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Approaches to the Synthesis of Guaianolide and Pseudoguaianolide Natural Products via Furan Terminated Cationic Cyclizations

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Gary Michael Johnson

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Major professor

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APPROACHES TO THE SYNTHESIS OF GUAIANOLIDE AND PSEUDOGUAIANOLIDE NATURAL PRODUCTS VIA FURAN TERMINATED CATIONIC CYCLIZATIONS

By

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ABSTRACT

APPROACHES TO THE SYNTHESIS OF GUAIANOLIDE AND PSEUDOGUAIANOLIDE NATURAL PRODUCTS VIA FURAN TERMINATED CATIONIC CYCLIZATIONS

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The guaianolides and pseudoguaianolides are members of a class of natural products which possess a bicyclo(5.3.0)decane skeleton. These functionally and stereochemically complex natural products have exhibited a broad and potent spectrum of biological activities; and as a result have been the targets of extensive synthetic studies.

As part of a general program in furan chemistry, we have examined and demonstrated the utility of furans as di-anions in annulation sequences. When coupled with the ability of the furan nucleus to serve as the operational equivalent of a variety of acyclic, carbocyclic, and heterocyclic systems, this methodology should serve well in the synthesis of complex systems such as those represented by the guaianolides and pseudo-guaianolides.

We will describe general and flexible approaches to guaianolide precursors, utilizing furan terminated cationic cyclizations to form the crucial bicyclo(5.3.0)decane ring system. Pseudoguaianolides are obtainable through a simple modification of these precursors.

For Vita

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INTRODUCTION

For close to a decade, our group has been actively pursuing new synthetic methodology applicable to the total synthesis of a wide array of biologically active natural products[1]. The thrust of our research has centered around the preparation of these natural products via heteroaromatic precursors, utilizing a strategy which employs the heterocycle as an integral part of the bioactive molecule.

This approach might be contrasted to many prior synthetic endeavors, directed toward furan or butyrolactone containing natural products, which involved the generation of complex carbocyclic intermediates to which the heteroaromatic ring was then appended (Figure 1). For example, consider the numerous syntheses of bicyclo(5.3.0)decane containing natural products.

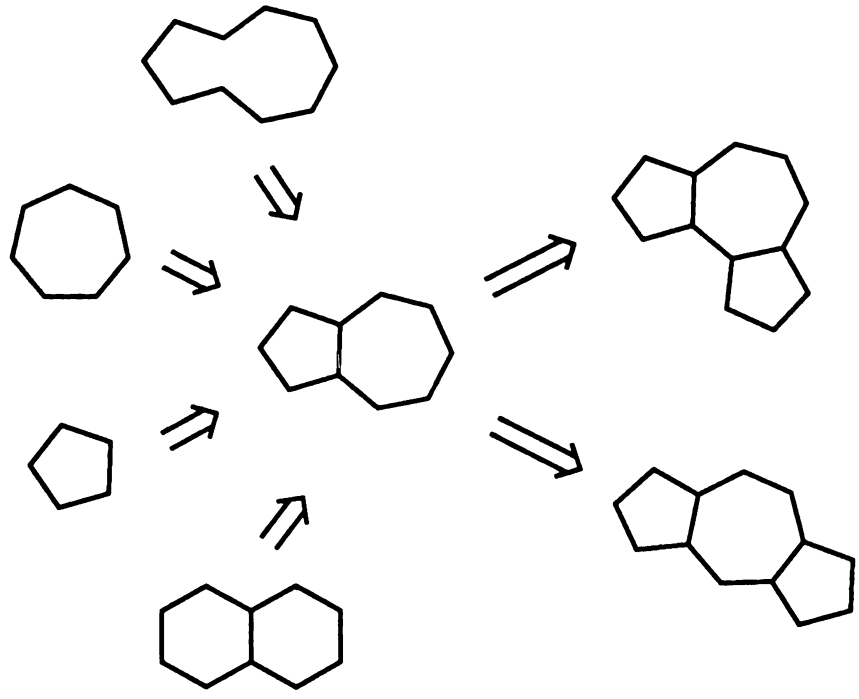
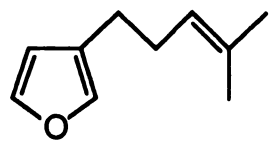


Figure 1: Early Transformations To Tricyclic 5.7.5 Systems

The approach most often followed (8 syntheses)[2] began with a cyclopentane ring, and appended on a cycloheptane; with the butyrolactone being added last. Several syntheses based on a trans-annular cyclization[3] of a cyclodecane precursor have been reported, as well as several others, proceeding by rearrangement of a hydronapthalene precursor[4] to provide the five-seven ring system directly. The final method which has been used is the construction of a five membered ring onto a preformed seven membered ring[5].

Our group has developed a novel approach, which employs unique heterocyclic chemistry as a profitable way to construct the core nuclei of a number of bioactive molecules[1]. Toward this end, the heterocycle furan was found to possess functional and structural features which would judiciously lend themselves to chemical exploitation, and allow the preparation of several diverse classes of complex natural products. We will illustrate this approach within the context of preparing a furan-containing bicyclo(5.3.0)-decane ring system.

Early successful syntheses in our group[1a] produced the simple natural products Perillene **1**, and Dendrolasin **2**, from readily available furan precursors in a concise and high yield approach (Figure 2). With these results



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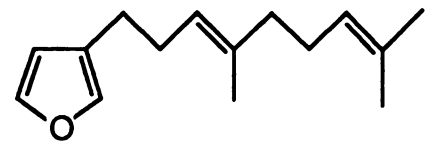


2

Figure 2: Perillene (1) and Dendrolasin (2)

in hand, we next examined methodology that would effect a practical approach to more complex molecules, possessing the framework and substitution patterns[1b-g] found in Figure 3. This protocol would lend itself well to the recognized ability of a furan to undergo electrophilic substitution

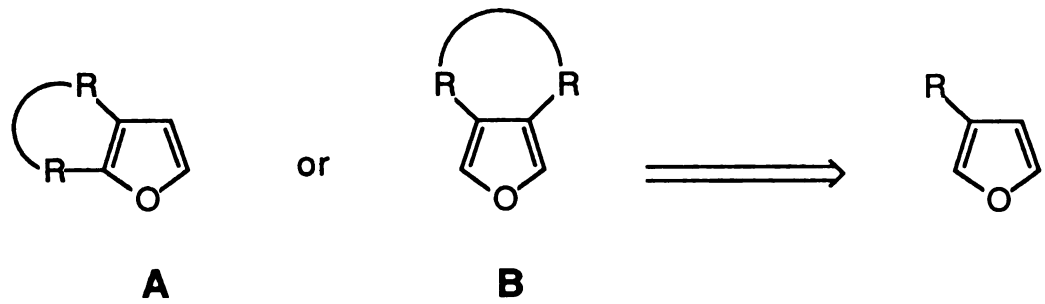


Figure 3: Furan Substitution Patterns

at the alpha position; allowing access to substructures with framework A, or B in the event that the alpha position was first blocked.

The postulated cationic cyclization (Figure 4), in which the furyl moiety was the cyclization terminator, was not well precedented in the literature. However we hoped to avail ourselves of the extensive body of knowledge accumulated in this field through the elegant studies[6] of Johnson, Van Tamelen, Goldsmith, and a number of other workers. It seemed likely that

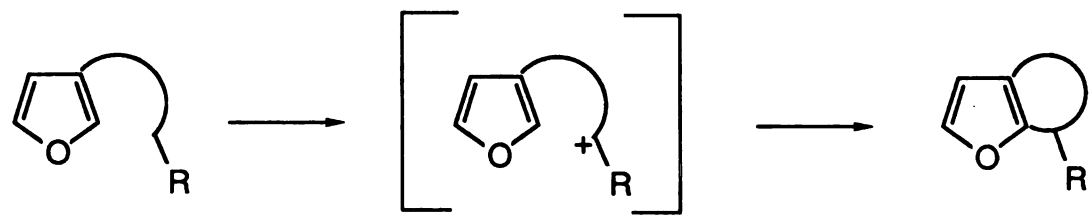


Figure 4: Furan Terminated Cationic Cyclization

the absence of literature precedent involving furans as cyclization terminators was due to a combination of factors, including the inaccessability of suitable starting substrates, the poor nucleophilic character of the furyl residue relative to standard terminator functions, and the increased acid lability of a disubstituted product furan relative to the starting material.[1c] It therefore became a goal of our group to solve these problems, and to demonstrate the ability of a furan to act as a terminator in cationic cyclizations. In addition, the furan in a cyclic framework, might then stabilize

a specific conformation of the cyclized product, allowing the development of peripherial stereocenters via standard cyclic strategy. Roberts[7] has shown that a double bond in the seven membered ring will place it in a chair conformation; thus a furan should provide an equivalent control element, allowing the use of established cyclic methodology. After serving this purpose, the furyl substituent might then be unravelled to a variety of useful functionalities.

We have now successfully incorporated a furan into the framework of a number of fused, spirocyclic, and bridged ring systems[1c-i] (Figure 5). Among the compounds prepared in the early studies were Pallescensin-A[1c] **3a**, and

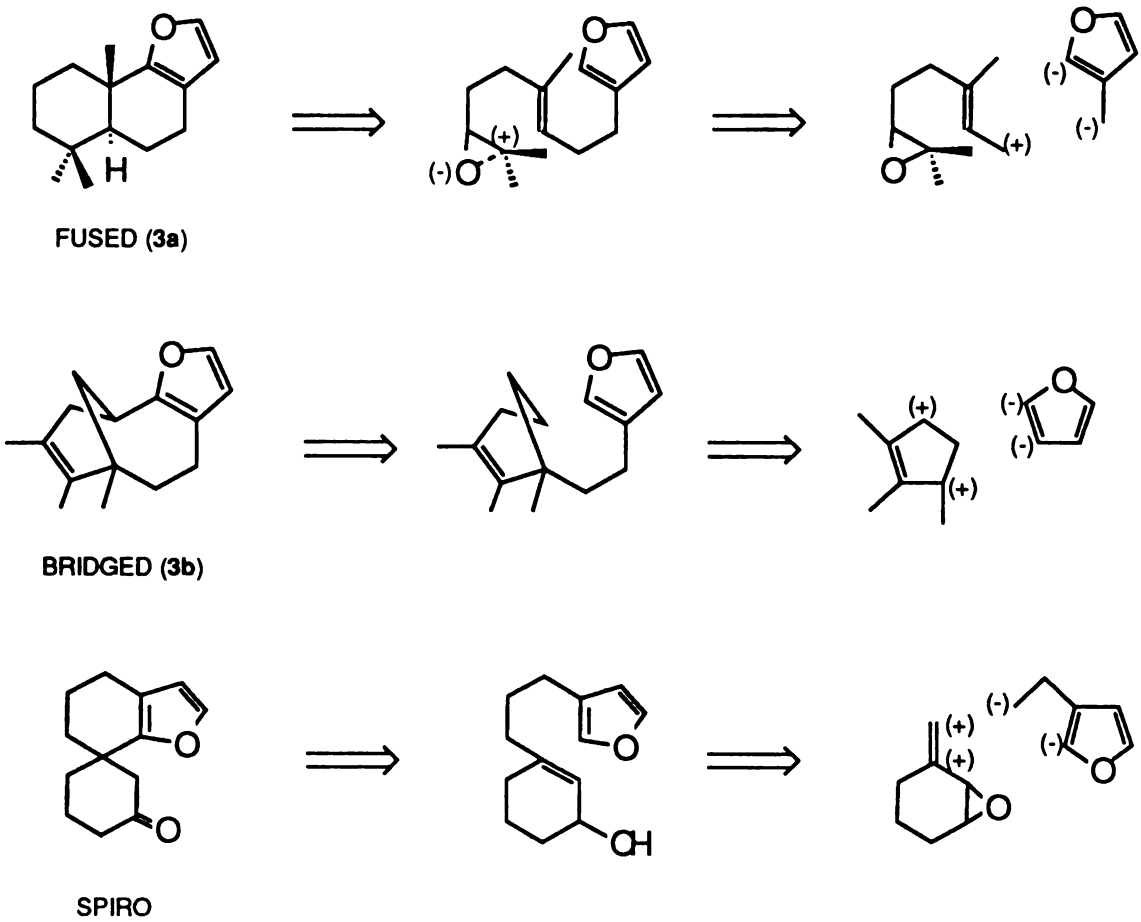
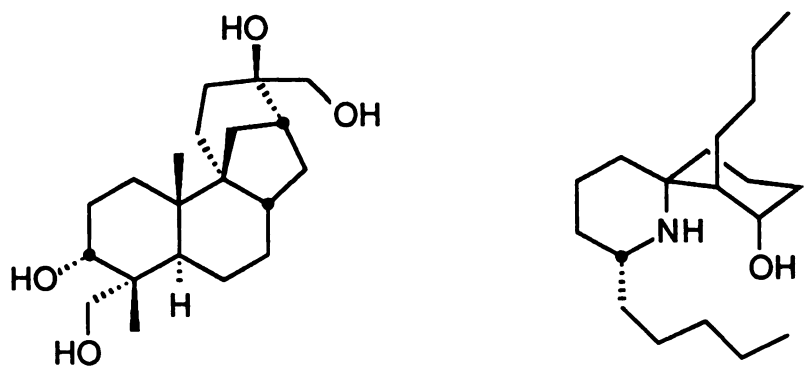


Figure 5: Fused, Bridged, and Spirocyclic Ring Systems

Nakafuran-9[1d] **3b**. More recent successes, utilizing a furan as a terminator, have included the formal total syntheses of the potent antiviral agent (±) Aphidicolin[1i] **4**, via an epoxide initiated cationic cyclization, and the neurotoxic alkaloid (±) Perhydrohistrionicotoxin[1j] **5**, via a regiospecific n-acyliminium ion initiated cationic cyclization (Figure 6). These successes



4 **5**

Figure 6: Aphidicolin (4) and Perhydrohistrionicotoxin (5)

encouraged us to concurrently pursue several other classes of stereochemically complex bioactive natural products that contained within their framework, five membered, oxygenated, heterocyclic rings, in various states of oxidation[8]. These classes included guaianolides[9a], pseudoguaianolides[9a-c], tiglanes[10], daphnanes[10], and ingenanes[10]. These classes of natural products, available in small quantities from their plant sources, have served as synthetic targets as a result of their broad and potent biological activities[11], which include anti-tumor, anti-neoplastic, anti-leukemic, allergenic, anti-helmenthic, anti-feedant, analgesic, contraceptive, molluscicidal, and anti-inflammatory properties. Many members of these classes of compounds have been prepared; however, most of the more complex pseudoguaianolides, daphnanes, ingenanes, and tiglanes have not yet yielded to total chemical synthesis. Many of the natural guaianolides and

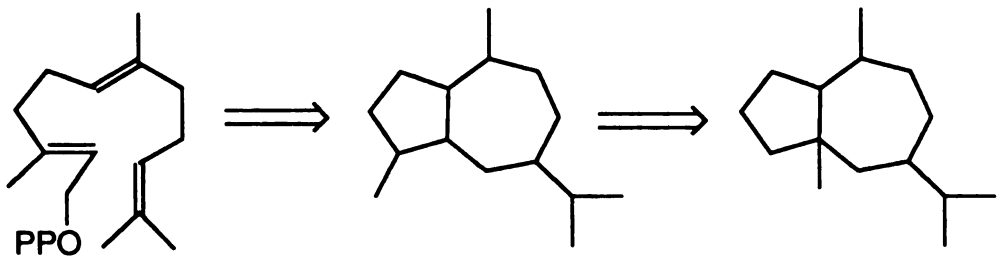


Figure 7: Biosynthetic Transformation From trans-Farnesyl Pyrophosphate

pseudoguaianolides possess bicyclo(5.3.0)decane nuclei to which is fused a butyrolactone ring. These sesquiterpene lactones are thought to be derived biosynthetically[9b] (Figure 7) from trans-farnesyl pyrophosphate. Furthermore, the pseudoguaiane skeleton is thought to result from a

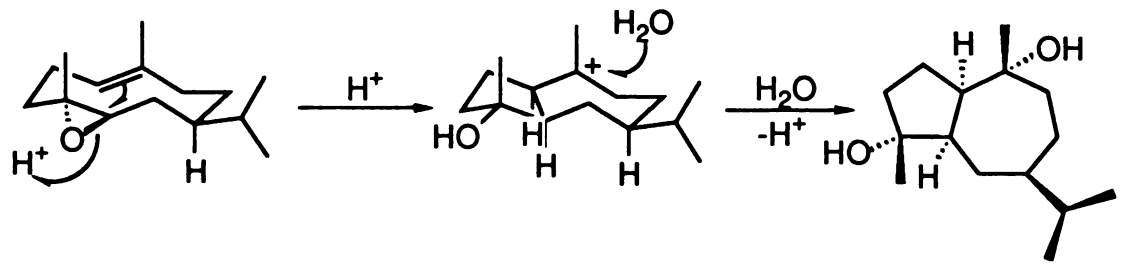


Figure 8: A. Biogenesis Of cis-Fused Guaianolides From A Germacrolide-4,5-Epoxide In A Chair Like Transition State

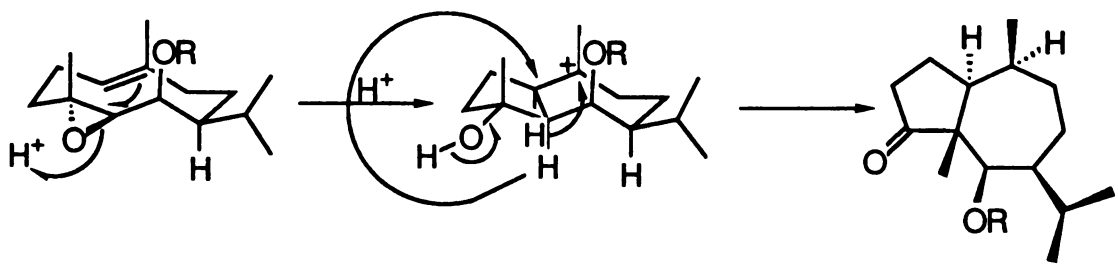


Figure 8: B. Biogenesis Of A trans-Fused Pseudoguaianolide From A Germacrolide-4,5-Epoxide In A Chair Like Transition State

migration of the C-4 methyl moiety to C-5 during biogenesis. While these transformations have yet to be experimentally proven, possible routes[12] are depicted in Figure 8. The pseudoguaianolide depicted in Figure 8 is further categorized as an ambrosanolide, which contains the C-10 methyl in the beta orientation; as opposed to the helenanolides, which have the C-10 methyl in the alpha orientation. The ambrosanolides are further differentiated from the helenanolides in that the former has a lactone ring closed predominently toward C-6, with the C-6 oxygen moiety in the beta orientation, and the latter has the lactone ring closed toward C-8, with the C-8 oxygen moiety having both alpha and beta orientations.

