9), 147 (39.4), 133 (28.9), 75 (base).

Silylation of 3-Trimethylsiloxymethyl-furan. Preparation of 2-Trimethylsilyl-4-hydroxymethyl-furan 68. To LDA (39.0 mmol), prepared in the usual way, in dry THF (100 mL) was added 3-trimethylsiloxymethyl-furan (6.6g, 39.0 mmol) in dry THF (10 mL) via syringe. The resulting solution was stirred for 10 minutes at 0°C during which time it took on a dark golden brown color. Trimethylsilyl chloride (4.95 mL, 39 mmol) was added followed by gradual warming to 25°C overnight. The reaction mixture was worked up and subjected to silyl ether cleavage as before (see the procedure for the preparation of **67**) to afford 5.59g of crude product.

The crude material was purified by chromatography on a column of silica gel (230-400 mesh, 400g, Et_2O-petroleum ether, 15:85) to afford 2.27g (34%) of 2-trimethylsilyl-3-hydroxymethyl-furan **63**, R_f 0.39 (Et_2O-petroleum ether, 1:1); 1.47g (16%) of 2,5-bis-trimethylsilyl-3-hydroxymethyl-furan **67**, R_f 0.50; and 0.65g (10%) of **68**, R_f 0.28, with the following spectral data. ^1H NMR (60 MHz) δ 7.28 (s, 1H), 6.58 (s, 1H), 4.45 (s, 2H), 2.36 (bds, 1H), 0.29 (bdm, 9H); IR (neat) 3320, 2955, 2880, 1595, 1465, 1405, 1250, 1155, 1070, 1010, 975, 905, 835, 755 cm^{-1}; EI-MS (70eV) 170 (M^+, 58.3), 155 (96.7), 127 (42.4), 97 (45.2), 75 (base).

2-Phenylthio-3-tbutyldimethylsiloxymethyl-furan 69. To a solution of 2-phenylthio-3-hydroxymethyl-furan **52** (5.65g, 27.4 mmol) and imidazole (4.66g, 68.5 mmol) in dry DMF (25 mL) was added t-butyldimethylsilyl chloride (4.97g, 32.9 mmol). The resulting solution was stirred at 25°C for 1h and then diluted with Et_2O (150 mL) followed by washing with water (100 mL) and saturated aqueous $Cu(NO_3)_2$ (100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded a yellow liquid which was purified by filtration through a column of silica gel (60-230 mesh, 35g, Et_2O-petroleum ether, 1:9) to afford 7.20g (81%) of **69** as a slightly yellow liquid. ^1H NMR (60 MHz) δ 7.53 (d, J=2Hz, 1H), 7.17 (bds, 5H), 6.60 (d, J=2Hz, 1H), 4.68 (s, 2H), 1.00 (s, 9H), 0.14 (m, 6H); IR (neat) 2970, 2880, 1590, 1485, 1445, 1265, 1105, 1070, 860, 790, 750 cm^{-1}; EI-MS (70eV) 320 (M^+, 2.4),

305 (1.3), 263 (96.5), 189 (base), 167 (21.8), 161 (29.0), 128 (34.0).

2-Phenylthio-5-trimethylsilyl-3-tbutyldimethylsiloxymethyl-furan 70. To a solution of nBuLi (2.08 M in hexane, 0.48 mL, 1.0 mmol) in dry Et_2O (3 mL) at 0°C (ice water) was added 2-phenylthio-3-tbutyldimethylsiloxymethyl-furan (0.32g, 1.0 mmol) in dry Et_2O (2 mL) via syringe. The solution was then warmed to 25°C and stirred for 2.5h or until a deep reddish-brown color was observed. Upon cooling to 0°C, trimethylsilyl chloride (0.15 mL, 1.25 mmol) was added and the solution was gradually warmed to 25°C over the course of 1h. A precipitate was observed soon after the addition of trimethylsilyl chloride. The reaction mixture was diluted with Et_2O (25 mL), washed with water (25 mL), and saturated aqueous NH_4Cl (25 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 0.35g of a dark brown oil. The crude product was purified by filtration through a column of silica gel (60-230 mesh, 10g, Et_2O-petroleum ether, 1:99) to afford 0.30g (76%) of **70** as a colorless liquid. ^1H NMR (60 MHz) δ 7.18 (bds, 5H), 6.83 (s, 1H), 4.67 (s, 2H), 0.98 (s, 9H), 0.35 (s, 9H), 0.10 (m, 6H); IR (neat) 2980, 2880, 1590, 1485, 1260, 1095, 1060, 940, 855, 785, 745 cm^{-1}; EI-MS (70eV) 392 (M^+, 4.0), 377 (1.6), 335 (17.1), 261 (27.8), 73 (base).