Representative guaianolides chosen for this study were Estafiatin[13] **6**, and Compressanolide[14] **7**, which possess a cis ring fusion, and a butyrolactone

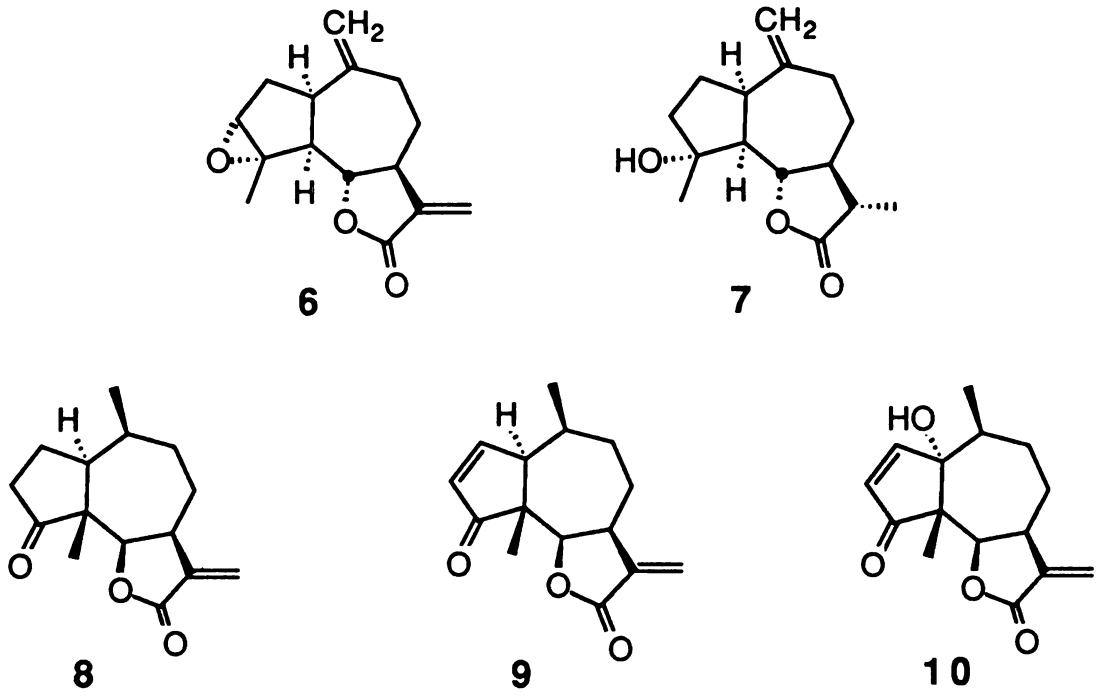
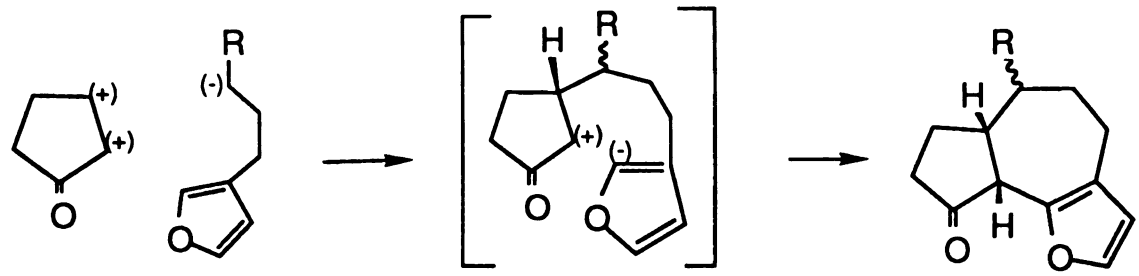


Figure 9: Estafiatin (6), Compressanolide (7), Damsin (8), Ambrosin (9), and Parthenin (10)

ring moiety fused to a seven membered ring (Figure 9). The pseudoguaianolide targets chosen were Damsin[15] **8**, Ambrosin[16] **9**, and

Parthenin[17] **10**; all ambrosanolides containing a trans fused 5 - 7 ring junction and a pendant butyrolactone moiety.

Having previously demonstrated the ability of the furyl moiety to successfully participate in annulation sequences, resulting in a regiocontrolled furan terminated cationic cyclization[1c,d], it was decided to approach compounds **6 - 10** via a similiar pathway. As illustrated in Figure 10, the coupling of a hypothetical cyclopentane di-cation equivalent, selectively at the beta position, with a furyl di-anion equivalent would lead to the substituted cyclopentane **13**, which after cyclization by a Friedal-Crafts type process, would afford **14**. For this sequence to succeed, the reactivities of the



11 **12** **13** **14**

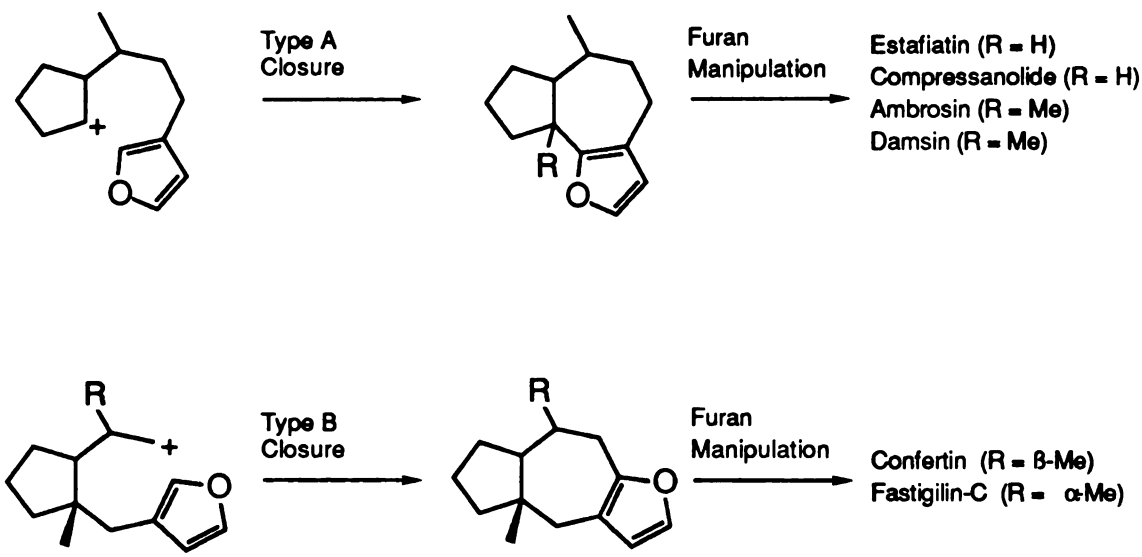
Figure 10: Furan Terminated Cationic Cyclization Sequence

di-anion and di-cation equivalents would need to be adjusted such that only one regioisomer results from the initial carbon-carbon bond formation. With respect to the furyl moiety, selectivity could be guaranteed by relying on the vastly different levels of reactivity displayed by a side chain furyl organometallic and the neutral furan with regard to an electrophile. In order to assure regiochemical integrity in the initial carbon-carbon bond forming sequence, we anticipated utilizing a cyclopentane di-cation equivalent in which the second site of electron deficiency was developed as a result of the chemistry employed in the first carbon-carbon bond formation. In such a fashion **14** could be produced possessing a variety of **R** functions, eventually leading to Estafiatin **6**, and Compressanolide **7**.

A second and important consideration that heightened our interest in **14**, was the possibility of introducing the requisite, ring junction methyl moiety as part of the starting cyclopentane equivalent, or via alkylation of the putative thermodynamic enolate of **14**; which would constitute entry into the pseudoguaianolides, perhaps affording eventually the ambrosanolides **8 - 10**. Finally, alteration of the nature of the di-cation and di-anion equivalents could also provide access to more highly oxygenated compounds, and yield products of annulation sequences with alternate furan placement; thus furnishing assorted helenanolides and tiglane diterpenes.

RESULTS AND DISCUSSION

As part of our general program in furan chemistry, we envisioned the construction of the substituted bicyclo(5.3.0)decane ring systems via furan terminated cationic cyclizations as is shown in Scheme 1. The placement of the furan terminator relative to the preformed five membered ring dictates



Scheme 1: Cyclization Types and Target Structures

that the *Type A* closure will provide us with a route towards the desired substrates of this study. This *Type A* closure might be accomplished by either of the two paths described in Figure 11. In *path a* , the initiating function is held exo to the forming cycle; whereas, in *path b* , the initiator is part of the

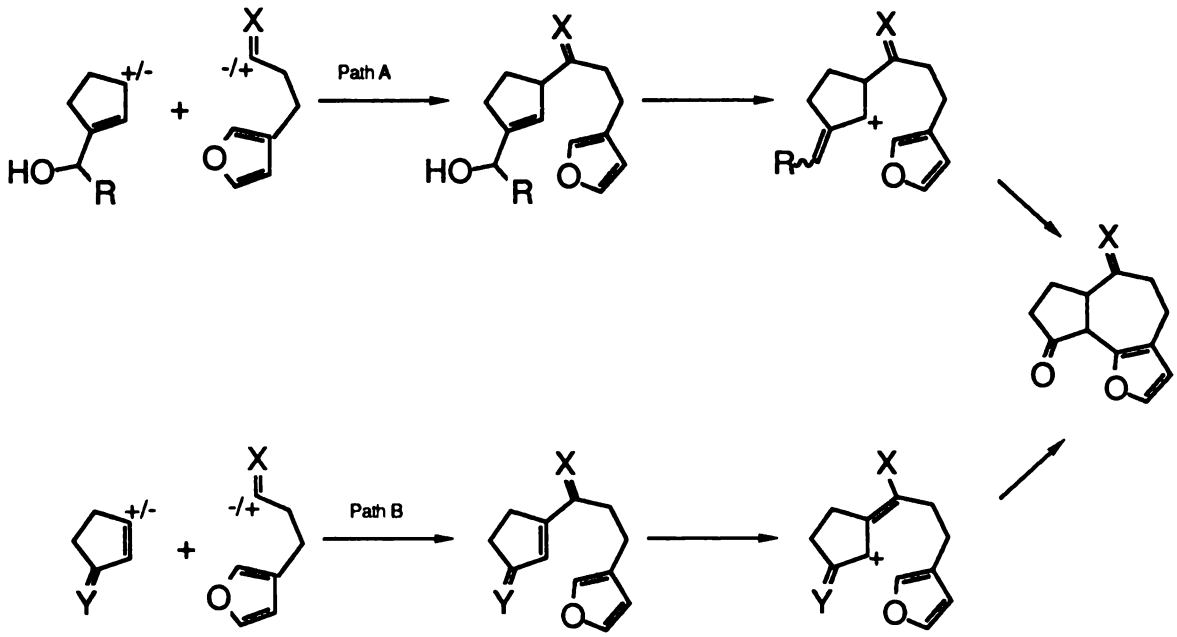
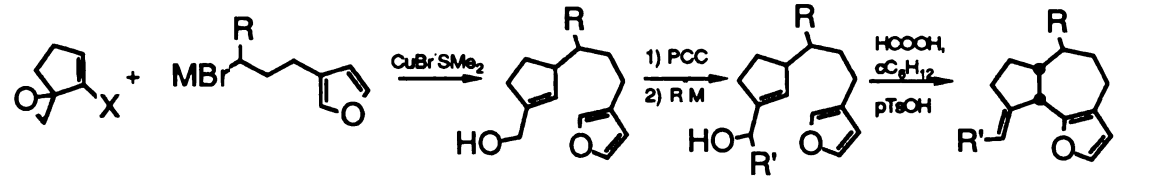


Figure 11: Type A Cyclization; Path A and Path B

forming seven membered ring. Having successfully utilized vinyl-spiro epoxides[18] as cyclohexane di-cation equivalents in the past, we chose to initially examine *path a*. These sequences, employing the vinyl-spiro epoxides prepared from cyclopentenone and 2-methyl-cyclopentenone, are shown in Scheme 2. The depicted scheme suggests that guaianolides and pseudoguaianolides might be readily approached by simply altering **X**=H to **X**=Methyl in the spiro epoxide **15**. In practice we were unable to realize this goal, for although we were able to prepare methyl substituted **15**, every attempt to react the compound in $Sn2'$ fashion with Grignard reagent[19] **16a** (Cu^{I}) resulted in epoxide opening and addition of the organometallic to the beta-gamma unsaturated aldehyde. However, **15** (**X**=H) reacted smoothly with organometallics **16** to afford allylic alcohols **17** (Scheme 2, 69-85% yields). Utilization of $CuBr{\cdot}SMe_2$[20] in the sequence (**16b => 17b**) was found to be crucial to its success, as CuCN provided only dimerization of the vinyl Grignard. Moreover, the use of the vinyl Grignard $MgBr_2{\cdot}Et_2O$[21], (**16b**, => **17b**) rather than the initially produced vinyl lithium, was found to be

important as the lithium derivative afforded less than 20% of the desired alcohol **17b**.

Our next task was the cyclization of the product primary allylic alcohols, an endeavour which we had examined previously in model systems without success. We exposed alcohols **17** to a variety of reaction conditions to no avail. We were unable to obtain even trace quantities of the desired tricyclic products. Our model structure suggested the utility of secondary allylic alcohols as initiators for furan terminated cyclizations, therefore we treated alcohols **17** with PCC to give the related aldehydes **18**, which were coupled

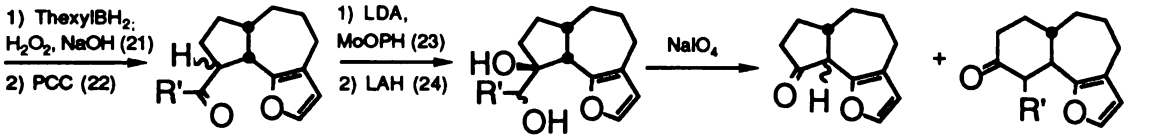


15 X=H

16 R	M	**17** R	Yield
a) H	Mg	a) H	85%
b) =CH_2	Li, $MgBr_2$	b) =CH_2	69%

19 R	R'	Yield
a) H	Me	84%
b) H	Ph	64%
c) H	pMeOPh	63%
d) =CH_2	Me	69%

20 R	R'	Yield
a) H	Me	95%
b) H	Ph	87%
c) H	pMeOPh	74%
d) =CH_2	Me	72%



22 R'	Yield
a) Me	42%
b) Ph	45%
c) pMeOPh	40%

24 R'	Yield
pMeOPh	60%

25 Yield: 35%

26 R'	Yield
pMeOPh	51%

Scheme 2: First Generation Synthesis of Type-A System

with several organometallic reagents to provide the corresponding secondary allylic alcohols **19** (63-84% yields, 2 steps). These secondary alcohols were readily cyclized upon exposure to a two phase mixture of cyclohexane-formic

acid, followed by a catalytic amount of tosic acid[22], providing olefins **20** (74-95% yields). During the course of this reaction we observed, via TLC, intermediate formate esters, which have been isolated and identified. The addition of catalytic tosic acid, a stronger acid, serves to either surpress the formation of allylic formates and facilitate cyclization, or to induce the allylic formates to cyclize. In the absence of tosic acid we obtain only 50 - 70% of **20**, along with 20 - 40% of the corresponding formate esters.

With **20a** readily in hand, we next studied its conversion to our desired common intermediate ketone **25** by either a direct cleavage, or via a two step sequence (Figure 12). Toward that end, we submitted **20a** (**R**=H, **R'**=Me) to a variety of reagents designed to vicinally hydroxylate the double bond or directly cleave the olefin. These included: a) (i) catalytic or stochiometric OsO_4[23], (ii) $NaIO_4$[24]; b) $KMnO_4$[25]; c) catalytic and stochiometric RuO_4[26]; d) O_3[27]; e) MCPBA followed by acidic aqueous periodate. With the exception of condition e (3%) we were unable to obtain **25**.

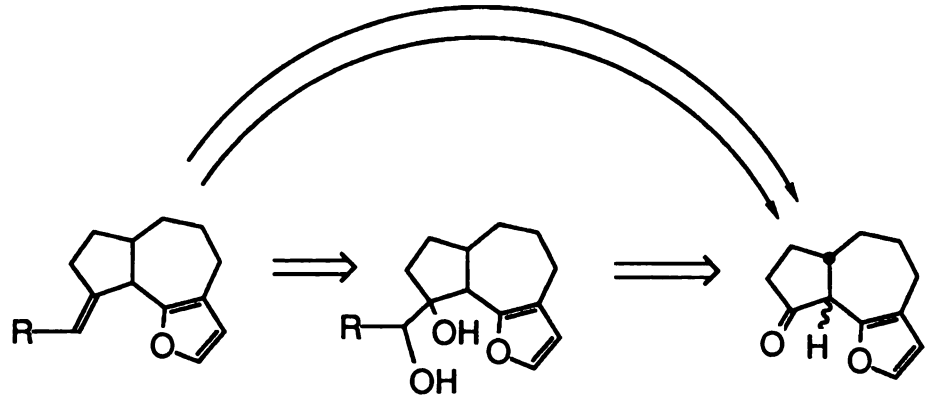
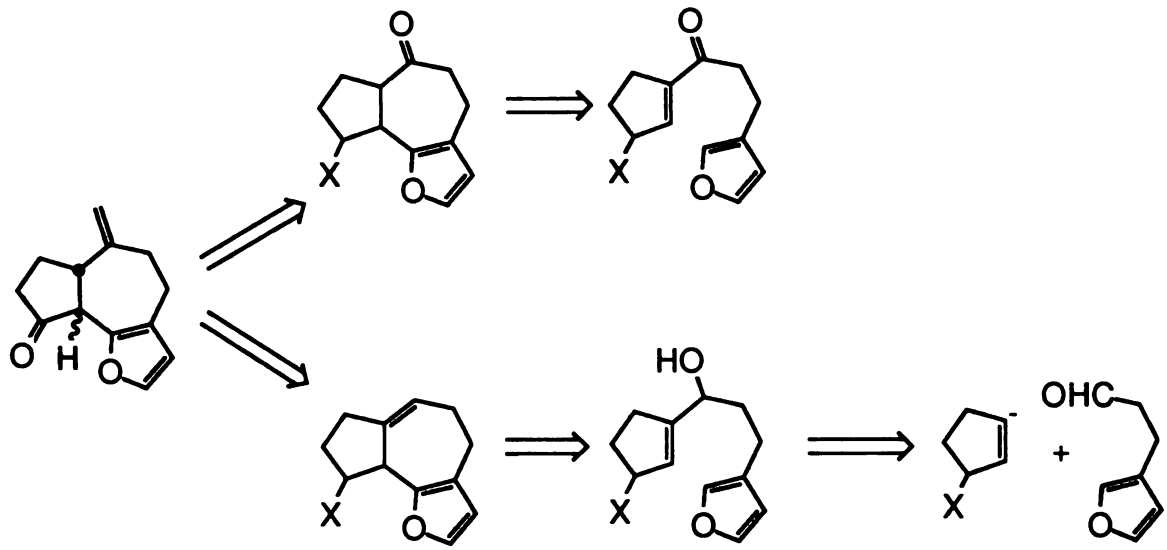


Figure 12: Olefin to Ketone Conversion (Direct or 2 Step)

Given these difficulties, we elected to examine the multi-step approach outlined in Scheme 2. Olefins **20** uneventfully afforded ketones **22** (40 - 45% overall yield for the three steps depicted). At this point, a number of alternatives were examined including Baeyer-Villager oxidation[28] and enol ether ozonolysis[29], all to no avail. In each of these cases we observed either no reaction, or destruction of the starting substrate. However, smooth hydroxylation (MoOPH[30]) of the enolate of **22c** (**R'**=pMeOH) led to diol **24**

after LAH reduction (60% yield two steps, stereochemistry not determined). Cleavage of **24** occured upon exposure to $NaIO_4$, affording an unoptimized mixture of desired ketone **25** (35% yield) and a pinacol-type rearrangement product **26** (51% yield).

While the *path a* route described in Scheme 2 does provide **25**, it is altogether too long, and the overall yield is an unacceptable 3%. This prompted us to examine the alternate *path b* (Figure 11) *Type A* cyclization,

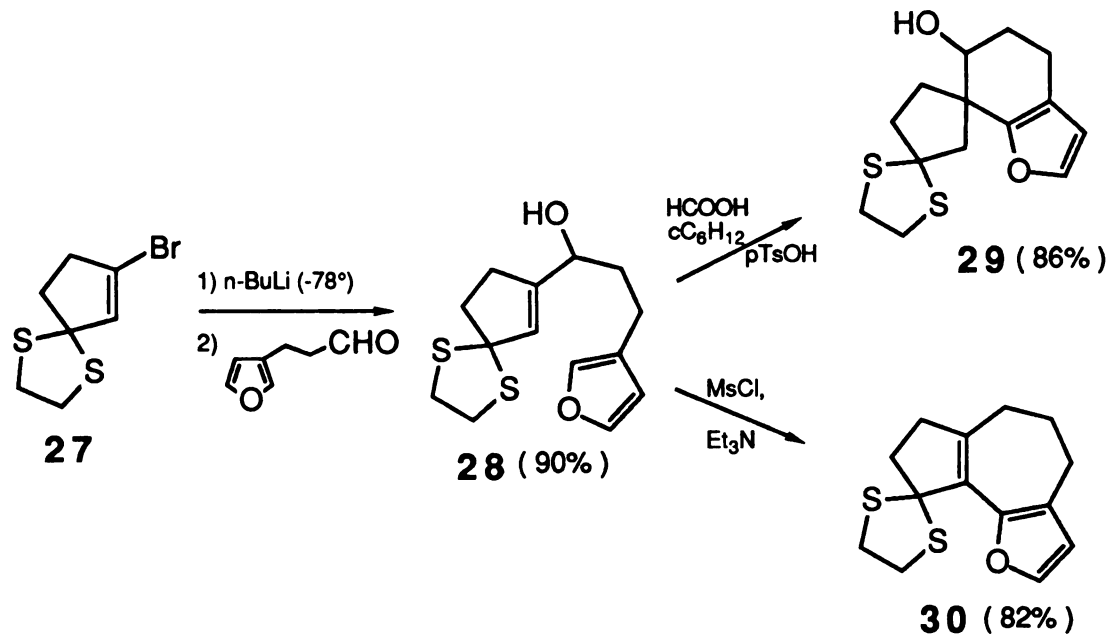


Scheme 3: Alternative Approaches to the Synthesis of the Type A System

as is outlined in Scheme 3. As shown, we had a choice of two intersecting approaches, an allylic alcohol mediated closure, and an enone initiated closure, both of which were available from the same starting materials. In this sequence, we hoped to avoid the troublesome C=C cleavage by carrying the necessary A-ring carbonyl center into the sequence either directly, or in a protected form. Both the allylic alcohol and enone substrates were available from 3-(3-furyl)propanal[31], and a substituted cyclopentene synthon which was prepared by the procedures[32] of Swenton and Piers.

The dithioketal **27**, synthesized from 1,3-cyclopentanedione[32], was metallated (n-BuLi, THF, -78°) and reacted with 3-(3-furyl)propanal to provide

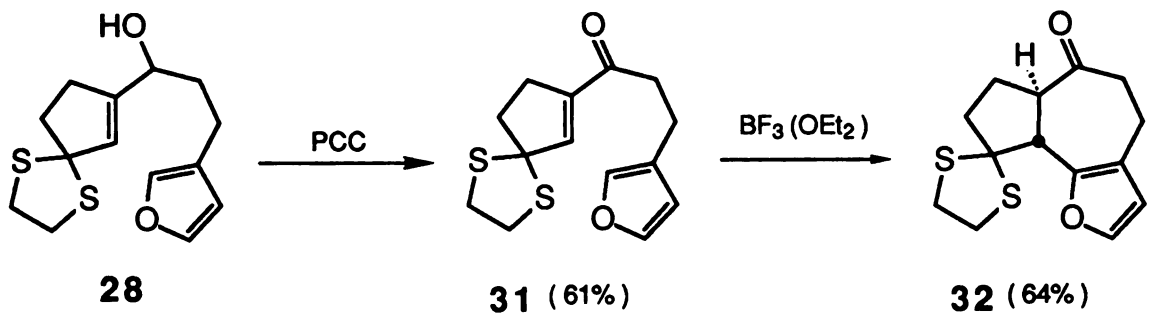
the desired allylic alcohol **28** in 78% yield (Scheme 4). Exposure of **28** to our "standard" allylic alcohol cyclization conditions (formic acid/cyclohexane; tosic acid) led exclusively to the spirocyclic **29** in 86% yield. A rationale for this unexpected observation is the formation of a sulfur stabilized allylic cation resulting from the rupture of the dithioketal sulfur - carbon bond.



Scheme 4: AlternativeType A Cyclization

An alternative procedure[33], to eliminate this unwanted competative process via specific C - O bond activation, involved treating **28** with mesyl chloride and triethyl amine. The resulting product was found to be **30** (82% yield), in which the double bond was observed to have migrated from the 1,10 position into the ring juncture. This event, though troublesome, would not necessarily doom the approach. Based upon the assumption that the derived enone (dithiolane deprotection) might be readily realized, we considered the likelihood that a "thermodynamic" enolization would provide access to the needed carbon-10 position vs formation of a homoannular cyclopentadiene-type dienolate.

Support for this rational came from calculations using the Dahlinger MM2 protocol[34] which suggested that the desired "thermodynamic" dienolate should be more stable by ca. 1.4 kcal/mole With this supporting evidence, we attempted to generate the requisite enone **25** (with 1,5 unsaturation) from the dithiolane **30**. However, under a wide variety of reaction conditions,[35] we were unable to effect this transformation. This difficulty added to the uncertainty resulting from the stranding of the double bond in the 1,5 position caused us to consider the enone initiated *path b* closure shown in Scheme 5.



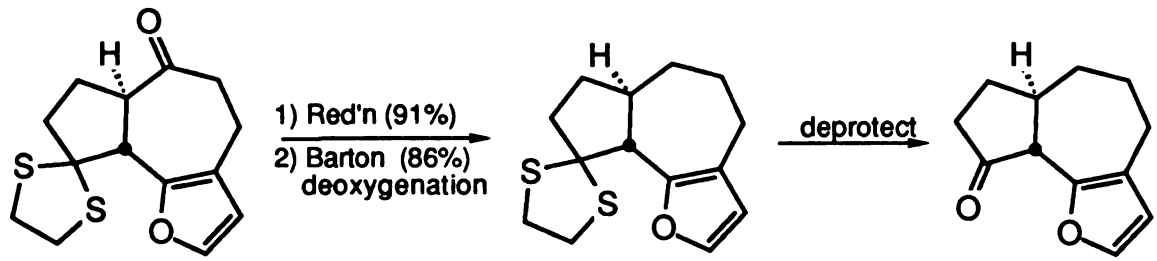
28 **31** (61%) **32** (64%)

Scheme 5: AlternativeType A Cyclization

Allylic alcohol **28** was oxidized with PCC to provide enone **31** in 61% yield. Having previously studied enone initiated cyclizations,[1c,d] we treated **31** with $BF_3 \cdot Et_2O$ to provide the trans fused product **32** in 64% yield (Scheme 5) with minimal amounts of the cis and spirocyclic fused isomers. Support for the trans configuration in **32** comes from a comparison of the cis and trans isomers with literature data, and is in agreement with MM2 calculations,[34] which suggest that the trans isomer is more stable than its cis adduct by about 2 kcal/mole.

With ketone **32** in hand, we next needed to examine the introduction of two carbon atoms for entry into the pseudoguaianolide manifold, and one carbon atom to prepare the guaianolide nucleus. However, we thought it

would be prudent to initially compare the product of Scheme 6 to the hard won ketone **25** of Scheme 2. Toward that end, we reduced **32** with $LiBH_4$

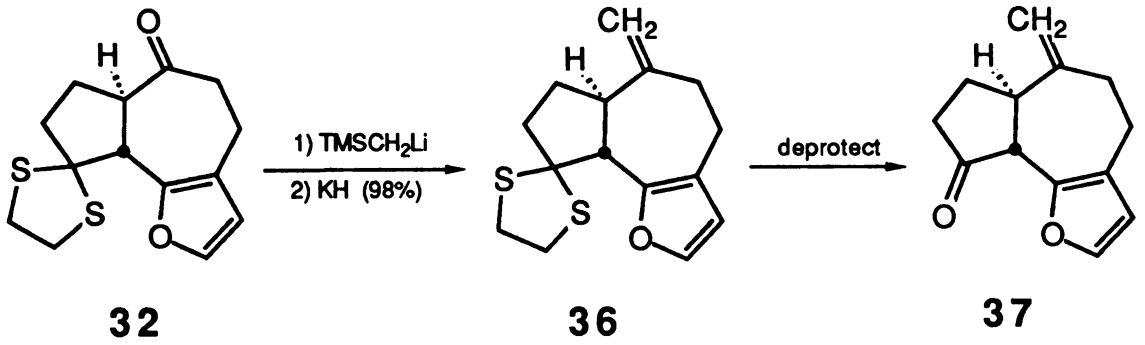


32 **33** **34**

Scheme 6: Deoxygenation, of Keto-dithiolane

(91%) to furnish a single alcohol of unknown configuration. Using Barton deoxygenation methodology,[36] we prepared the corresponding xanthate ester (86%), which was cleaved using $HSnBu_3$ to provide dithiolane **33**. Finally, we sought to deprotect **33** to provide ketone **34** for a direct comparision to compound **25**. Again, despite using a variety of reagents and conditions,[35] we were unable to obtain **34** in yields greater than 5%. We concluded that **34** and **25** were identical, based on NMR, MS, and IR data, and next considered the introduction of the needed exo-methylene carbon and the angular methyl moiety.

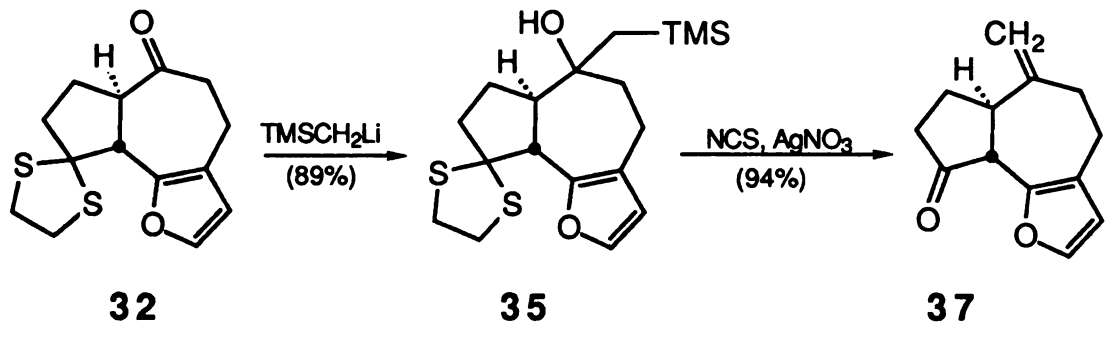
To effect the requisite ketone - olefin transposition of substrate **32**, we had available to us a number of synthetic techniques, namely Wittig chemistry,[37] Lombardo's reagent,[38] Peterson olefination,[39] or the Tebbe reagent,[40] among others. An examination of half a dozen variations[37] on the Wittig technology failed to provide the desired conversion with reproducible results or in good yields. The use of Lombardo's reagent, $ZnCH_2Br_2 \cdot TiCl_4$, (8-10 equivelents) provided olefin **36** in quantitative crude yield (94% purified). In addition, Peterson olefination, $TMSCH_2Li$ followed by KH, also provided olefin **36** in 87% yield for the two steps (Scheme 7). This latter result would



32 **36** **37**

Scheme 7: Attempted Deprotection of Olefin-dithiolane

later turn out to be fortuitous since we were once again frustrated in our attempt to deprotect dithiolane **36** to keto-olefin **37**. Under a variety of reagents and conditions,[35] we were unable to deprotect dithiolane **36** (Scheme 7) to obtain ketone **37** in more than 17% yield (grossly contaminated with mercury). We reasoned that many of the standard dithiolane deprotection protocols such as those involving Hg^{II}, Ag^{II}, tetrafluoroboric acid, NBS, etc., were likely to attack not only sulfur, but also possibly react with the exocyclic olefin or the disubstituted furan. Given these additional concerns, along with the previously indicated failures, we opted for a "simplified" substrate, i.e. the tertiary silylmethylcarbinol intermediate **35** (Scheme 8), for deprotection studies.