2-Phenylthio-5-trimethylsilyl-3-hydroxymethyl-furan 71. A solution of 2-phenylthio-5-trimethylsilyl-3-tbutyldimethylsiloxymethyl-furan **70** (6.65g, 17.0 mmol), glacial acetic

acid (50 mL), water (20 mL) and THF (50 mL) was heated to reflux while being monitored by TLC analysis (Et_2O-petroleum ether, 1:1). After 70 minutes, most of the solvent was removed in vacuo and the residue was diluted with water (50 mL) followed by addition of solid $NaHCO_3$ until gas evolution ceased. The aqueous solution was then extracted with Et_2O (2 x 100 mL) and the combined ether extracts were dried (Na_2SO_4). Removal of solvent in vacuo provided 6.1g of crude product which was purified by chromatography on a column of silica gel (60-230 mesh, 300g, Et_2O-petroleum ether, 1:1) to afford 2.46g (52%) of **71** along with 0.39g (11%) of **52** and 0.60g (9%) of recovered starting material. The cleavage of the silyl ether to give **71** was verified by ^1H NMR and it was subjected to desulfurization below without further characterization.

Desulfurization of 71. Preparation of 2-Trimethylsilyl-4-hydroxymethyl-furan 68. 2-Phenylthio-5-trimethylsilyl-3-hydroxymethyl-furan (2.9g, 10.4 mmol) and a suspension of W-2 grade raney-nickel catalyst (58.0g) in absolute ethanol (150 mL) was heated to reflux for 6h. The solution was then filtered through celite followed by rinsing of the catalyst with ethanol (3 x 50 mL) and filtration of the combined rinse solvent. Rinse and filtrate were combined and removal of solvent in vacuo followed by distillation, BP_{3mm} = 90°C, afforded 1.0g (56%) of **68**, identical in all respects to that obtained previously.

Silylation of 2-Bromo-4-furoic acid. Preparation of 2-Trimethylsilyl-4-hydroxymethyl-furan 68. To a solution of 2-bromo-4-furoic acid[57] (0.43g, 2.25 mmol) in dry Et_2O (10 mL) cooled to -78°C was added nBuLi (2.9 M in hexane, 1.71 mL, 4.95 mmol), after which a precipitate formed. The solution was stirred at -78°C for 30 minutes and then trimethylsilyl chloride (0.63 mL, 5.0 mmol) was added via syringe. The solution was then warmed to 0°C (ice water) and gradually warmed to 25°C over 1h. After this time, the solution was diluted with Et_2O (50 mL) and washed with 0.1 M aqueous HCl (2 x 50 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo afforded 0.45g crude product. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50g, Et_2O-petroleum ether-MeOH, 5:94.5:0.5) to afford 0.09g (15%) of 2,5-bis-trimethylsilyl-3-furoic acid, R_f 0.24 (Et_2O-petroleum ether-MeOH, 10:89.5:0.5) and 0.30g of a mixture of two components which was directly submitted to hydride reduction conditions as before (see preparation of **63**). The crude material from this reduction was purified by chromatography on a column of silica gel (60-230 mesh, 30g, Et_2O-petroleum ether, 15:85) to afford 0.23g (81%) of 2-trimethylsilyl-4-hydroxymethyl-furan **68** (51% overall from 2-bromo-4-furoic acid) which was identical in all respects to that obtained previously.

2-Trimethylsilyl-4-chloromethyl-furan 72. On the same scale and utilizing a procedure identical to that used in the preparation of chloride **24**, **72** was prepared from alcohol

68 in 78% yield as a colorless liquid, BP_{10mm} = 90°C. ^1H NMR (60 MHz) δ 7.57 (s, 1H), 6.61 (s, 1H), 4.42 (s, 2H), 0.27 (bds, 9H); IR (neat) 2980, 2925, 1685, 1600, 1455, 1385, 1260, 1185, 1140, 1085, 855, 715 cm^{-1}; EI-MS (70eV) 188 (M^+, 28.3), 173 (89.2), 153 (18.2), 93 (base).

2,6-Dimethyl-9-(2-trimethylsilyl-4-furyl)-nona-2,6-diene-2,3-epoxide 73. On the same scale and utilizing a procedure identical to that used previously (see the procedure for the preparation of **65**), 2-trimethylsilyl-4-chloromethyl-furan **72** was converted to the corresponding Grignard reagent (64% by titration) and coupled with epoxygeranyl chloride[51,52] to afford a 90% yield (based on epoxygeranyl chloride) of **73** after purification by chromatography on a column of silica gel (60-230 mesh, Et_2O-petroleum ether, 5:95), R_f 0.58 (Et_2O-petroleum ether, 1:1). ^1H NMR (60 MHz) δ 7.29 (s, 1H), 6.45 (s, 1H), 5.18 (m, 1H), 2.00-2.80 (bdm, 5H), 1.64 (bds, 7H), 1.27 (s, 6H), 0.27 (m, 9H); IR (neat) 2990, 2880, 1465, 1385, 1255, 1130, 1090, 920, 855, 770 cm^{-1}; EI-MS (70eV) 306 (M^+, 2.3), 291 (1.9), 233 (2.8), 220 (4.3), 207 (13.6), 153 (96.7), 73 (base).

General Procedure for the Coupling of Silyl-substituted Furylmethyl Grignard Reagents with Alkyl Halides. Preparation of 2-Trimethylsilyl-3-decyl-furan 74 and 2-Trimethylsilyl-4-decyl-furan 77. To a solution of dry 2-trimethylsilyl-3-chloromethyl-furan **64** or regioisomer 2-trimethylsilyl-4-chloromethyl-furan **72** (1.0g, 5.3 mmol) in dry THF (15 mL) was added magnesium powder (0.13g, 5.3 mmol) with stirring at 25°C.

The solution was heated to 50°C and Grignard formation soon became initiated. After 45 minutes at 50°C, most of the magnesium had been consumed producing a slightly turbid blackish-brown colored solution. Titration[26] of an aliquot showed Grignard formation to be 77% and 64% from chlorides **64** and **72**, respectively. The solution was cooled to 0°C (ice water) and Li_2CuCl_4 catalyst (0.1 M in THF, 0.27 mL, 0.027 mmol) was added followed by a solution of nonyl-iodide (1.2g, 4.8 mmol or 0.9g, 3.4 mmol, respectively based on the Grignard conversion of **64** or **72**) in dry THF (2 mL). The resulting solution was slowly warmed to 25°C over the course of 1h. Most of the solvent was removed <u>in vacuo</u> and the residue was diluted with Et_2O-pentane, 1:1 (50 mL) followed by washing with water (50 mL), saturated aqueous NH_4Cl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and drying (Na_2SO_4). Removal of solvent <u>in vacuo</u> afforded the crude product which was purified by chromatography on a column of silica gel (60-230 mesh, 70g, petroleum ether) to afford 1.1g (82% of **74**, R_f 0.51 (petroleum ether) and 0.7g (77%) of **77**, R_f 0.51 (petroleum ether) with yields based on the Grignard conversions of **64** and **72**, respectively. <u>Spectral data for **74**</u>: ^1H NMR (60 MHz) δ 7.45 (d, J=2Hz, 1H), 6.20 (d, J=2Hz, 1H), 2.25 (bdt, J=6Hz, 2H), 1.35 (bds, 16H), 0.90 (m, 3H), 0.28 (s, 9H); IR (neat) 2980, 2950, 2880, 1575, 1470, 1400, 1260, 850, 770 cm^{-1}; EI-MS (70eV) 280 (M^+, 15.8), 265 (5.1), 195 (39.0), 181 (31.6), 154 (43.1), 73 (base). <u>Spectral data for **77**</u>: ^1H NMR (60 MHz) δ 7.34 (s, 1H), 6.46 (s, 1H), 2.41

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(bdt, J=6Hz, 2H), 1.34 (bds, 16H), 0.92 (m, 3H), 0.29 (s, 9H); IR (neat) 2960, 2920, 1465, 1250, 1075, 710, 840, 750 cm^{-1}; MS (EI/70eV) 280 (M^+, 3.3), 265 (2.2), 251 (1.8), 237 (1.9), 196 (2.5), 167 (12.6), 154 (base).

2-Trimethylsilyl-3-(6-heptenyl)-furan 75. According to the general procedure above, on an identical scale, 2-trimethylsilyl-3-chloromethyl-furan **64** afforded a Grignard reagent which was coupled with 6-bromo-1-hexene and purified to afford a 74% yield of **75**, R_f 0.43 (petroleum ether). ^1H NMR (60 MHz) δ 7.43 (d, J=2Hz, 1H), 6.20 (d, J=2Hz, 1H), 5.46-6.00 (m, 1H), 4.80-5.18 (m, 2H), 2.46 (bdt, J=6Hz, 2H), 2.04 (m, 2H), 1.39 (m, 6H), 0.29 (s, 9H); IR (neat) 2980, 2950, 2880, 1645, 1575, 1460, 1495, 1255, 1155, 1000, 920, 860, 770 cm^{-1}; EI-MS (70eV) 236 (M^+, 13.5), 221 (25.0), 207 (12.8), 195 (15.9), 163 (10.1), 153 (54.7), 111 (base).

2-Trimethylsilyl-3-(3-heptenyl)-furan 76. According to the general procedure above, on an identical scale, 2-trimethylsilyl-3-chloromethyl-furan **64** afforded a Grignard reagent which was coupled with 1-chloro-2-hexene and purified to afford a 67% yield of **76**, R_f 0.38 (petroleum ether). ^1H NMR (60 MHz) δ 7.40 (s, 1H), 6.18 (s, 1H), 5.37 (bds, 2H), 1.89-2.52 (m, 6H), 1.30 (m, 2H), 0.90 (m, 3H), 0.29 (s, 9H); IR (neat) 2955, 2920, 2880, 1675, 1570, 1450, 1390, 1250, 1090, 965, 835, 755 cm^{-1}; EI-MS (70eV) 236 (M^+, 4.4), 221 (3.3), 208 (9.3), 193 (16.6), 163 (8.8), 153 (60.4), 73 (base).