32 **35** **37**

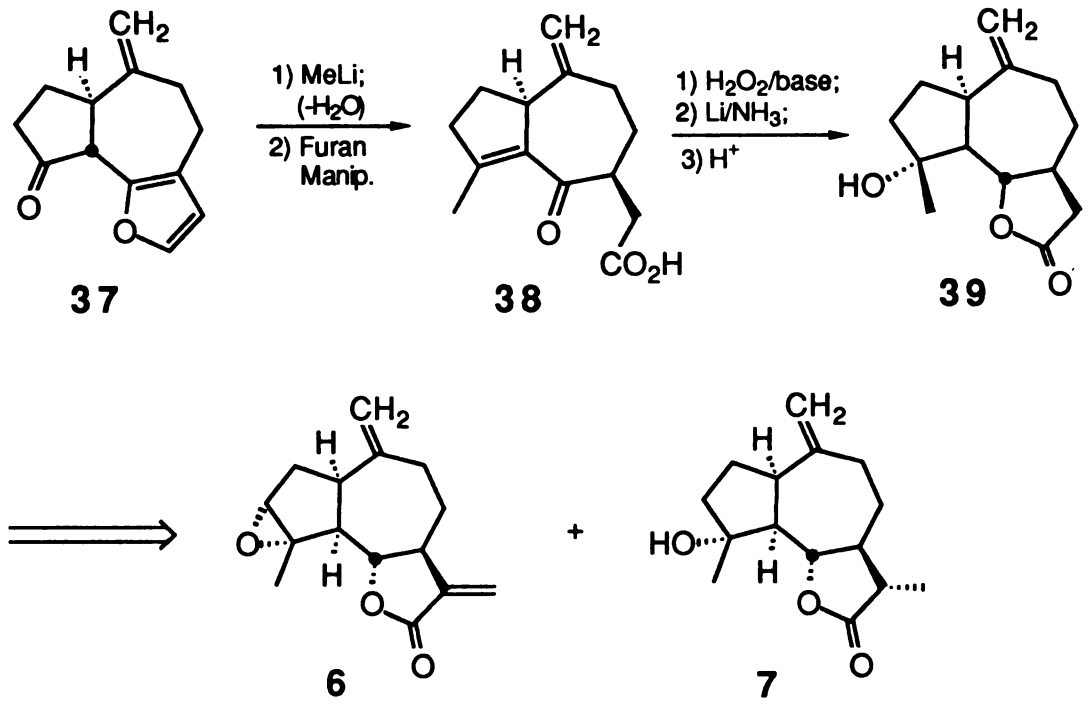
Scheme 8: Deprotection-Olefination of Keto-dithiolane

After a number of unsuccessful deprotection attempts, tertiary carbinol **35** was treated with NCS and $AgNO_3$, according to the procedure of Corey,[41]. To our delight, intermediate **35** underwent deprotection with concomminent hydrolysis to provide keto-olefin **37** directly in 94% yield. We believe that the ring juncture in **37** is trans, as would be expected via the synthesis of **37** from trans **32**. Further evidence for this configuration is given by Gonzalez.[42] He finds that the olefin resonances in the proton NMR for trans compounds similar to **37** appear as two distinct singlets, whereas in the cis compounds only one singlet is seen for both exo methylene protons.

The $AgNO_3$/NCS deprotection procedure failed when attempted on the substrates **30, 31, 33,** and **36**. Introduction of these substrates to the aqueous acetonitrile solution of $AgNO_3$ and NCS resulted in a black heterogeneous reaction mixture that provided either none or trace (<1%) amounts of the deprotected products. However, addition of substrate **35** to the reaction solution resulted in a pale yellow mixture, which became a snow white heterogeneous mixture over the course of the reaction. To date, we have not examined in detail the hydrolysis of dithiolane **35** in the presence of the by-products assumed to result from NCS, $AgNO_3$ catalyzed olefin formation. An observation which might be relevent is the complete absence, by TLC, of olefin **36** in the reaction mixture leading to **37**. We hope to examine these questions in more detail at a later date.

With tricyclic ketone **35** in hand (39% overall yield from **27**) we could now progress toward the preparation of both guaianolide and pseudoguaianolide natural products. The initial projected routes to Estafiatin **6** and Compressanolide **7** are shown in Scheme 9. Treatment of the trans ketone **37** with MeLi would give a tertiary alcohol which might be dehydrated to provide enone **38** after furan manipulation according to our previously published conditions.[43] Epoxidation, lithium/ammonia reduction, and lactonization should yield the desired intermediate **39**, which has previously been converted to Compressanolide by Vanderwalle.[44] Estafiatin[13] should also be readily available from **37**, via the corresponding Δ 3 - 4 olefin after dehydration and epoxidation as precedented in the literature.[45]

Our initial attempts to prepare **38** have not met with success. Alkyllithium addition to the ketone **37** was moderately successful, resulting in a 30 - 40% yield of tertiary alcohol, and 40 - 50% recovered ketone. This result was



Scheme 9: Guaianolide Route from Keto-Olefin 37

likely due to the enolization of the cyclopentanone. Attempts to add TMS-methyl-lithium resulted in almost quantitative recovery of starting substrate. We again examined Wittig chemistry[37] in an attempt to convert this ketone to an olefin, in a slight modification of our projected route. Once again, we were rebuffed, realizing gross mixtures of products in less than 50% recovered yields. Success was finally achieved by the treatment of ketone **37** with Lombardo's reagent[38], $ZnCH_2Br_2 \cdot TiCl_4$. Utilization of 8 - 10 equivalents, added in one portion provided the bis olefin **40** in 95% yield (Figure 13) as a 6/1 mixture of exocyclic/endocyclic olefins. We are presently working to unravel the furan in compound **40** to provide a lactone as in compound **39**. Initial attempts via direct silylation[1e] (n-BuLi, TMSCl) or indirect silylation[11] (bromination, followed by n-BuLi, TMSCl) have not proved fruitful, but we are continuing to examine these procedures at present. In addition we still have the option of utilizing a ketone intermediate like substrate **38**, which should ultimately provide us with **39**.

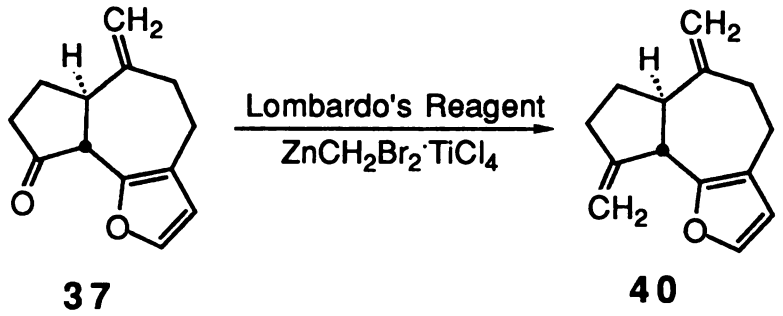
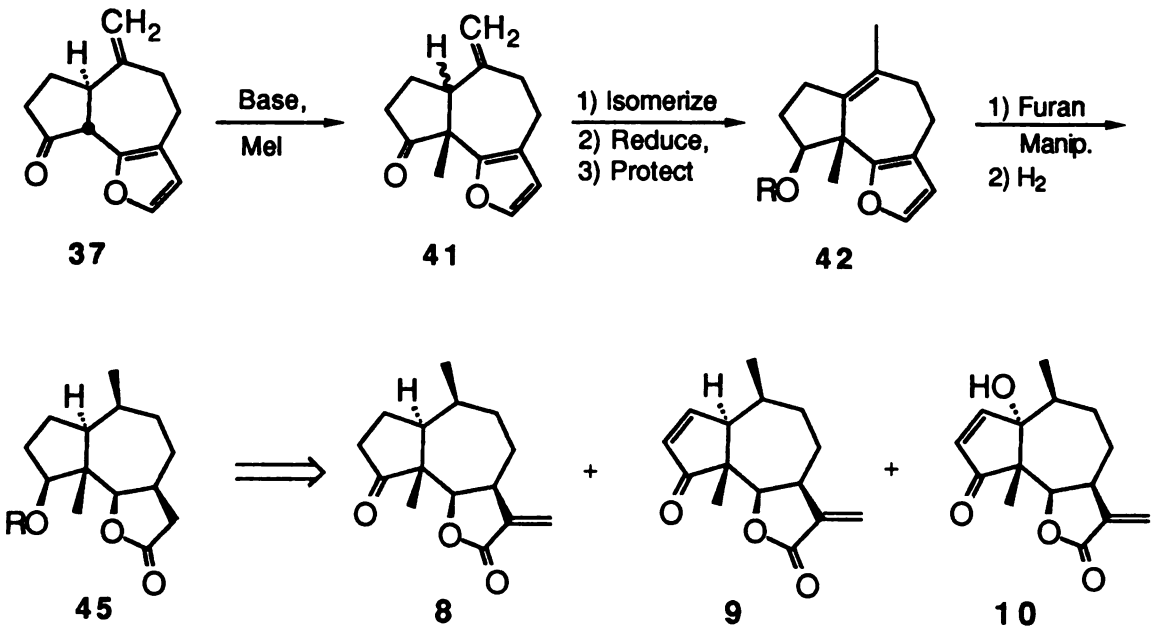


Figure 13: Preparation of Bis-Olefin

Our projected route to the pseudoguaianolides from ketone **37** is shown in Scheme 10. Alkylation of the thermodynamic enolate of **37** should provide substrate **41**, for which models suggest that a cis fusion might be favored. There appears to be a large degree of configurational freedom in the seven membered ring in the cis configuration, while the trans configuration is a

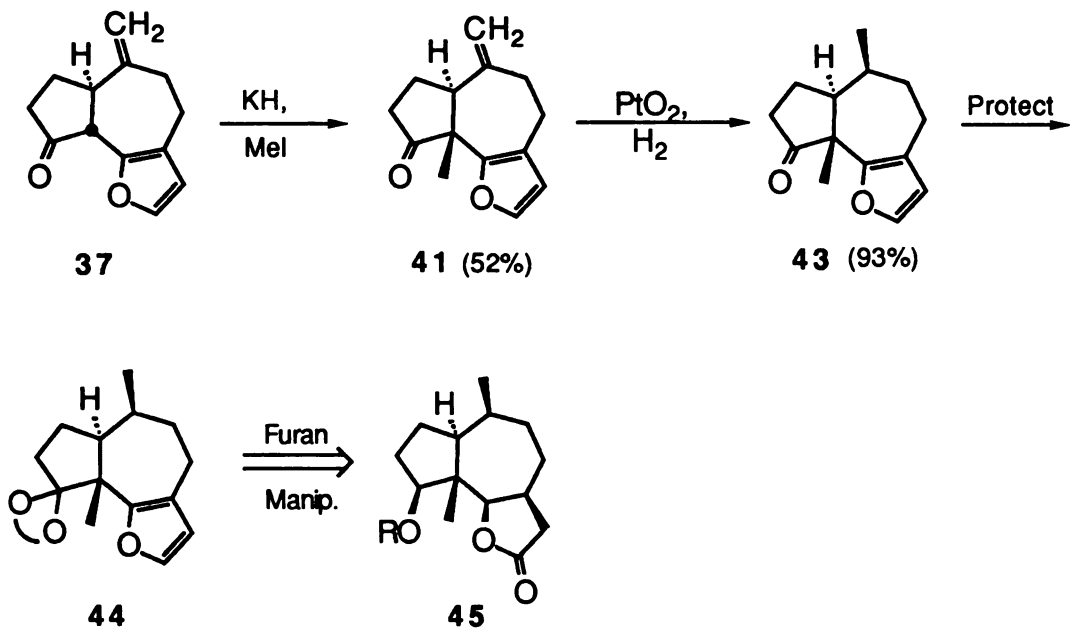


Scheme 10: Pseudoguaianolide Route from Keto-Olefin 37

rigidly locked, seven membered chair. Should this be the case, there is established literature procedures[46] for isomerizing the olefin in **41** to provide intermediate **42** after carbonyl reduction and protection. Manipulation of the furyl moiety, followed by hydrogenation should then lead to **45**, which has previously been transformed[15-17] into Damsin **8**, Ambrosin **9**, and Parthenin **10**.

Our initial attempts to prepare **41**, via LDA or KDA, followed by MeI resulted in mixtures of mono, bis, and tri methylated products in relatively low yields. However, the use of KH, followed by MeI provided 52% (unoptimized yield) of a single isomer, along with 35% of what appears to be a mixture of mono, di and/or tri substituted product. After literature comparison[47], and extensive proton, carbon, and 2D, studies[48], we have determined to the best of our knowledge that the adduct we obtained in 52% yield, **41**, has the desired trans ring juncture configuration. We believe the 35% mixture to contain the cis isomer along with di and tri methylated products, which are not separable.

With pseudoguaianolide intermediate **41** (trans ring juncture) in hand, we next attempted to reduce the seven membered ring olefin with Pd/C and hydrogen. At atmospheric and elevated pressures 35 - 100 psi (1-24 hours), we recovered almost exclusively starting material. However, using PtO_2/C[49] and hydrogen (atmospheric, 1 hour), we obtained a single product **43**, in 86-93% yields (Scheme 11). Once again, via literature comparison[47], and extensive proton, carbon, and 2D NMR,[48] we concluded that we have obtained adduct **43**, with both methyl groups in the cis conformation. Protection of ketone **43** as its ethylene ketal, **44**, was attempted with Noyori's[50] kinetic ketalization conditions. Initial results provided a mixture of a rearranged product, (methyl migration), and ketal **44**. We are presently working to improve these conditions, and unravel the furan, which should lead to compound **45**, and thus a formal total synthesis of our pseudoguaianolides Damsin, Ambrosin, and Parthenin.



Scheme 11: Pseudoguaianolide Route to Ketone 45

CONCLUSION

The bicyclo(5.3.0)decane products prepared during the course of this work have demonstrated that the furan terminated cationic cyclization sequences are viable routes for the preparation of functionally and stereochemically complex natural product precursors. The cyclization intermediates are readily available in concise high yield sequences from suitably functionalized furyl precursors. These materials should serve well as substrates for completing the preparation of both the guaianolide and pseudoguaianolide classes of natural products.

The unexpected difficulties encountered in the modification of the tri-cyclic intermediate prepared by our initial *path a, Type A* cyclization, proved to be only a minor annoyance, as our flexible furan methodology allowed us to circumvent the problems via our *path b Type A* cyclization. Starting from a dithiolane protected bromo-enone, the *path b* sequence provided a single precursor **37** for both guaianolides and pseudoguaianolides in five steps and 39% overall yield; after a tedious but successful search for a ketal deprotection protocol.

As previously discussed, vide infra, initial attempts to convert precursor **37** into our guaianolide targets have not met with success, i.e. the failure to unravel the furan to a butyrolactone ring. This may have been due to an over-abundance of olefinic sites in compound **40**, which causes interference with the normal reaction processes that have been used on past substrates[1]. Overcoming this difficulty might be accomplished by hydrolysis of compound **37**, followed eventually by olefin incorporation; or by the

preparation/manipulation of a tri-substituted furan in which a silicon, sulfur, or selenium substituent has been incorporated into the molecule.

Incorporation of a methyl group into the ring juncture of adduct **37**, followed by olefin reduction, has provided us with an advanced pseudoguaianolide intermediate **43**. To complete the synthesis of our pseudoguaianolide targets, the final obstacle is again the unraveling of the furan moiety to a butyrolactone ring, or butenolide equivalent. It has become increasingly apparent through this work, and that of co-workers using similiar methodology, that furan hydrolysis/oxidation is a substrate dependant phenomenon. We are confident in this case however, that our previously published methodology[1e,k] should result in the conversion of the furyl moiety in compound **43** to a lactone containing adduct. The presence of oxygen, and lack of olefinic sites should aid in this transposition, and hopefully remove the obstacles which are currently present in the guaianolide sequence.

In summary, this work has utilized furan as a terminator in cationic cyclization methodology to prepare tri-cyclic intermediates suitable for the synthesis of guaianolide and pseudoguaianolide natural products. Transformation of these intermediates to the desired bioactive products remains to be accomplished, with the hydrolysis/oxidation of the furyl moiety being the final major task.

EXPERIMENTAL

General: Tetrahydrofuran, ethyl ether, benzene, and hexane were dried by distillation under argon from sodium benzophenone ketyl. Di-isopropyl amine, collidine, and methylene chloride were dried by distillation from calcium hydride. N,N dimethyl formamide was dried by distillation from phosphorous pentoxide. N-butyl-, sec-butyl-, and t-butyl lithium in hexane were purchased from Aldrich Chemical Co., Milwaukee, Wis., and were titrated by the method of Watson and Eastham.[51] Magnesium metal was activated by successive washings with 0.1N aq. HCl, distilled water, acetone, and anhydrous ether respectively, and then dried in a dessicator over phosphorous pentoxide at reduced pressure.

Chromatography was performed using the flash technique of Still et. al.[52], using the silica gel and solvents mentioned. The column outer diameter (o.d.) is listed in millimeters. Thin layer chromatography used Merck SIL G/UV precoated glass plates. Spots were visualized by dipping into one of the following: 1) a solution of vanillin (1.5 g) in absolute ethanol (100. ml) and conc. sulfuric acid (0.5 ml), 2) a solution of phosphomolybdic acid (5.0 g) in absolute ethanol (100. ml); and then heating the plate.