2-Trimethylsilyl-4-(6-heptenyl)-furan 78. According to the general procedure above, on an identical scale, 2--trimethylsilyl-4-chloromethyl-furan **72** afforded a Grignard reagent which was coupled with 6-bromo-1-hexene and purified to afford a 70% yield of **78**, R_f 0.36 (petroleum ether). ^1H NMR (60 MHz) δ 7.32 (s, 1H), 6.44 (s, 1H), 5.46-6.06 (bdm, 1H), 4.79-5.07 (m, 2H), 2.37 (bdt, J=6Hz, 2H), 2.00 (m, 2H), 1.40 (m, 6H), 0.29 (s, 9H); IR (neat) 2960, 2930, 2860, 1640, 1450, 1250, 1075, 910, 840, 755 cm^{-1}; EI-MS (70eV) 236 (M^+, 8.1), 221 (4.8), 193 (6.2), 167 (11.3), 154 (63.6), 73 (base).

2-Trimethylsilyl-4-(3-heptenyl)-furan 79. According to the general procedure above, on an identical scale, 2--trimethylsilyl-4-chloromethyl-furan **72** afforded a Grignard reagent which was coupled with 1-chloro-2-hexene and purified to afford a 60% yield of **79**, R_f 0.31 (petroleum ether). ^1H NMR (60 MHz) δ 7.34 (s, 1H), 6.43 (s, 1H), 5.40 (m, 2H), 1.84-2.48 (m, 6H), 1.32 (m, 2H), 0.90 (m, 3H), 0.29 (s, 9H); IR (neat) 2960, 2920, 1450, 1250, 1075, 910, 840, 750 cm^{-1}; EI-MS (70eV) 236 (M^+, 11.2), 221 (5.9), 207 (3.9), 193 (9.7), 154 (98.5), 73 (base).

General Procedure for the Oxidation of Silyl-substituted Furans to Butenolides: Oxidation of 74. Preparation of 3-Decyl-2(5H)-furanone 80 and 3-Decyl-2(3H)-furanone 81. According to the procedure of Kuwajima,[59] to a stirred suspension of 40% peracetic acid (1.9g, 10.0 mmol) and sodium acetate trihydrate (0.41g, 3.0 mmol) in methylene chloride (10 mL) was added 2-trimethylsilyl-3-decyl-furan **74** (0.70g, 2.5 mmol)

in methylene chloride (1 mL) at 0°C (ice water). The reaction mixture was stirred for 3h then diluted with Et_2O (50 mL) and washed with water (50 mL), saturated aqueous $NaHCO_3$ (2 x 25 mL), saturated aqueous sodium thiosulfate (2 x 25 mL) and saturated aqueous $NaHCO_3$ (25 ml) followed by drying (Na_2SO_4). Removal of solvent in vacuo afforded 0.60g of crude product which was purified by chromatography on a column of silica gel (60-230 mesh, 60g, Et_2O-Petroleum ether, 1:3) to afford 0.22g (39%) of **80**, R_f 0.33 (Et_2O-petroleum ether, 1:1) and 0.22g (39%) of **81**, R_f 0.22. Spectral data for **80**: ^1H NMR (60 MHz) δ 7.15 (m, 1H), 4.77 (m, 2H), 2.27 (m, 2H), 1.30 (m, 16H), 0.89 (m, 3H); IR (neat) 2920, 2850, 1750, 1655, 1455, 1350, 1230, 1190, 1110, 1060, 1000, 825 cm^{-1}; EI-MS (70eV) 224 (M^+, 15.0), 195 (2.5), 179 (5.3), 167 (4.9), 153 (8.4), 139 (16.4), 125 (20.9), 98 (base). Spectral data for **81**: ^1H NMR (60 MHz) δ 6.80 (m, 1H), 5.57 (m, 1H), 3.17 (bdm, 1H), 1.30 (m, 18H), 0.90 (m, 3H); IR (neat) 3350, 2925, 2850, 1760, 1660, 1465, 1335, 1190, 1100, 1050, 1000, 825 cm^{-1}; EI-MS (70eV) 224 (M^+, 2.0), 195 (2.1), 179 (3.0), 167 (3.5), 153 (1.2), 98 (base).

Oxidation of 75. Preparation of 3-(6-Heptenyl)-2(5H)-furanone 82. According to the general procedure above, on an identical scale, 2-trimethylsilyl-3(-6-heptenyl)-2(5H)-furanone **75** was oxidized to **82** in 67% yield after purification by chromatography on silica gel, R_f 0.29 (Et_2O-petroleum ether, 1:1). ^1H NMR (60 MHz) 7.19 (m, 1H), 5.49-6.15 (bdm,

1H), 4.73-5.10 (m, 2H), 4.80 (m, 2H), 2.03-2.36 (bdm, 4H), 1.43 (bds, 6H); IR (neat) 2950, 2880, 1765, 1645, 1460, 1355, 1210, 1075, 1010, 925, 845 cm^{-1}; EI-MS (70eV) 180 (M^+, 0.5), 165 (1.3), 151 (3.2), 135 (7.0), 123 (6.4), 98 (base).