Proton magnetic resonance spectra were recorded at 60 MHz (Varian T-60), 80 MHz (Varian FT-80), and 250 MHz (Bruker WM-250) as solutions in deuterochloroform unless otherwise indicated. Chemical shifts are reported in parts per million on the δ scale relative to a tetramethylsilane internal standard. Data are reported as follows: chemical shift (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, brs=broad singlet), coupling constant (Hz), integration). ^{13}C magnetic resonance spectra were recorded on a Bruker WM-250 spectrometer (68.9 MHz) and are reported in parts per million from tetramethylsilane on the δ scale.

High resolution mass spectra were performed by the M. S. U. Regional Mass Spectroscopy Facility; Dept. of Biochemistry, East Lansing, Michigan 48824. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 utilizing an INCOS 4021 data system. A Pye-Unicam SP-1000 infrared spectrophotometer was used to record infrared spectra using polystyrene as a standard. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All reactions, unless otherwise stated, were carried out under a blanket of argon in flame dried glassware, with the rigid exclusion of moisture from all reagents. Base washed glassware was prepared as follows: washing in an KOH/EtOH base bath, followed by distilled water, ammonium hydroxide, distilled water, absolute ethanol, and flame drying. Syringes, cannulas, needles, and spin bars employed with base washed glassware were also prepared in the same manner.

The preparation of 3-bromocyclopentenone and its dithiolane derivative were prepared according to the procedures of Piers[32a] or Swenton[32b].

3-(3-furyl)-propyl-1-bromide[19] (16a) - To a solution of triphenyl-phosphine (25.99 g, 99.2 mmol) in CH_2Cl_2 (600. ml), cooled in an ice water bath, was added 3-(2-furyl)-propan-1-ol[12h] (10.0 g, 79.4 mmol), followed by addition of NBS (17.66 g, 99.2 mmol) in 4 portions over ten minutes. After stirring at 0°C for four hours, the solution was warmed to RT and stirred one hour further. The solution was concentrated in vacuo; cast into hexane (350. ml), and stored overnight in a freezer. The precipitated Ph_3PO was removed by filtration through a pad of celite, the filter cake washed with hexane, and the combined filtrates were washed with $NaHCO_3$, and brine (250. ml ea.), dried ($MgSO_4$), and concentrated in vacuo to provide the crude product as a pleasant smelling, pale yellow liquid. Distillation (BP_{24} 93-97°C) provided 11.0 g, (73.3%) of **16a**. Rf=0.68 in hex/ether (1/1).

1-(1-hydroxymethyl)-3-(3-(3-furyl)-propyl)-1-cyclopentene (17a) - (A) To a solution of 1-((dimethylsulfonio)methyl)cyclopent-2-en-1-ol[1h], (3.78 g, 13.23 mmol) in THF (150 ml) in a 250 ml base washed round bottom flask, was added NaH (0.480 g, 15.87 mmol) in one portion. The mixture stirred for five and one half hours and was then cooled in a dry ice-isopropanol bath (-78°C). (B) To activated Mg metal (0.50 g, 20.6 mmol), in a 500 ml base washed round bottom flask with condenser, is added 10% of a solution of 3-(3 furyl)-propyl bromide[19] **16a** (3.00 g, 15.87 mmol) in THF (10. ml). After reaction began, the remaining 90% of the bromide solution was diluted with THF (85. ml) and added over one half hour, followed by gentle refluxing for two hours. The mixture was cooled in a dry ice-isopropanol bath, and CuCN (1.42 g, 15.87 mmol) was added in one portion. After stirring at -78°C for one hour, the

mixture was warmed to -45°C (dry ice-acetonitrile) for one half hour, then cooled to -78°C for one quarter hour. The spiroepoxide (A) at -78°C, was then added via cannula over one half hour. After stirring at -78°C for three hours, the mixture was warmed to RT over one and one half hours. The solution was then quenched with sat. aq. NH_4Cl (100 ml) and NH_4OH/H_2O (220 ml, 1:1). The mixture was saturated with NaCl, separated, and the aqueous phase was extracted with ether (3 x 100 ml). The combined organic layers were washed with $NaHCO_3$, and brine (200 ml ea.), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 200. g, 230-400 mesh, packed hexane/ether (4/1), run hexane/ether (2/1), 100 ml fractions) using the flash technique. Fractions 11-23 provided 2.089 g (76.6%) of **27a**. Rf=0.28 in (1/1) hexane/ether) as a pale yellow viscous liquid.

EI/MS (70 eV): 206(M+, 8.8), 188(14.9), 175(19.3), 159(5.5), 147(3.5),131(6.6), 123(8.6), 106(14.8), 95(47.3), 79(base), 67(83.3),53(56.3), 41(86.7)

^{1}H-NMR(250 MHz): δ : 7.31(t, J=1 Hz, 1), 7.18(brs, 1), 6.26(brs, 1), 5.06(m, 1), 4.16(s, 2), 2.67(m, 1), 2.40(t, J=7.5 Hz, 2),2.30(m, 2), 2.10(m, 1), 1.65-1.20(m, 5)

IR (Neat): 3640-3100, 2980-2880, 2860, 1500, 1450, 1430, 1380, 1160, 1020(w), 875, 775, 720 cm-1

3-(3-(3-furyl)-propyl)-cyclopent-1-ene-1-carboxaldehyde (Intermediate 18a) - To a solution of alcohol **17a** (1.00 g, 4.854 mmol) in CH_2Cl_2 (400 ml), in a 1L base washed round bottom flask, was added celite (25. g), followed by PCC (1.57 g, 7.28 mmol). After stirring two hours at room temperature, ice cold hexane (200 ml) was added and the mixture was filtered through a plug of celite/silica gel. The filtrate was dried ($MgSO_4$), and concentrated in vacuo, to give the crude aldehyde as a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 100. g, 230-400 mesh, hexane/ether (5/1), 30 ml fractions) using the flash technique. Fractions 10-16 afforded 0.667 g. (67.4%) of intermediate aldehyde **18a**. Rf=0.48 in (1/1) hexane/ether.

EI/MS (70 eV): 204(M+, 30.2), 186(3.2), 175(7.7), 147(13.1), 133(5.0), 122(base), 109(13.2), 95(34.0), 81(74.1), 67(55.5), 53(45.6)

1H-NMR(250 MHz): δ : 9.73(s, 1), 7.31(m, 1), 7.20(brs, 1), 6.75(m, 1), 6.26(brs, 1), 2.89(m, 1), 2.55(m, 2), 2.45(t, J=6.3 Hz, 2),2.18(m, 1), 2.00-1.35(m, 5)

IR (Neat): 2980-2880, 2860, 2710, 1675, 1610, 1500, 1430, 1350, 1255, 1160, 1020, 870, 770, 720 cm-1

1-(1-hydroxyethyl)-3-(3-(3-furyl)-propyl)-1-cyclopentene (19a) - To a solution of the intermediate aldehyde **18a** (1.151 g, 5.642 mmol) in ether (500. ml), in a 1L base washed round bottom flask cooled in a dry ice-isopropanol bath to -78°C, is added MeLi (1.4M, 7.6 ml, 10.64 mmol), and the mixture stirred for one hour. Additional MeLi (0.33 equiv.) was then added and the mixture stirred for one additional half hour until no starting material was observed by TLC. The solution was warmed to room temperature over one half hour, and was quenched with sat. aq. NH_4Cl (200 ml). After separation, the aqueous phase was extracted with ether (3 x 150 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 125. g, 230-400 mesh, hexane/ether (2.5/1), 40 ml fractions) using the flash technique. Fractions 14-35 afforded 1.161 g (94%) of **19a**. Rf=0.20 in (1/1) hexane/ether.

EI/MS (70eV): 220(M+, 3.0), 202(7.4), 187(1.1), 175(3.0), 159(2.5), 147(2.4), 133(2.4), 120(9.9), 111(4.4), 95(15.4), 81(18.5), 67(15.3) 53(12.8), 43(base)

1H-NMR(250 MHz): δ : 7.34(t, J=1.5 Hz, 1), 7.19(brs, 1), 6.23(brs, 1), 5.51 (brs, 1), 4.39(q, J=6.3 Hz, 1), 2.64(m, 1), 2.40(t, J=8.4 Hz,2), 2.28(m, 2), 2.09(m, 1), 1.66-1.30(m, 6), 1.27(d of d, J=5.4, 1 Hz, 3)

IR (Neat): 3700-3100, 3000-2820, 1500, 1450-1430, 1370, 1160, 1060, 1020, 870, 840, 770 cm-1

Cyclization of Alcohol (19a) - To a solution of the alcohol **19a** (0.100 g, 0.4545

mmol) in cyclohexane (40 ml), in a 100 ml base washed round bottom, was added formic acid (10 ml) in one portion. After stirring twenty minutes, pTsOH (two crystals) was added and the mixture was heated gently (50°) for five minutes. After stirring twenty five minutes, the mixture was diluted with cyclohexane (25 ml) and carefully quenched with sat. aq. $NaHCO_3$ (60 ml). This was followed by solid $NaHCO_3$ until pH 9.0 was obtained. The aqueous phase was extracted with ether (3 x 50 ml), and the combined organic layers were washed with brine (75 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (40 mm o.d., 30. g, 230-400 mesh, hexane/ether (15/1), 10 ml fractions) using the flash technique. Fractions, 5-10 afforded 0.089 g (95%) of **20a**. Rf=0.64 in (10/1) hexane/ether.

EI/MS (70eV): 202(M+, base), 187(47.3), 173(62.8) 159(19.4), 145(16.3),131(23.8), 117(16.8), 105(14.9), 91(37.5), 77(28.8), 65(24.9)

^{1}H-NMR(250 MHz): δ : 7.20(d, J=1.5 Hz, 1), 7.17(d, J=1.5 Hz, .33), 6.19(d, J=1.5 Hz, .33), 6.15(d, J= 1.5 Hz, 1), 5.26(t, J=1 Hz, .33), 4.88 (d of q, J=6, 4 Hz, 1), 3.78(m, 1), 2.8-1.2(m, 13)

IR (Neat): 3000-2800, 1505, 1460-1420,1150, 890, 830, 790, 725, 690 cm-1

2-bromo-4-(3-furyl)-but-1-ene (16b) - To a solution of 3-furylmethy-tri-n-butylstannane[1c,d] (12.0 g, 32.42 mmol) in THF (75. ml), in a 250 ml base washed round bottom flask, cooled in a dry ice-isopropanol bath, was added n-BuLi (2.4M, 17.6 ml, 1.3 eq.) over fifteen minutes. After stirring for one hour at -78°C, CuCN (3.78 g, 42.2 mmol, 1.3 eq.) was added in one portion and the reaction stirred one hour further. The mixture was warmed (-45°) in a dry ice-acetonitrile bath for one half hour, and then cooled again to -78°C. To the cuprate was added a solution of 2,3-dibromopropene[19d] (8.43 g, 42.2 mmol) in THF (15. ml) by cannula over one half hour. After stirring at -78°C for three hours, the reaction was quenched with sat. aq. NH_4Cl (100 ml) and the organic phase separated. The aqueous phase was extracted with ether (3 x 250 ml), and the combined organic layers were then dried ($MgSO_4$) and concentrated in vacuo **(NO HEAT)**. The crude product was purified by

chromatography on a column of silica gel (60 mm o.d., 500. g., 230-400 mesh, (99/1) hex./ether, 250 ml fractions) using the flash technique. Fractions 23-40 gave 5.15 g. (79%) of the pure product **16b**. Rf=0.19 in hexane.

EI/MS (70 eV): 202(M++1, 4.9), 200(5.11), 121(66.9), 103(5.59), 91(15.2), 81(base), 53(57.6), 39(42.7)

^{1}H-NMR (250MHz): δ : 7.28 (m, 2), 6.28 (m,2), 5.58 (m, 1), 5.42 (m, 1), 2.70(s, 4)

IR (Neat): 3000-2860, 1630, 1570, 1500, 1450, 1430, 1385, 1190, 1160, 1115, 1070, 1035, 890, 875, 780, 725 cm-1

1-(1-hydroxymethyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (17b) - (A) To a solution of 1-((dimethylsulfonio)methyl)-cyclopent-2-en-1-ol[1h] (0.10 g, 0.350 mmol) in THF (4.0 ml), in a 25 ml base washed round bottom flask, was added NaH (0.01 g, 0.420 mmol, 85%) in one portion. After stirring at room temperature for three hours, the mixture was cooled to -78°C, in a dry ice-isopropanol bath. (B) To a solution of 2-bromo-4-(3-furyl)-butene (0.211 g, 1.05 mmol) in ether (4.0 ml) in a 25 ml base washed round bottom flask cooled in a dry ice-isopropanol bath was added n-BuLi (1.3M, 1.05 mmol, 0.81 ml). After stirring for one hour at -78°C, the mixture was warmed to -45°C (dry ice-acetonitrile bath) and the reaction stirred for one hour. The solution was then cooled to -78°C once more, and was added via cannula to 1.10 mmol of $MgBr_2$ at -78°C; prepared in situ from 1.10 mmol of ethylene dibromide and 1.25 mmol of magnesium metal in 5.0 ml of ether.

After addition was complete, the mixture was warmed to -45°C for one half hour, and then cooled back to -78°C, and copper bromide dimethyl sulfide (0.108 g, 0.525 mmol) was added in one portion. After stirring one half hour at -78°C, the in situ generated spiroepoxide (A), at -78°C, was added via cannula over fifteen minutes. The reaction stirred at -78°C for three hours and was then allowed to warm to room temperature and quenched with $NaHCO_3$ (10 ml). This solution was diluted with ether (200 ml), and cast into $NaHCO_3$/sat. aq. NH_4Cl/H_2O (90/60/40 ml). After separation, the aqueous phase was extracted with ether (3 x 100 ml), and the combined etheral layers were washed with $NaHCO_3$, brine, (200 ml ea.), dried ($MgSO_4$), and

concentrated in vacuo. The crude product was purified by chromotography on a column of silica gel (30. mm o.d., 30. g., 230-400 mesh, packed in hexane/ether (6/1), run in hexane/ether (3/1),10 ml fractions) using the flash technique. Fractions 20-72, gave 0.0525 g (68.9%) of pure **17b**. Rf=0.25 in (1/1) hexane/ether.

EI/MS (70eV): 218(M+, 3.7), 200(2.4), 187(2.6), 171(1.5), 162(2.8), 149(5.5), 137(base), 119(19.9), 105(22.2), 96(41.9), 81(88.6), 67(84.9)

^{1}H-NMR (250MHz): δ :7.33(t, J=2 Hz, 1), 7.21(m, 1), 6.28(m, 1), 5.56(m,1), 4.81(m, 1), 4.73(m, 1), 4.21(brs, 2), 3.35(m, 1), 2.59 (t, J=7.4 Hz, 2), 2.27(m, 5), 1.76-1.35(m, 2)

IR (Neat): 3640-3100, 3000-2800, 1630, 1500, 1450, 1430, 1380, 1150,1020(w), 890, 870, 780, 720 cm^{-1}

3-(4-(3-furyl)-but-1-en)-cyclopent-1-ene-1-carboxaldehyde (Intermediate 18d) - To a solution of the alcohol **17b** (0.375 g, 1.72 mmol) in CH_2Cl_2 (150. ml), in a 500 ml base washed round bottom flask, is added celite (10 g) followed by PCC (0.593 g, 2.75 mmol) in one portion. After stirring for one and one half hours, ice cold hexane (75 ml) was added and the mixture filtered through a plug of celite/silica gel. The solution was dried ($MgSO_4$), and concentrated in vacuo to provide the aldehyde as a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (30 mm o.d., 30. g, 230-400 mesh, hexane/ether (5/1), 10 ml fractions) using the flash technique. Fractions 12-27 afforded 0.240 g (65%) of intermediate aldehyde **18d**. Rf=0.51 in (1/1) hexane/ether.

EI/MS (70 eV): 217(M++1, 2.3), 216(M+, 15.6), 201(2.1), 187(12.7), 172(1.94), 145(3.9), 135(24.9), 122(12.9), 107(16.1), 95(11.8), 81(base), 67(21.6), 53(36.6), 41(25.6)

^{1}H-NMR(250MHz): δ : 9.71(s, 1), 7.34(t, J=2.1 Hz, 1), 7.21(m, 1), 6.73(m, 1), 6.28(brs, 1), 4.85(brs, 1), 4.81(brs, 1), 3.53(m, 1), 2.71-2.0(m, 7), 1.79(m, 1)

IR (Neat): 3000-2880, 2850, 2700, 1720, 1670, 1620, 1500, 1450, 1430,1380, 1350, 1300-1250(w), 1160-1100(w), 1015, 890, 780 cm-1

1-(1-hydroxyethyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (19d) - To a solution of the intermediate aldehyde, **18d**, (0.0438 g, 0.203 mmol) in ether (25. ml) in a 50 ml base washed round bottom cooled in a dry ice-isopropanol bath, was added MeLi (1.1M, 0.304 mmol, 0.19 ml), and the mixture stirred for one half hour. Additional MeLi (0.5 equiv.) was added, and the mixture stirred one half hour further until no starting material was seen by TLC. The solution was slowly warmed to 0°C, quenched with sat. aq. NH_4Cl (35 ml), and extracted with ether (3 x 50 ml). The ether layers were combined, washed with brine (75 ml), dried ($MgSO_4$), , and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (10 mm o.d., 10.0 g, 230-400 mesh, packed hexane/ether (4/1), run hexane/ether (2/1), 6 ml fractions) using the flash technique. Fractions 8-18 provided 0.042 g (89%) of **19d**. Rf=0.18 in (1/1) hexane/ether.