Oxidation of 76. Preparation of 3-(3-Heptenyl)-2(5H)-furanone 83 and 3-(3-Heptenyl-3,4-epoxy)-2(5H)-furanone 84. According to the general procedure above, on an identical scale, 2-trimethylsilyl-3-(3-heptenyl)-furan **76** was oxidized to a mixture of **83** and **84** which was purified by chromatography on silica gel to provide a 52% yield of **83** and a 36% yield of **84**, R_f 0.28 and 0.14 (Et_2O-petroleum ether, 1:1), respectively. Spectral data for **83**: ^1H NMR (60 MHz) δ 7.09 (m, 1H), 5.40 (m, 2H), 4.77 (m, 2H), 2.36 (bds, 4H), 1.84-2.10 (m, 2H), 1.29 (m, 2H), 0.91 (m, 3H); IR (neat) 2980, 2955, 2880, 1755, 1660, 1460, 1355, 1210, 1080, 980, 925, 840, 740 cm^{-1}; MS (EI/70eV) 180 (M^+, 10.3), 165 (1.7), 151 (4.1), 135 (6.6), 123 (7.3), 98 (base). Spectral data for **84**: ^1H NMR (60 MHz) δ 7.23 (m, 1H), 4.80 (m, 2H), 2.74 (m, 2H), 2.43 (m, 2H), 1.78-2.04 (m, 2H), 1.47-1.59 (m, 4H), 1.00 (m, 3H); IR (neat) 3430, 2995, 2960, 2900, 2280, 1765, 1660, 1460, 1355, 1215, 1085, 925, 845, 745 cm^{-1}; MS (EI/70eV) 196 (M^+, 0.4), 178 (0.6), 167 (3.9), 139 (7.5), 124 (61.4), 85 (base).

Oxidation of 65. Preparation of 2,6-Dimethyl-9-(2-trimethylsilyl-3-furyl)-nona-2,6-diene-2,3-6,7-dioxirane 85. According to the general procedure above, on an identical scale, 2,6-dimethyl-9-(2-trimethylsilyl-3-furyl)-nona-2,6-diene-2,3-epoxide **65** was oxidized to **85** in 93% yield after

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purification by chromatography on silica gel, R_f 0.50 (Et_2O-petroleum ether, 1:1). ^1H NMR (60 MHz) δ 7.48 (s, 1H), 6.25 (s, 1H), 2.54-2.86 (m, 4H), 1.56-2.01 (bds, 6H), 1.26 (bds, 9H), 0.31 (s, 9H); IR (neat) 2990, 2890, 1460, 1390, 1260, 1110, 860, 770 cm^{-1}; EI-MS (70eV) 322 (M^+, 2.1), 306 (3.3), 281 (1.2), 233 (4.7), 153 (34.2), 73 (base).

Oxidation of 77. Preparation of 4-Decyl-2(5H)-furanone 86. According to the general procedure above, on an identical scale, 2-trimethylsilyl-4-decyl-furan **77** was oxidized to **86** in 91% yield after purification by chromatography on silica gel, R_f 0.16 (Et_2O-petroleum ether, 1:1). ^1H NMR (6C MHz) δ 5.86 (m, 1H), 4.78 (bds, 2H), 2.45 (bdt, J=7Hz, 2H), 1.31 (m, 16H), 0.90 (m, 3H); IR (neat) 3400, 2960, 2880, 1785, 1755, 1650, 1475, 1345, 1185, 1145, 1040, 950, 900 cm^{-1}; EI-MS (70eV) 224 (M^+, 2.3), 195 (10.1), 181 (3.6), 164 (26.8), 98 (19.1), 85 (base).

Oxidation of 78. Preparation of 4-(6-Heptenyl)-2(5H)-furanone 87. According to the general procedure above, on an identical scale, 2-trimethylsilyl-4-(6-heptenyl)-furan **78** was oxidized to **87** in 77% yield after purification by chromatography on silica gel, R_f 0.15 (Et_2O-petroleum ether, 1:1). ^1H NMR (60 MHz) δ 5.39-6.00 (m, 1H), 5.77 (m, 1H), 4.80-5.08 (m, 2H), 4.73 (s, 2H), 2.34 (m, 2H), 2.04 (m, 2H), 1.42 (bds, 6H); IR (neat) 2955, 2885, 1785, 1755, 1645, 1455, 1380, 1140, 1035, 920, 745 cm^{-1}; EI-MS (70eV) 181 (M^+, 1.1), 165 (3.9), 151 (22.4), 139 (12.8), 121 (26.4), 111 (39.8), 98 (73.3), 85 (base).

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Oxidation of 79. Preparation of 4-(3-Heptenyl)-2(5H)-furanone 88. According to the general procedure above, on an identical scale, 2-trimethylsilyl-4-(3-heptenyl)-furan **79** was oxidized to **88** in 51% yield after purification by chromatography on silica gel, R_f 0.22 (Et_2O-petroleum ether, 1:1). ^1H NMR (60 MHz) δ 5.87 (m, 1H), 5.45 (m, 2H), 4.75 (m, 2H), 2.46 (m, 4H), 1.99 (m, 2H), 1.33 (m, 2H), 0.98 (m, 3H); IR (neat) 2990, 2960, 2910, 1785, 1755, 1645, 1455, 1185, 1145, 1045, 985, 900, 745 cm^{-1}; MS (EI/70eV) 180 (M^+, 2.4), 165 (0.4), 151 (12.1), 137 (3.1), 123 (10.0), 98 (base).