EI/MS (70eV): 232(M+, 2.8), 214(1.6), 189(2.7), 171(1.2), 162(3.0) 151(23.6), 133(4.14), 121(4.9), 107(24.2), 93(18.3), 81(51.1), 67(12.5), 43(base)

^{1}H-NMR(250MHz): δ : 7.12(t, J=2 Hz, 1), 7.06(brs, 1), 6.09(brs, 1), 5.45(m, 1), 4.90(brs, 1), 4.77(brs, 1), 4.15(m, 1), 3.25(m,1), 2.49(t, J=8.5 Hz, 2), 2.20(m, 2), 2.02(m, 1), 1.57(m, 1), 1.4-1.15(m, 3), 1.13(d of d, J=6.3 Hz, 1 Hz, 3)

IR (Neat): 3660-3100, 3000-2840, 1630, 1500, 1450, 1430, 1370, 1160, 1065, 1020, 890, 870, 780 cm-1

Cyclization Of Alcohol (19d) - To a solution of the alcohol **19d** (0.058 g, 0.250 mmol) in cyclohexane (10 ml) in a 25 ml base washed round bottom was added formic acid (2.5 ml, 98%) in one portion . After one half hour the mixture was cast into cyclohexane (50 ml), and carefully quenched with sat. aq. $NaHCO_3$ (50 ml). After separation, the aqueous phase was extracted with ether (3 x 40 ml), and the combined organic layers were washed with brine (75 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude product was

purified by chromatography on a column of silica gel (30 mm o.d., 30. g, 230-400 mesh, packed hexane/ether (15/1), run in hexane/ether (10/1), 8-10 ml fractions) using the flash technique. Fractions 5-9 and 11-22, respectively, resulted in 0.0271 g (51%) of the cyclized product **20d**, and 0.0355 g (49%) of the formate ester of **19d**. Rf=0.7 (**20d**), and 0.21 (formate ester) in (10/1) hexane/ether.

EI/MS (70eV): (**cyclized**): 214(M+, base), 199(43.7), 185(48.0), 171(19.2), 157(24.7), 143(13.0), 129(17.7), 115(15.1), 105(9.1), 91(24.1), 77(14.9), 65(10.5), 55(8.3)

^{1}H-NMR (250 MHz): δ : (**cyclized**): 7.23 (d, J=1 Hz, 1), 6.14(d, J=2 Hz, 1), 5.01(d of q, J=6.4, 2.1 Hz, 1), 4.86(brs, 1), 4.78(m, 1), 3.83(m, 1), 2.98(q, J=6 Hz, 1), 2.52(t, 2), 2.54-2.16(m, 5), 1.92(m, 1), 1.58(d of d, J=8.3, 1 Hz, 3)

IR (Neat): (**cyclized**): 3000-2820, 1630, 1505, 1460-1420, 1260, 1180-1000(w), 890, 830-790(w), 725 cm-1

EI/MS (70eV): (**formate**): 260(M+, 12.8), 214(37.4), 199(10.8), 185(14.9), 172(35.7), 157(13.6), 145(8.81), 133(base), 119(23.4), 105(22.3), 91(39.8), 81(55.6), 65(10.3), 53(19.2)

^{1}H-NMR(250 MHz): δ : (**formate**): 7.76(brs, 1), 7.70(s, .57), 7.22(m, 1), 7.18 (m, 1), 6.2(m, 1), 5.65(m, 1), 5.58(m, 1), 4.98(s, .58), 4.95(s,1), 4.85(t, J=1 Hz, 1), 4.55(brs, .57), 3.25(m, 1), 2.49(m, 2), 2.20(m, 2), 2.02(m, 1), 1.57(m, 1), 1.14s, 3), 1.15(d of d, J=6.3, 2.4 Hz, 1.57)

IR (Neat): (**formate**): 3000-2820, 1720, 1630, 1500, 1450, 1380, 1200- 1150(w), 1050(w), 890, 870, 830, 780, 730 cm-1

MODIFIED CYCLIZATION: The combined reagents were allowed to stir at RT for twenty minutes. PTSA (2 crystals) was then added and the solution heated gently (50°) for two minutes, and after stirring for twenty minutes further, the reaction was diluted with cyclohexane (20 ml). The aqueous phase was separated, diluted with cyclohexane (20 ml), quenched with $NaHCO_3$ (20 ml sat. aq. and then solid), saturated with NaCl, and extracted with ether (3 x 50

ml). The combined organic layers were washed with $NaHCO_3$ and brine (50 ml ea.), dried ($MgSO_4$), and concentrated in vacuo. The cyclized product **20d** was obtained in 72% yield after purification by flash chromatography.

1-(1-hydroxy-p-methoxybenzyl)-3-(4-(3-furyl)-but-1-en)-1-cyclopentene (19c) - To Mg metal (0.233 g, 9.59 mmol) was added ten percent of a solution of p-bromoanisole (1.570 g, 8.400 mmol) in THF (10 ml). After the reaction began the remaining bromide was diluted with THF (90 ml) and then added over one quarter hour. After two hour of gentle reflux, the solution was cooled in a dry-ice isopropanol bath (-78°), and a solution of the intermediate aldehyde **18a**, (0.979 g, 4.799 mmol) in THF (25 ml) was added over one half hour. After stirring for three hours at -78°, the mixture was warmed to RT and stirred overnight until no further starting material could be seen by TLC. The mixture was quenched with sat. aq. NH_4Cl (25 ml), separated, and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50. mm o.d., 100. g, 230-400 mesh, 200. ml forerun, hexane/ether(2.5/1), 50 ml fractions) using the flash technique. Fractions 8-18 provided 1.305 g. (87.%) of **19c**. Rf=0.21 in (1/1) hexane/ether.

EI/MS (70 eV): 312(M+, 1.1), 241(1.1), 171(12.2), 161(1.1), 147(2.2), 129(base), 111(18.9), 101(8.9), 83(20.0), 71(34.4), 55(94.4)

^{1}H-NMR (250 MHz): δ : 7.34(brs, 1), 7.24(d, J=8.4 Hz, 2), 7.18(brs, 1), 6.85(d,J=8.4 Hz, 2), 6.75(d, J=1 Hz, 1), 6.24(brs, 1), 5.63(m, 1), 5.22(brs, 1), 3.8(s, 3), 3.75(s, 1), 2.66(brs, 1), 2.4(t, J=10.5 Hz, 2), 2.1(m, 3), 1.83(brs, 1), 1.64-1.22 (m, 5)

IR (NEAT): 3640-3080, 2930, 2850, 1610, 1585, 1510, 1460, 1440, 1305, 1250, 1175, 1105, 1025, 875, 830, 780, 735 cm-1

High Res. EI/MS: calculated for $C_{20}H_{24}O_3$: 312.1725; observed: 312.1724

Cyclization of Alcohol (19c) - To a solution of the alcohol **19c** (1.300 g, 4.170 mmol) in cyclohexane (500 ml) was added formic acid (35 ml, 98%) in one portion. After stirring ten minutes, the mixture was separated and the organic phase washed twice with sat. aq. $NaHCO_3$ (150 ml). The solution was dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 50. g., 230-400 mesh, (8/1) hexane/ether, 25 ml fractions) using the flash technique. Fractions 5-8 gave 0.9063 g. 74% of **20c**. Rf=0.77 in (1/1) hexane/ether.

EI/MS (70eV): 294(M+ base), 264(8.4), 251(3.6), 235(5.0), 186(15.4), 173(59.1), 147(44.9), 121(34.9), 105(14.1), 91(30.6), 77(18.9)

1H-NMR (250 MHz): δ : 7.26(d, J=1 Hz, 1), 7.2(d, J= 8.4 Hz, 2), 6.81(d, J=8.4 Hz, 1), 6.19(d, J=1 Hz, 1), 5.73(m, 1), 3.94(m, 1), 3.78 (s, 3), 2.65(m, 2), 2.58-1.18(m, 9)

IR (Neat): 2920, 2840, 1740(w), 1605, 1510, 1460, 1440, 1295, 1245, 1175,1150, 1125, 1060, 1035, 900, 860, 820, 735, 690 cm^{-1}

High Res. EI/MS: calculated for $C_{20}H_{22}O_3$: 294.1620; observed: 294.1614

Intermediate Compound (21c): To a THF solution of borane-dimethyl sulfide[21] (2.0 M, 0.272 ml, 0.544 mmol) cooled to -10°C in a ice-salt water bath, was added 2,3-dimethyl-2-butene (64.7 ul, 0.544 mmol) dropwise. The mixture was warmed to 0°C, stirred one hour, warmed to room temperature, and stirred one hour further. A solution of cyclized product **20c** (64.0 mg., 0.218 mmol) in THF (1.0 ml) was added dropwise and the mixture stirred 20 hours at room temperature. The mixture was cooled to 0°C, quenched with water (1.0 ml), followed by 3N NaOH (2.0 ml), and 30% hydrogen peroxide (3.0 ml). The solution stirred at 0°C for one hour, warmed to RT over one hour, and was cast into sat. aq. NH_4Cl (30 ml) and ether (50 ml). The organic layer was separated and washed with 10% sodium bisulfite, and sat. aq. $NaHCO_3$ (30 ml ea.). The aqueous phases were combined, saturated with sodium chloride, and extracted with ether (3 x 50 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude alcohols were purified by chromotagrophy on a column of silica gel (10

mm o.d., 1.5 g., 230-400 mesh, hexane/ether (2/1), 2 ml fractions) using the flash technique. Fractions 2,3 gave 5.4 mg. (8.%) recovered starting material **20c**. Fractions 8-14 gave 40.6 mg. (59.8%) of intermediate **21c**.

EI/MS (70 eV): 312(M+, 6.5), 294(24.4), 186(3.9), 176(17.0), 147(36.7),137(base), 121(26.6), 109(12.7), 91(22.3), 77(20.9), 55(10.0)

1H-NMR (250 MHz): δ : 7.28(d, J=1.2 Hz, 1), 7.21(d, J=8.9 Hz, 1.3), 6.83(d, J=1.2 Hz, 1.3), 6.19(d, J=8.9 Hz, 1), 4.39(d, J=10.1 Hz, 1), 3.78, 3.79(s, s, 3.7), 3.58(t, J=15.6 Hz, 1), 2.62(m,4), 2.30(m, 2), 2.15-1.15(m, 7)

IR (Neat): 3600-3320, 3080-2800, 1730(w), 1610, 1580, 1510, 1465, 1450, 1380, 1305, 1250, 1175, 1105, 1025, 895, 830, 735, 690 cm-1

High Res. EI/MS: calculated for $C_{20}H_{24}O_3$: 312.1725; observed: 312.1728

Compound (22c): To the intermediate alcohol **21c** (0.038 g, 0.1218 mmol) in CH_2Cl_2 (10. ml) was added celite (0.5 g), followed by PCC (0.066 g, 0.305 mmol) in one portion. After stirring 2.5 hours another 15 mg. (0.075 mmol) of PCC was added, and the mixture stirred one half hour further. The mixture was then diluted with ice cold hexane (30 ml), and filtered through a plug of celite/silica gel. The filter cake was rinsed with hexane/ether (200 ml, 95/5), and the combined organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (10. mm o.d., 2. g., 230-400 mesh, hexane/ether (2/1), 1 ml fractions) using the flash technique. Fractions 2-5 gave 0.0221 g. (58.5%) of the products **22c** as a (6-8):1 mixture (alpha R'/beta R') which could be further separated by flash chromatography. Mp (major isomer): 93-94°, Mp(mixture):78-81°, Minor isomer: oil.

EI/MS (70eV): **(major isomer)**: 310(M+, 47.1), 174(13.3), 163(74.8), 149(43.2), 135(base), 119(16.3), 105(18.4), 91(37.7), 77(37.9), 55(60.4)

1H-NMR (250MHz): δ : **(major isomer)** :7.79(dd, J=8.9, 1 Hz, 2), 6.80(dd, J=8.9,

1 Hz, 2), 6.74(d, J=1 Hz, 1) 5.74(d, J=1 Hz, 1), 4.24(m, 1), 3.82(s,1), 3.71(m, 1), 2.60-1.21(m, 11)

IR (neat): **(major isomer)**: 3010-2860, 1760(w), 1670, 1605, 1580, 1515, 1460, 1450, 1420, 1375, 1260, 1235, 1190-1170, 1118, 1070, 1030, 920, 850, 820,790, 750, 700, 690 cm-1

High Res. EI/MS **(major isomer)**: calculated for $C_{20}H_{22}O_3$: 310.1569; observed: 310.1566

EI/MS (70eV): **(minor isomer)**: 310(M+, 24.0), 293(4.89), 202(5.01), 174(16.6), 163(46.7), 148(17.3), 135(base), 107(8.81), 91(19.8), 77(25.2)

1H-NMR (250MHz): δ :**(minor isomer)**: 7.80(dd, J=8.9, 1 Hz, 2), 6.96(d, 1 Hz, 1), 6.86(dd, J= 8.9, 1 Hz, 2), 6.03(d, J=1 Hz, 1), 3.92(m, 1), 3.84(s, 1), 3.80(m,1), 2.60-1.40(m, 11)

IR (Neat): **(minor isomer)**: 3010-2820, 1725(w), 1670, 1600, 1580, 1510, 1455, 1420, 1365, 1310, 1260, 1215, 1170, 1070, 1030, 900, 840, 740, 695 cm-1

Intermediate Alpha Hydroxy Ketone (23): To a solution of the major ketone **22c**, (0.1467 g, 0.4732 mmol) in THF (6. ml) at -78°c was added LDA (1.5 M, 1.5 eq., 0.47 ml) dropwise. The mixture stirred for one half hour, was warmed to -45°c (dry-ice/acetonitrile) for one half hour, and then cooled back to -78°c . MoOPh·HMPA·PYR[30] (0.410 g, 0.710 mmol, 2 eq.) was then added in one portion, and the mixture was allowed to warm from -78° to RT over 2.5 hours. The mixture was diluted with ether (50 ml), and washed with sodium sulfite (20 ml) and citric acid (30 ml). The aqueous layers were salted and extracted with ether (3 x 50 ml), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude was purified via chromatography on a column of silica gel (30 mmm o.d., 20. g. 230-400 mesh, (10/1) hexane/ether for fract. 1-36, (3/1) hexane/ether for fract. 37-72, 8 ml fractions, 30 ml forerun) using the flash technique. Fractions 2-15 gave 35.2 mgs (24%) recovered **22c**, and fractions 30-68 gave 111. mgs (72%) of the intermediate alpha hydroxy ketone **23**. Rf = 0.32 in (1/1) hexane/ether.

EI/MS (25eV): 308(M-18, base), 191(4.1), 179(53.4), 148(22.5), 135(71.2), 119(13.9), 105(11.5), 91(8.4), 84(27.4)

CI/MS (25eV): 367(M+41, .98), 355(M+29, 1.97), 327(M+1, 17.3), 309(79.7), 191(22.4), 163(2.95), 147(22.4), 135(base), 121(13.4)

1H-NMR (250MHz): δ : (C_6D_6): 8.24, 8.2,(d, J=8.9 Hz, 2), 6.79 (d, J=1 Hz, 1), 6.65, 6.61(d, J=8.9 Hz, 2), 5.80(d, J=1 Hz, 1), 3.65(d, J=8.9 Hz, 1), 3.25(d, J= 6.5 Hz,1), 3.18(s, 3), 2.88(brs, 1), 2.72(d of t, 13.4, 8. Hz, 1), 2.6-1.2(m, 9)

IR (neat): 3620-3200, 3080-2800, 1710(w), 1670, 1600, 1510, 1450, 1420, 1370, 1300, 1245, 1170, 1030, 860-780, 735, 685 cm-1.

High Res. EI/MS: calculated for $C_{20}H_{22}O_4$: 326.1518; observed: 326.1546

Diol (24): To a solution of LAH (12.4 mg., 0.326 mmol) in ether (1.5 ml) at 0°C was added a solution of intermediate alpha hydroxy ketone **23** (0.1061 g., 0.3255 mmol) in ether (1.5 ml). The mixture was stirred for one half hour at 0°C, and then warmed to RT over 1.5 hours. LAH (6.2 mgs, 0.5 eq.) was added and the mixture stirred one hour further. The mixture was quenched with water (1 ml), diluted with ether (50 ml), and washed with 15% NaOH (25 ml). The aqueous layers were saturated with salt and extracted with ether (3 x 50.ml), and the combined organic layers were dried ($MgSO_4$), and concentrated in vacuo to give 88.6 mgs. (83%) of the crude diol **24**, which was used without further purification.