6,7-Epoxy-8-hydroxygeranyl-acetate 89. To a solution of (E)-8-hydroxygeranyl acetate[65] (3.0g, 14.1 mmol) in dry methylene chloride (50 mL) was added metachloroperbenzoic acid (85%, 3.0g, 15.0 mmol) at 0°C (ice water). The solution was warmed to 25°C and stirred for 2h. After this time, the mixture was diluted with Et_2O (150 mL) and washed with saturated aqueous $Na_2S_2O_3$ (2 x 150 mL) and saturated aqueous $NaHCO_3$ (2 x 150 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo afforded 3.0g (94%) of **89** which was not purified further. ^1H NMR (60 MHz) δ 5.37 (m, 1H), 4.57 (d, J=7Hz, 2H), 3.58 (s, 2H), 3.18 (bds, 1H, -OH), 2.97 (t, J=5Hz, 1H), 2.00-2.30 (m, 4H), 2.05 (s, 3H), 1.73 (s, 3H), 1.30 (s, 3H); IR (neat) 3480, 2965, 1740, 1675, 1450, 1385, 1260, 1135, 1080, 1040, 965, 910, 880, 760, 690 cm^{-1}; EI-MS (70eV) 213 (M^+-O, 0.5), 169 (1.0), 153 (2.2), 137 (3.9), 126 (10.8), 111 (11.9), 43 (base).

6,7-Epoxy-8-tbutyldimethylsiloxygeranyl chloride 90. To a solution of 6,7-epoxy-8-hydroxygeranyl-acetate **89** (3.0g, 13.0 mmol) in dry methylene chloride (25 mL) was added triethylamine (2.23 mL, 15.0 mmol), dimethylaminopyridine (65 mg, catalytic) and tbutyldimethylsilyl chloride (2.21g, 14.0 mmol). The resulting solution was stirred at 25°C for 1h and then diluted with Et_2O (200 mL) and washed with 0.01 N aqueous HCl (200 mL) and saturated aqueous $NaHCO_3$ (200 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded 4.1g of the crude TBDMS ether which was not purified further, R_f 0.61 (Et_2O-petroleum ether, 6:4). The crude material was directly submitted to deacetylation conditions as follows: a solution of the TBDMS ether (4.1g, 12.0 mmol) in methanol (30 mL) was cooled to 0°C (ice water) and potassium carbonate (5g) was added. The resulting solution was stirred at 0°C for 30 minutes and then diluted with Et_2O (200 mL) followed by washing with water (2 x 200 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded 3.3g (91%) of crude deacetylated alcohol, R_f 0.24 (Et_2O-petroleum ether, 6:4) which was readily transformed into the chloride below without further purification. To a solution of the alcohol (3.3g, 11.0 mmol) in dry Et_2O (10 mL) and HMPA (4.5 mL) at 0°C (ice water) was added nBuLi (2.08 M in hexane, 5.2 mL, 11.0 mmol) via syringe. The resulting solution was warmed to 25°C and stirred for 10 minutes. Toluenesulfonyl chloride (2.09g, 11.0 mmol) in dry Et_2O (5 mL) was then added followed by anhydrous lithium

chloride (0.63g, 15 mmol). The resulting solution was stirred at 25°C overnight followed by dilution with Et_2O-petroleum ether, 1:1 (100 mL) and washing with water (100 mL), saturated aqueous NaCl (100 mL), and drying (Na_2SO_4). Removal of solvent in vacuo afforded the crude product which was purified by bulb-to-bulb (Kugelrohr) distillation, oven 160°C (0.04 mm) to afford 2.7g (77%, 65% overall) of **90** as a slightly yellow liquid, R_f 0.69 (Et_2O-petroleum ether, 6:4). ^1H NMR (60 MHz) δ 5.55 (bdt, J=8Hz, 1H), 4.13 (bdd, J=8Hz, 2H), 3.65 (m, 2H), 2.75 (m, 1H), 2.10-2.30 (m, 4H), 1.82 (bds, 3H), 1.35 (bds, 3H), 1.00 (m, 9H), 0.15 (m, 6H); IR (neat) 2920, 2855, 1660, 1460, 1380, 1350, 1250, 1160, 1085, 1035, 775 cm^{-1}; EI-MS (70eV) 261 (M^+-tBu, 1.1), 225 (2.9), 198 (16.1), 157 (30.4), 93 (base).

1-tButyldimethylsiloxymethyl-6-methyl-9-(3-furyl)-nona-2,6-diene-2,3-epoxide 91. In the usual procedure,[8] 3-chloromethylfuran (0.49g, 4.2 mmol) was converted to the corresponding Grignard reagent and coupled with 6,7-epoxy-8-tbutyldimethylsiloxygeranyl chloride **90** (1.3g, 4.2 mmol) to yield, after purification by chromatography on a column of silica gel (60-230 mesh, 100g, Et_2O-petroleum ether, 5:95), 0.91g (60%) of **91**, R_f 0.24 (Et_2O-petroleum ether, 5:95). ^1H NMR (80 MHz, d_6 acetone) δ 7.37 (t, J=2.5Hz, 1H), 7.27 (bds, 1H), 6.30 (bds, 1H), 5.21 (bdt, J=6.2Hz, 1H), 3.65 (d, J=11Hz, 1H), 3.49 (d, J=11Hz, 1H), 2.76 (t, J=6.3Hz, 1H), 2.38 (bd, t, J=8Hz, 1H), 2.15 (m, 2H), 1.61 (m, 7H), 1.23 (s, 3H), 0.90 (s, 9H), 0.07 (d, 6H); IR (neat) 2970, 2880, 1470, 1390,

1265, 1100, 850, 785, 690 cm^{-1}; EI-MS (70eV) 307 (M^+-tBu, 0.6), 249 (1.4), 225 (6.0), 215 (8.1), 175 (18.8), 131 (39.4), 81 (base).

Cyclization of 91. Preparation of 92. To a solution of 1-tbutyldimethylsiloxymethyl-6-methyl-9-(3-furyl)-nona-2,6-diene-2,3-epoxide **91** (3.55g, 8.24 mmol), in dry methylene chloride (30 mL), benzene (15 mL) and pentane (15 mL) was added triethylamine (2.04 mL, 12.36 mmol). The resulting solution was cooled to -60°C (dry ice-isopropanol) and boron trifluoride etherate (3.60 mL, 24.72 mmol) was added via syringe. The resulting solution was stirred at -60°C for 10 minutes taking on a deep golden yellow color, followed by quenching with Et_2O (10 mL) and saturated aquecus $NaHCO_3$ (20 mL). The reaction mixture was then diluted with Et_2O (200 mL) and washed with saturated aqueous $NaHCO_3$ (200 mL), saturated aqueous NH_4Cl (200 mL) and water (200 mL). The organic phase was dried (Na_2SO_4) and removal of solvent afforded 3.5g crude product. This material was purified by chromatography on a cclumn of silica gel (60-230 mesh, 300g, Et_2O-petroleum, 15:85) to afford 1.95g (55%) of uncyclized ketone product, R_f 0.43 (Et_2O-petroleum ether, 15:85) and 1.00g (28%) of **92** as a slightly yellow liquid, R_f 0.24 (Et_2O-petroleum ether, 15:85). ^1H NMR (80 MHz, d_6 acetone) δ 7.18 (d, J=2Hz, 1H), 6.08 (d, J=2Hz, 1H), 3.70 (d, J=10Hz, 1H), 3.40 (dd, J-14,7Hz, 1H), 3.33 (d, J=10Hz, 1H), 2.30-2.48 (m, 2H), 1.50-1.78 (m, 7H), 1.19 (s, 3H), 0.88 (s, 9H), 0.75 (s, 3H), 0.08 (s, 6H); IR (neat) 3500, 2970, 2890, 1510,

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1475, 1390, 1255, 1095, 1030, 855, 785, 735 cm^{-1}; EI-MS (70eV) 307 (M^+-tBu, 8.8), 289 (1.3), 215 (base), 187 (13.0), 175 (58.8).

Preparation of Ketone 93. To a solution of **92** (0.10g, 0.28 mmol) in dry methylene chloride (1 mL) was added anhydrous sodium acetate (23mg, 0.05 mmol) followed by pyridinium chloro-chromate (0.12g, 0.55 mmol) at 0°C (ice water). After 30 minutes, the mixture was warmed to 25°C and stirred to 1.5h. Saturated aquecus $NaHCO_3$ (5 mL) was added followed by dilution with Et_2O (25 mL), and washing with saturated aqueous $NaHCO_3$ (2 x 25 mL), 1 N aquecus HCl (25 mL) and saturated aqueous NaCl (25 mL). The organic phase was dried (Na_2SO_4) and removal of solvent <u>in vacuo</u> afforded 0.95g crude product which was purified by chromatography on a column of silica gel (60-230 mesh, 50g, Et_2O-petroleum ether, 3:97) to provide 0.91g (91%) of ketone **93** as a slightly yellow liquid, R_f 0.57 (Et_2O-petroleum ether, 2:8). ^1H NMR (80 MHz, d_6 acetone) δ 7.26 (d, J=1.7Hz, 1H), 6.14 (d, J=1.7Hz, 1H), 3.65 (d, J=9.0Hz, 1H), 3.46 (d, J=9.0Hz, 1H), 2.20-2.73 (m, 6H), 1.59-1.84 (m, 3H), 1.19 (s, 3H), 0.96 (s, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); IR (neat) 2960, 2880, 1705, 1510, 1475, 1390, 1260, 1100, 850, 785 cm^{-1}; EI-MS (70eV) 305 (M^+-tBu, 55.0), 223 (3.8), 213 (33.2), 171 (23.5), 157 (40.0), 147 (base).