EI/MS (25eV): 310(M-18, 2.65), 190(25.2), 163(35.9), 147(base), 137(52.1), 121(15.1), 109(8.13), 91(27.1), 77(26.7), 55(45.7)

CI/MS (25eV): 369(M+41, .50), 355(M+29, 3.65), 339(M+11, 4.92), 329(M+1, 11.7), 311(M-18, base), 293(11.3), 190(13.3), 175(21.2), 147(43.4), 137(29.3), 121(12.0), 85(25.6)

1H-NMR (250MHz): δ : (C_6H_6): 7.29, 7.26,(d, J=8.9 Hz, 2), 7.10 (d, J=1 Hz, 1), 6.74, 6.70(d, J=8.9 Hz, 2), 5.93(d, J=1 Hz, 1), 4.31(d, J=4.4 Hz, 1), 3.82(d, J= 6.7 Hz,1), 3.31(s, 3), 2.55-0.90(m, 13)

IR (neat): 3700-3100, 3020-2810, 1735(w), 1620, 1520, 1460, 1300, 1250,1190, 1100-1000, 970, 910, 840, 810, 750 cm-1

High Res. EI/MS: calculated for $C_{20}H_{24}O_4$: 328.1675; observed: 328.1671

Ketone (25): To diol **24** (0.0886 g., 0.2701 mmol) in t-BuOH (3.5 ml) was added $NaIO_4$ (0.145 g., 0.675 mmol) in H_20 (3.5 ml). The mixture was stirred for 1.5 hours, diluted with ether (50 ml), and separated. The aqueous layer was diluted with brine (6.5 ml), and extracted with ether (3 x 50 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography (30 mm o.d., 40. g 230-400 mesh, 50 ml fractions, fract. 1-20 (10/1) Hexane/ether, fract. 21-40 (8/1) hexane/ether, fract. 41-60 (5/1) hexane/ether, fract. 61-80 (2/1) hexane/ether, fract. 81-100 (ether), 200. ml forerun) using the flash technique. Fractions 7-40 gave 25.8 mg. (49%) of a 3/1 mixture of compound **25** and anisaldehyde. Fractions 41-70 gave 62.0 mg. of a compound (**26**) M.W. 310 (CI/MS). The anisaldehyde/product mixture was taken up in ethanol (50 ml) and washed with cold sat. aq. $NaHCO_3$. The aqueous was extracted with ether (3 x 10 ml), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to provide 17.7 mg. (35%) of ketone **25.**

EI/MS (25eV): 190(M+,13.6), 163(7.14), 149(37.1), 134(base), 119(18.6), 105(7.14), 96(10.0), 91(20.0), 77(10.0), 69(7.14), 55(25.7)

1H-NMR (250MHz): δ : 7.28(d, J=1 Hz, 1), 6.15(d, J=1 Hz, 1), 3.66(d, J=6.6 Hz, 1), 2.6-1.0(m, 11)

IR (neat): 3080-2800, 1730, 1600, 1515, 1460, 1385, 1340-1230, 1125, 1075, 905, 880, 840, 740, 700 cm-1

High Res. EI/MS: calculated for $C_{12}H_{14}O_2$: 190.0999; observed: 190.0979

3-bromocyclopentenone - Prepared according to the method of Piers/ Swenton[32] with the following modifications: To a solution of 1,3-cyclopentanedione (10.0 g., 102.0 mmol) in $CHCl_3$ (250 ml) is added phosphorus tribromide (19.37 ml, 204.0 mmol) in one portion. The mixture was stirred at reflux for 18 hours, cooled, and 50 ml of ice/water was added. The aqueous layer was separated and extracted with $CHCl_3$ (3 x 75 ml). The combined organic extracts were passed through a four inch plug of celite/silica gel , and the filter cake was rinsed with $CHCl_3$. The combined solutions were dried ($MgSO_4$) and concentrated in vacuo (NO HEAT) to provide 9.42 g (57.7 %) of the haloenone.

EI/MS (25eV): 161(M^{+1} ,189), 81(6.42), 53(base)

^{1}H-NMR (60MHz): δ : 6.4(m, 1), 3.0(m, 2), 2.45(m, 2)

1-dithianyl-3-bromo-2-cyclopentene (27)[32] - To a solution of the bromoenone (5.80 g., 36.0 mmol) in $CHCl_3$ (175 ml) was added vacuum dried, crushed, 4Å molecular sieves (12 g), followed by ethane dithiol (3.81 ml, 45.03 mmol) in one portion via syringe. $BF_3{\cdot}OEt_2$ (0.9 ml, 7.31 mmol) was then added dropwise, and the mixture stirred for 18 hours. The solid residue was removed by filtration through celite, washed with sat'd. NH_4Cl, $NaHCO_3$, and brine (2 x 50 ml each), dried ($MgSO_4$), and carefully concentrated in vacuo (NO HEAT). The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 200 g., 230-400 mesh, packed hexane/ether (99/1), run hexane/ether (35/1), 400 ml forerun, 50 ml fractions) using the flash technique. Fractions 5-12 provided 5.42 g (64%) of **27**. Rf=.73 in (1/1) hexane/ether.

EI/MS (25eV): 238(M^+,23.1), 210(77.3), 178(46.6), 157(6.79), 146(14.2), 129(56.6), 97(base), 85(9.16)

^{1}H-NMR (60MHz): δ : 5.84(brs, 1), 3.33(s, 4), 2.66(s, 4)

Methyl-3-(3-furyl)acrylate - To oil free NaH (17.2 g., 0.5491 mmol,) covered with dry ether (1L) was added trimethyl phosphonoacetate (100.0 g., 0.5491

mmol) in dry ether (250 ml), dropwise over two hours. After stirring an additional 4.5 hours, a solution of 3-furylaldehyde (50.0 g., 0.520 mmol) in dry ether (200 ml) was added dropwise over one hour. After stirring overnight, the reaction was carefully quenched with brine (400 ml), and cast into hexane/water (1L, 1:1). The organic phase was separated, washed with water and brine (0.5L each), dried ($MgSO_4$), and concentrated in vacuo to provide 77.88 g, (99%) of product as a fluffy white solid, which was used without further purification. Rf=0.59 in hexane/ether (1:1).

EI/MS (25eV): 152(M+,80.97), 121(base), 109(11.5), 93(49.0), 81(13.3), 65(52.6)

1H-NMR (60MHz): δ : 7.62(m, 2), 6.65(s, 1), 6.33(s, 1), 6.08(s, 1), 3.78(s, 3)

3-(3-furyl)-3-methylpropionate - To a solution of $Ni(OAc)_2 \cdot 4(H_2O)$ (9.92 g., 40.0 mmol) in 95% EtOH (400 ml) was added $NaBH_4$ (72 ml, 1M in EtOH/NaOH, prepared by addition of 4.0 g $NaBH_4$ to 95 ml abs. EtOH and 5 ml 2N NaOH)[53]. After one hour, hydrogen evolution was complete, and 3-(3-furyl)-2-methylacrylate (107.0 g., 0.7070 mmol) in 95% EtOH (300 ml) was added in one portion. The mixture was hydrogenated at 100 psi for 18 hours, the catalyst removed by filtration through a pad of celite, and the filter cake was rinsed with EtOH. The solution was cast into brine (1.5L) and extracted with hexane/ether (4/1, 4 x 500 ml). The combined organic layers were dried ($MgSO_4$), and concentrated in vacuo to provide 99.6 g (91.5%) of product as a colorless oil, used without further purification. Rf=0.62 in hexane/ether (1:1).

EI/MS (25eV): 154(M+,71.3), 123(34.3), 115(12.4), 95(base), 81(90.2), 67(32.9), 53(26.2)

1H-NMR (60MHz): δ :7.27(m, 2), 6.21(m, 1), 3.61(s, 3), 2.8-2.0(m, 4)

3-(3-furyl)-propanol[19] - To a solution of LAH (29.5 g., 0.776 mol) in dry ether (1.2L) cooled to 0°C in an ice/water bath was added the propionate (99.6 g., 0.647 mmol) in ethanol (200 ml) over one hour. The solution was warmed to room temperature and stirred overnight (15 hrs.). The reaction was cerefully quenched with water (75 ml), 2N NaOH (125 ml), and again with water (300

ml), in sequence. After separation, the aqueous phase was extracted with ether (4 x 500 ml). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo. Distillation, BP_5 122-128°, provided 57.1 g (70%) of the alcohol as a water white oil.

EI/MS (25eV): 126(M+,14.4), 107(4.98), 95(13.4), 82(base), 67(38.5), 54(26.8), 41(32.1)

^{1}H-NMR (60MHz): δ : 7.30(m, 2), 6.25(brs, 1), 3.6(m, 2), 2 42(m, 2), 1.9(m, 2)

Allylic alcohol (28) - To a solution of the the protected bromoenone **27** (3.60 g., 15.8 mmol) in THF (225 ml), cooled to -78°C in a Dry Ice/isopropanol bath, was added n-BuLi (2.4M, 11.90 ml, 28.4 mmol) dropwise via syringe over fifteen minutes. After stirring at -78°C for two hours, 3-(3-furyl)-propanal (1.77g., 14.3 mmol) in THF (50 ml) at -78°C is added via cannula over fifteen minutes. The reaction mixture is stirred at -78°C for 2.5 hours, allowed to warm to 0°C over one hour, and quenched with sat'd. Na_2CO_3 (50 ml). The aqueous phase was separated, and extracted with THF (3 x 100ml). The combined organic phases were washed with brine (100 ml), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 200 g, 230-400 mesh, packed in hexane/ether (9:1), 1.5L forerun in hexane/ether (7:1), then 1.0L forerun in hexane/ether (4:1), followed by 125 ml fractions) using the flash technique. Fractions 4-16 provided 3.12 g (78%) of **28** as a clear viscous oil. Rf=0.19 in hexane/ether (1:1).

EI/MS (25eV): 282(M+, 2.90), 264(1.68), 238(6.58), 200(2.30), 188(6.43), 159(6.75), 131(29.6), 99(33.8), 81(base), 65(27.0), 53(46.7)

^{13}C NMR (62.95 MHz):(C_6D_6): δ : 147.95, 142.96, 139.32, 130.61, 124.76, 111.26, 69.66, 45.48, 40.58, 35.73, 30.72, 30.98, 29.90

^{1}H-NMR (250MHz): δ : 7.35(brs, 1), 7.21(brs, 1), 6.25(brs, 1), 5.70(brs, 1), 4.25(t, J=13 Hz, 1), 3.32(s, 4), 2.50(m, 7), 1.82(t, J=15 Hz, 2)

IR (neat): 3650-3050, 3000-2800, 1500, 1450, 1420, 1380, 1280, 1100-900 cm^{-1}.

High Res. EI/MS: calculated for $C_{14}H_{18}O_2S_2$: 282.0748; observed: 282.0755

Cyclization of allylic alcohol (28) to Compound (30) - To a solution of the allylic alcohol (0.700 g, 2.482 mmol) in CH_2Cl_2 (50 ml) is added Et_3N (1.52 ml, 10.92 mmol) dropwise. After stirring for five minutes, MsCl[33] (0.580 ml, 7.45 mmol) is added dropwise. The mixture is stirred for 0.5 hours, and quenched with NH_4Cl. The aqueous phase was separated, and extracted with CH_2Cl_2 (4 x 25 ml). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (40 mm o.d., 50 g, 230-400 mesh, packed in hexane/ether (12:1), run in hexane/ether (5:1), 25 ml fractions) using the flash technique. Fractions 2-8 provided 0.5386g, (82%) of the cyclized product **30**. Rf=0.72 in hexane/ether (1:1).

EI/MS (25eV): 264(M+, 62.7), 236(26.9), 208(base), 183(6.29), 147(13.4), 115(15.3), 91(24.7), 77(20.2), 69(17.7), 55(29.3)

^{13}C NMR (62.95 MHz):(C_6D_6): δ : 153.13, 141.30, 123.15, 119.02, 110.38, 53.63, 35.56, 35.49, 35.01, 27.20, 26.57, 22.63, 22.01

^{1}H-NMR (250MHz): δ : 7.27(d, J=2 Hz, 1), 6.18(d, J=2 Hz, 1), 3.15(m, 1), 2.45-1.60(m, 10)

IR (neat): 3000-2800, 1590, 1500, 1440, 1410, 1305, 1285, 1230, 1195-1100, 1040, 1020 cm-1.

High Res. EI/MS: calculated for $C_{14}H_{16}OS_2$: 264.0643; observed: 264.0629

Cyclization of allylic alcohol (28) to Spirocyclic Compound (29) - To a solution of the allylic alcohol **28** (0.114 g., 0.404 mmol) in cyclohexane (5 ml) was added 98% formic acid (20 ul) dropwise. After five minutes, the reaction was quenched with $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried ($MgSO_4$), and concentrated **in vacuo**. The crude product was purified by chromatography on a column of silica gel (10 mm o.d., 5 g, 230-400 mesh, hexane/ether (1:1), 2 ml fractions) using the flash technique, to provide 98.0 mgs, (85.5%) of spirocyclic **29**.

EI/MS (25eV): 282(M+, 68.9), 238(21.4), 189(34.6), 178(15.6), 150(54.2), 145(18.7), 135(14.1), 131(base), 118(49.2), 115(31.6), 107(25.3)
^{13}C NMR (75.45 MHz): δ : 154.36, 141.47, 114.31, 109.97, 74.33, 70.48, 53.91, 48.37, 45.12, 39.60, 39.51, 33.50, 28.07, 18.08

^{1}H-NMR (300MHz): δ : 7.27(d, J=2 Hz, 1), 6.14(d, J=2 Hz, 1), 3.94(dd, J=6.6, 3.3 Hz, 1), 3.36(m, 4), 2.63(d, J=15 Hz, 1), 2.31(d, J=15 Hz, 1), 2.61-2.18(m, 6), 2.08(m, 4)

IR (neat): 3430, 2930, 2860, 1600, 1508, 1440, 1268, 1210, 1168, 1129, 1066, 1030, 960, 893, 880, 742 cm-1.

Enone (31) - To a solution of the allylic alcohol **28** (1.486 g., 5.2695 mmol) in CH_2Cl_2 (750 ml) was added celite (30 g), followed by PCC (2.04 g., 9.46 mmol) in one portion. After stirring three hours, ice cold hexane (300 ml) was added and the mixture was filtered through a pad of celite/silica. After washing the pad with CH_2Cl_2 (300 ml), the combined filtrates were dried ($MgSO_4$), and concentrated in vacuo. The crude product was filtered through a four inch pad of silica using hexane/ether (1:1) as elutant to provide 0.900 g (61%) of the enone **31**. Rf=0.41 in hexane/ether (1:1).

EI/MS (25eV): 280(M+, 14.4), 252(4.50), 219(8.14), 187(11.3), 157(11.7), 131(12.2), 105(12.5), 95(45.9), 81(base), 65(27.0)

^{13}C NMR (62.95 MHz):(C_6D_6): δ : 196.46, 144.39, 143.08, 142.90, 141.96, 139.40, 124.38, 111.32, 73.71, 43.13, 40.75, 39.66, 30.48, 19.22

^{1}H-NMR (250MHz): δ : 7.33(t, J=4.2 Hz, 1), 7.22(brs, 1), 6.55(t, J=4.2 Hz, 1), 6.25(brs, 1), 3.35(s, 4), 2.91(m, 2), 2.73(t, J=14 Hz, 2) 2.59(m, 4)

IR (neat): 3000-2800, 1665, 1605, 1505, 1450-1350, 1340, 1310-1120, 1105, 1070, 1025, 970, 950, 875, 860, 790, 740 cm-1.

High Res. EI/MS: calculated for $C_{14}H_{16}O_2S_2$: 280.0592; observed: 280.0580

Cyclization of Enone (31) - The Preparation of Furan (32) - To a solution of enone **31** (1.70 g., 6.071 mmol) in CH_2Cl_2 (100 ml) was added $BF_3{\cdot}OEt_2$ (75 ul, 0.61 mmol) over 1 minute. After stirring for four hours,an additional portion

of $BF_3 \cdot OEt_2$ (35 ul) was added, and the reaction stirred another 1.5 hours. The mixture was quenched with sat'd. NH_4Cl (40 ml), and the aqueous phase was separated and extracted with CH_2Cl_2 (4 x 75 ml). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 200 g, 230-400 mesh, packed in hexane/ether (7:1), run in hexane/ether (4:1), 500 ml forerun, 50 ml fractions) using the flash technique. Fractions 3-7 provided 0.222 g (13%) of spirocyclic adduct (**29**, C10=carbonyl), fractions 8-20 provided 0.939 g (55%) of the desired trans product **32**, and fractions 21-32 provided a 2% mixture of cis isomers, an unidentified product, and a small amount of trans isomer. Rf=0.52 (spiro), Rf=0.46 (trans), Rf=0.29 (cis) in hexane/ether (1:1).