Preparation of Diol 94. To a solution of ketone **93** (0.417g, 1.15 mmol) in dry THF (0.5 mL) at 0°C (ice water) was added tetra-butyl ammonium fluoride (1 M in THF, 2.3

mL, 2.30 mmol) via syringe. The solution was stirred for 2h at 0°C and then diluted with Et_2O (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) followed by saturated aqueous NaCl (10 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo afforded 0.268g (94%) of crude product which rapidly turned brown in color at 25°C. Due to the instability of the compound, it was directly submitted to subsequent reduction conditions without further purification. To a solution of lithium tri-sec-butyl borohydride (1 M in THF, 2.16 mL, 2.16 mmol) in dry THF (3 mL) at -78°C was added the crude keto-alcohol (0.268g, 1.08 mmol) in dry THF (1.5 mL) via syringe. The resulting solution was stirred at -78°C for 1h then warmed to 0°C (ice water) and stirred for 1h. The reaction was quenched by carefully adding methanol (2 mL) followed by 20% aqueous NaOH (3 mL) and 30% aqueous hydrogen peroxide (6 mL). The solution was stirred overnight and then diluted with Et_2O (100 mL), washed with water (100 mL), saturated aqueous NH_4Cl (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was dried (Na_2SO_4) and removal of solvent in vacuo followed with purification by chromatography on a column of silica gel (60-230 mesh, 50g, EtOAc-methylene chloride, 1:9) afforded 0.212g (79% overall from **93**) of diol **94** as a white solid, R_f 0.13 (EtOAc-methylene chloride, 1:9). ^1H NMR (80 MHz, d_6 acetone with D_2O) δ 7.20 (d, J=1.7Hz, 1H), 6.08 (d, J=1.7Hz, 1H), 3.69 (bdt, J=3.3Hz, 1H), 3.59 (d, J=14.8Hz, 1H), 3.33 (d, J=14.8Hz, 1H), 2.31-2.47 (m, 2H), 1.52-1.89 (m, 7H), 1.19 (s, 3H), 0.78 (s, 3H); IR

(neat) 3350, 2950, 1505, 1480, 1455, 1385, 1270, 1210, 1165, 1135, 1055, 1000, 890, 745 cm^{-1}; EI-MS (70eV) 250 (M^+, 29.5), 235 (14.4), 217 (base), 199 (19.6), 159 (32.4), 149 (40.1).

Acetonide 95. To a solution of diol **94** (25 mg, 0.10 mmol) in dry methylene chloride (1 mL) and acetone (99.5%, 0.5 mL) at 25°C was added a few crystals of oxalic acid followed by stirring overnight. The solution was diluted with Et_2O (20 mL), washed with saturated aqueous $NaHCO_3$ (2 x 20 mL) and dried (Na_2SO_4). Removal of solvent followed with purification by chromatography on a column of silica gel (60-230 mesh, 10g, Et_2O-petroleum ether, 2:98) afforded 26 mg (90%) of acetonide **95** as a white solid, R_f 0.47 (Et_2O-petroleum ether, 2:8). ^1H NMR (80 MHz, d_6 acetone) δ 7.20 (d, J=1.7Hz, 1H), 6.09 (d, J=1.7Hz, 1H), 3.74 (m, 1H), 3.69 (d, J=12.2Hz, 1H), 3.33 (d, J-12.2Hz, 1H), 2.33-2.52 (m, 2H), 1.61-1.89 (m, 7H), 1.37 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H), 0.82 (s, 3H); IR (KBr) 3010, 2970, 2890, 1505, 1480, 1380, 1205, 1165, 1095, 1010, 860, 765 cm^{-1}; EI-MS (70eV) 290 (M^+, 41.5), 275 (25.8), 232 (4.5), 217 (base), 149 (47.6).

Bis-MEM Ether 96. To a solution of diol **94** (20 mg, 0.08 mmol) in dry methylene chloride (1.0 mL) was added diisopropyl, ethyl amine (0.11 mL, 0.64 mmol) and methoxyethoxymethyl chloride (0.073 mL, 0.64 mmol) at 25°C. The resulting solution was stirred for 2h. The reaction mixture was diluted with Et_2O (25 mL) followed by washing with saturated aqueous NH_4Cl (25mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic phase was dried (Na_2SO_4) and removal of

solvent <u>in vacuo</u> followed with purification by chromatography on a column of silica gel (60-230 mesh, 5g, Et_2O-petroleum ether, 5:95) afforded 29 mg (85%) of bis-MEM ether **96** as a colorless liquid. ^1H NMR (80 MHz) δ 7.13 (d, J=1.7Hz, 1H), 6.07 (d, J=1.7Hz, 1H), 4.76 (d, J=5.0Hz, 2H), 4.69 (d, J=5.0Hz, 2H), 3.53-3.72 (m, 11H), 3.38 (s, 3H), 3.39 (s, 3H), 2.33-2.48 (m, 2H), 1.55-1.86 (m, 7H), 1.22 (s, 3H), 1.00 (s, 3H); IR (neat) 2980, 2880, 1510, 1455, 1370, 1290, 1250, 1205, 1000-1200, 855, 740, 705 cm^{-1}; EI-MS (70eV) 335 (M^+-2 x MOM, 0.1), 274 (14.2), 261 (15.6), 247 (M^+-2 x MEM, 9.5), 163 (68.7), 121 (base).

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