EI/MS (25eV): (**Spiro isomer**): 280(M+, 60.7), 252(12.8), 224(16.8), 192(19.5), 159(17.7), 148(base), 131(51.4), 119(35.7), 105(29.0), 91(64.8), 81(35.9)

^{1}H-NMR (250MHz): (**Spiro isomer**): δ : 7.35(d, J=2 Hz, 1), 6.20(d, J=2 Hz, 1), 3.35(m, 4), 2.90, 2.58(d of d, J=15, 9.5 Hz, 1) 2.80-2.08(m, 10)

EI/MS (25eV): (**Trans isomer**): 280(M+, base), 219(3.12), 187(11.2), 149(33.3), 131(53.6), 119(31.3), 105(20.5), 91(49.2), 77(11.5)

^{13}C NMR (62.95 MHz):(C_6D_6): δ : (**Trans isomer**): 209.10, 140.03, 123.19, 113.15, 110.02, 75.36, 56.22, 54.31, 42.57, 42.40, 40.57, 39.25, 24.37, 23.06

^{1}H-NMR (250MHz): δ : (**Trans isomer**): 7.30(d, J=2 Hz, 1), 6.25(d, J=2 Hz, 1), 3.86(d, J=8.8 Hz, 1), 3.25-2.10(m, 12)

IR (neat): (**Trans isomer**): 3000-2800, 1700, 1510, 1440, 1340, 1315, 1275, 1210, 1175, 1170, 1090, 1070, 1055, 1020 cm-1.

High Res. EI/MS: (**Trans isomer**): calculated for $C_{14}H_{16}O_2S_2$: 280.0592; observed: 280.0589

De-Oxygenation of Ketone (32)

A - Reduction of Ketone 32 - To the trans cyclized product **32** (100.0 mgs, 0.3570 mmol) in ether (6.0 ml) was added Lithium borohydride (2M, 1.3x, 0.23 ml, 0.4623 mmol) dropwise over five minutes. After stirring ten minutes,

NaOH (20%, 4.0 ml) was added and the mixture stirred for twenty minutes. The mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to provide 92.0 mgs, (91%), of the resulting alcohol used without further purification. Rf=0.15 in (1:1) hexane/ether.

EI/MS (25eV): 282(M+, 28.5), 264(5.97), 188(base), 171(18.5), 149(33.8), 131(94.4), 119(39.8), 105(76.0), 91(52.9), 77(28.3)

1H-NMR (250MHz): δ : 7.24(m, 1.63), 6.17(d, J=2 Hz, .63), 6.15(d, J=2 Hz, 1), 3.85(d, J=11 Hz, 1),.3.65(d, J=6.6 Hz, .63), 4.0-1.65(m, 15)

IR (neat): 3620-3100, 3010-2700, 1510, 1480-1200, 1180-1000, 980, 925, 900, 850, 745, 680 cm-1.

High Res. EI/MS: calculated for $C_{14}H_{18}O_2S_2$: 282.0748; observed: 282.0751

B - Xanthate Ester Preparation - To the alcohol (0.0415 g, 0.1472 mmol, prepared from ketone **32**) in THF (2.0 ml) was added 2 crystals of imidazole and 80% NaH (10.0 mgs, 2x, 0.2944 mmol) in one portion. After stirring at reflux for 3.5 hours, carbon disulfide, CS_2, (0.44 ml, 7.36 mmol, 50x) was added and the mixture stirred .5 hours at reflux. Methyl iodide (0.46 ml, 7.36 mmol, 50x) was added, and the mixture stirred .5 hours further at reflux. The mixture was then cooled, and acetic acid (0.5 ml) was added. After two minutes, the mixture was diluted with water (10 ml). The aqueous phase was separated, and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were rinsed with 0.1 N HCl (20 ml), followed by sat'd aq. $NaHCO_3$ (40 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a pipette column of silica gel (5 mm o.d., 2 g, 230-400 mesh, eluted in hexane/ether (3:1), 1 ml fractions) using the flash technique. Fractions 3-5 provided 0.0470 g (86%) of the xanthate ester intermediate. Rf=0.5 in (5:1) hexane/ether.

EI/MS (25eV): 372(M+, 7.79), 339(4.59), 325(2.30), 265(22.4), 236(7.43), 223(10.4), 171(41.5), 147(84.6), 131(base), 118(26.936.9), 105(35.2), 91(23.8), 75(33.7)

1H-NMR (250MHz): δ : 7.26(d, J=2.2 Hz, 1), 7.25(d, J=2.2 Hz, .55) 6.20(d, J=2.2 Hz, .55), 6.18(d, J=2.2 Hz, 1) 3.92(d, J=11 Hz, 1),.3.75(d, J=6.6 Hz, .55) 3.3-1.9(m, 10), 2.55(s, 1.65), 2.50(s, 3)

IR (neat): 3000-2800, 1640, 1510, 1450-1400, 1220, 1050, 965, 915, 900, 865, 820, 740 cm-1.

C- Cleavage of Xanthate Ester to Dithiolane 33 - To the xanthate ester (0.0215 g., 0.578 mmol) in benzene (1.5 ml) was added $HSnBu_3$ (23.3 ul, 0.0867 mmol, 1.5 x) and the mixture was refluxed for six hours. After cooling, the mixture was concentrated in vacuo. The crude product was purified by chromatography on a pipette column of silica gel (5 mm o.d., 2 g, 230-400 mesh, eluted in hexane/ether (25:1), 1 ml fractions) using the flash technique. Fractions 3 - 6 provided 0.0120g., 78% of the deoxygenated adduct **33**. Rf=0.62 in (5:1) hexane/ether.

EI/MS (25eV): 266(M+, 61.4), 238(2.29), 205(4.81), 172(98.4), 147(45.0), 131(base), 119(26.9), 105(69.2), 91(45.9), 77(23.9)

1H-NMR (250MHz): δ : 7.22(d, J=2.2 Hz, 1), 6.15(d, J=2.2 Hz, 1), 3.69(d, J=6.6 Hz, 1),.3.21(m, 4), 2.65-1.22(m, 11)

IR (neat): 3000-2800, 1510, 1450, 1275, 1180, 1070, 900, 840, 740 cm-1.

High Res. EI/MS: calculated for $C_{14}H_{18}OS_2$: 266.0799; observed: 266.0794

Preparation of Trimethylsilyl-methylcarbinol (35) - To a solution of trans ketone **32** (0.098 g., 0.350 mmol) in THF (25 ml) was added TMS-methyllithium (0.46 ml, 0.455 mmol, 1M, 1.3x) dropwise over ten minutes. After six hours the reaction appeared to procede no further (TLC), and was quenched with sat'd. NH_4Cl (5 ml). The aqueous phase was separated, and extracted with CH_2Cl_2 (4 x 15 ml). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (50 mm o.d., 200 g, 230-400 mesh, hexane/ether (15:1), 2.0L forerun, 100 ml fractions) using the flash technique. Fractions 3-10 provided 0.0579 g (45%) of the desired alcohol **35** as a white

waxy solid, and fractions 12-19 provided 0.0476 g (49%) recovered trans cyclized ketone. M.P. 66.5-68.5°C. Rf=0.58 in hexane/ether (1:1).

EI/MS (25eV): 368(M+, 2.83), 350(8.62), 256(3.55), 232(4.38), 219(9.60), 185(6.26), 149(15.1), 131(62.2), 115(15.2), 91(13.7), 73(base)

1H-NMR (250MHz): δ : 7.24(d, J=1.8 Hz, 1), 6.16(d, J=1.8 Hz, 1), 3.75(d, J=9.8 Hz, 1), 3.31-3.05(m, 4), 3.85-1.40(m, 10), 1.01(d, J=4.4 Hz, 2), 0.02(s, 9)

IR (neat): 3500, 3150-3100, 3000-2800, 1550, 1510, 1450-1420, 1350, 1320, 1250, 1210, 1160, 1050, 1020, 980, 935, 905, 850, 750, 700 cm-1.

High Res. EI/MS: calculated for $C_{18}H_{26}O_2S_2Si$: 368.1321; observed: 368.1311

Synthesis of olefin (36) - To a solution of KH (0.0088 g, 0.2196 mmol, oil free) in THF (5 ml) was added tertiary alcohol **35** (0.0404 g., 0.1098 mmol) in THF (2 ml). After stirring for two hours, the reaction was quenched with sat'd. NH_4Cl (5 ml), and diluted with CH_2Cl_2 (25 ml). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (15 mm o.d., 5 g, 230-400 mesh, packed in hexane/ether (10:1), eluted in hexane/ether (3:1), 5 ml fractions) using the flash technique. Fractions 3-7 provided 0.0302 g (99%) of the exocyclic olefin **36**

EI/MS (25eV): 278(M+, 24.22), 250(19.1), 217(8.87), 185(26.8), 160(16.5), 145(8.51), 131 (base), 118(15.0), 104(13.4), 91(22.4), 81(27.2), 71(38.9)

13C NMR (62.95 MHz):(C_6D_6): δ : 150.34, 140.16, 121.52, 113.19, 112.61, 110.32, 77.23, 56.10, 49.07, 44.69, 39.99, 39.16, 32.07, 31.87, 27.75

1H-NMR (250MHz): δ : 7.27(d, J=1.8 Hz, 1), 6.15(d, J=1.8 Hz, 1), 4.8(s, 2), 3.90(d, J=10 Hz, 1), 3.35-3.0(m, 4), 2.86-1.80(m, 9)

IR (neat): 3060, 3000-2800, 1635, 1510, 1450, 1270, 1145, 1070, 975, 845, 740, 700 cm-1.

High Res. EI/MS: calculated for $C_{15}H_{18}OS_2$: 278.0799; observed: 278.0789

Preparation of keto-olefin (37) - To a solution of NCS (0.2260 g., 1.608 mmol) in CH_3CN/H_2O (120 ml, 4:1) was added $AgNO_3$ (0.3080 g., 1.810 mmol) in one portion. After stirring for three minutes, tertiary alcohol **36** (0.1480 g., 0.4022 mmol) in CH_3CN (3 ml) was added in one portion. The yellow colored reaction mixture turned snow white after stirring 25 minutes and was quenched by treating the mixture at one minute intervals with sat'd aq. Na_2SO_3, Na_2CO_3, and brine (1 ml each), successively. The mixture was then diluted with hexane/CH_2Cl_2 (20 ml, 1:1), filtered through celite, rinsed, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a pipette column of silica gel (5 mm o.d., 2 g, 230-400 mesh, packed in hexane/ether (10:1), eluted in hexane/ether (5:1), 1 ml fractions) using the flash technique. Fractions 4 - 8 provided 0.0763 g (94%) of the keto-olefin **37**. Rf=0.45 in hexane/ether (1:1).

EI/MS (25eV): 202(M+, 56.7), 187(2.85), 173(5.72), 159(12.9), 146(base), 131 (44.6), 117(48.1), 107(14.2), 99(53.4), 91(43.5), 77(33.7), 65(24.3), 56(61.4)

^{13}C NMR (76.702 MHz):(C_6D_6): δ : 214.1 (C10), 150.34 (C2), 141.26 (C11), 140.2 (C6), 120.5 (C3), 112.64 (C12), 112.48 (C13 methylene), 53.39 (C1), 45.48 (C4), 35.32 (C9), 34.39 (C7), 27.51 (C8), 26.94 (C5)

^{1}H-NMR (250MHz): δ : 7.28(d, J=1.8 Hz, 1), 6.15(d, J=1.8 Hz, 1), 4.93(d, J=20 Hz, 2), 3.75(d, J=8.7 Hz, 1), 3.21(m, 1), 2.55(t, J=11.2 Hz, 2), 2.30-2.10(m, 6)

IR (neat): 3000-2800, 1740, 1630, 1500, 1440, 1400, 1020, 1070-1000, 890, 730 cm-1.

High Res. EI/MS: calculated for $C_{13}H_{14}O_2$: 202.1004; observed: 202.0997

Preparation of Bis-olefin (40) - To a solution of keto-olefin **37** (0.0600g., 0.2970 mmol) in CH_2Cl_2 (6 ml) was added Lombardo's reagent[38] - $ZnCH_2Br_2TiCl_4$ (7.70 ml, 1.78 mmol, 0.23M, 6x) rapidly in one portion. After stirring five minutes, an additional equivalent of Lombardo's reagent (1.30 ml, 0.297 mmol, 1x) was added. After stirring forty minutes further, the reaction was diluted with CH_2Cl_2 (50 ml), and quenched with cold $NaHCO_3$ (10 ml). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel

(5 mm o.d., 3 g, 230-400 mesh, packed in hexane/ether (10:1), eluted in hexane/ether (6:1), 1 ml fractions) using the flash technique. Fractions 3-14 provided 0.0564 g (95%) of the bis-olefin **40** as a 6/1 mixture of isomers (^{1}H NMR). Rf=0.43 in hexane/ether (1:1).

EI/MS (25eV): 200(M+, 42.1), 185(24.2), 171(24.9), 157(22.4), 143(20.1), 131 (24.0), 115(26.9), 105(11.7), 91(46.1), 77(38.4), 65(29.5), 51(42.9), 39(base)

1H-NMR (250MHz):(C_6D_6): δ : 7.24(d, J=1.8 Hz, 1), 7.20(brs, .16), 6.18(brs, .16), 6.16(d, J=1.8 Hz, 1), 5.44(brs, .16), 5.14(brs, .16), 4.85(m, 2.33), 4.76(brs, 1), 4.57(brs, 1), 3.87(d, J=4.9 Hz, 1), 3.04(q, J=6.6 Hz, 1), 2.8-1.75(m of m, 8)

IR (neat): 3080, 3000-2850, 1655, 1635, 1505, 1435, 1250, 1130, 1065, 885, 835, 800, 725 cm-1.

High Res. EI/MS: calculated for $C_{14}H_{16}O$: 200.1201; observed: 200.1139

Pseudoguaianolide Intermediate (41) - To a solution of keto-olefin **37** (0.0200 g., 0.09901 mmol) in THF (3 ml) was added KH (0.0113 g., 0.09901 mmol, 1x, 35%KH) in one portion. After stirring for twenty minutes, MeI (7.4 ul, 0.1188 mmol, 1.1 x, filtered through P_2O_5/silica) was added dropwise over 0.5 minute. After stirring for two hours, the mixture was diluted with THF (20 ml) and quenched with sat'd. NH_4Cl (5 ml). The aqueous phase was separated and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on a column of silica gel (5 mm o.d., 5 g, 230-400 mesh, packed in hexane/ether (99:1), 30 ml forerun in hexane/ether (40:1), 1 ml fractions) using the flash technique. Fractions 5-25 (20:1 hexane/ether) provided 7.5 mgs (Ca. 35%) of a mixture of bis methylated and isomeric product. Rf=0.50 in hexane/ether (1:1). Fractions 26-36 (1:1 hexane/ether) provided 11.1 mgs (52%) of the desired alpha methyl ketone **41** as a microcrystalline solid, M.P. = 71-74°C. Rf=0.43 in hexane/ether (1:1).

EI/MS (25eV): 216(M+, 32.3), 201(7.45), 187(2.34), 173(8.77), 160(base), 145(46.6), 131 (22.2), 115(25.1), 105(9.92), 91(43.0), 77(36.0), 65(27.1), 55(34.3)

^{13}C NMR (76.702 MHz):(C_6D_6): δ : 215.3 (C10), 146.6 (C2), 140.4 (C11), 120.8 (C3), 112.30 (C12), 111.39 (C13 methylene), 51.0 (C1), 48.88 (C4), 36.99 (C9), 36.14 (C7), 23.17 (C8), 22.38 (C5), 18.43 (C14 methyl)

^{1}H-NMR (250MHz): δ : 7.28(d, J=1.8 Hz, 1), 6.12(d, J=1.8 Hz, 1), 5.05(brs, 1), 4.85(brs, 1), 3.17(d od d, J=13.4, 5.5 Hz, 1), 2.75-1.75(m, 8), 1.11(s, 3)

IR (neat): 3000-2800, 1738, 1700-1600, 1450, 1375, 1230-1020, 885 cm-1.

High Res. EI/MS: calculated for $C_{14}H_{16}O_2$: 216.1150; observed: 216.1154

Pseudoguaianolide Intermediate (Olefin Reduction) (43) - To Pseudoguaianolide **41** (0.0250 g., 0.1157 mmol) in EtOAc (3.0 ml) was added activated charcoal (10 mgs) and PtO_2 (0.0031g., 0.137 mmol) in one portion. The mixture was stirred for one hour under a balloon atmosphere of H_2 at room temperature. The mixture was then filtered through a plug of celite, rinsed with EtOAc, dried ($MgSO_4$), and concentrated in vacuo to provide 0.0235 g., (93%) of a single pure product **43**. Rf=0.43 in (1:1) hexane/ether.

EI/MS (25eV): 218(M+, 69.4), 175(19.5), 1162(base), 147(92.5), 133(344.9), 119(15.0), 105
(21.8), 91(34.5), 77(40.0), 65(27.0), 54(30.5), 41(46.2)

^{13}C NMR (76.702 MHz):(C_6D_6): δ : 217.0 (C10), 152.0 (C2), 140.5 (C11), 121.8 (C3), 112.25 (C12), 52.0 (C1), 46.41 (C4), 38.0 (C6), 35.95 (C9), 34.95 (C7), 23.56 (C8), 23.10 (C5), 20.9 (C13 methyl), 22.95 (C14 methyl)

^{1}H-NMR (250MHz): δ : 7.26(d, J=2 Hz, 1), 6.10(d, J=2 Hz, 1), 2.68 (d of t, J=6.8, 11.3 Hz, 1), 2.52(t, J=4.5 Hz, 2), 2.50-2.40(m, 1), 2.38-1.8(m, 6), 1.31(s, 3), 1.08(d, J=6.8, 3)

High Res. EI/MS: calculated for $C_{14}H_{18}O_2$: 218.1307; observed: 218.1311

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