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FURAN TERMINATED CATIONIC CYCLIZATIONS AND THEIR USE IN SYNTHESIS. APPROACHES TO THE SYNTHESES OF HELENANOLIDE PSEUDO GUAIANOLIDES, DAPHNANE DITERPENES, AND INDOLIZIDINE ALKALOID NATURAL PRODUCTS.

presented by

MARK CHAD MCMILLS

has been accepted towards fulfillment
of the requirements for

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Stuart P Davis

Major professor

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FURAN TERMINATED CATIONIC CYCLIZATIONS AND THEIR USE IN SYNTHESIS. APPROACHES TO THE SYNTHESES OF HELENANOLIDE PSEUDOGUAIANOLIDES, DAPHNANE DITERPENES, AND INDOLIZIDINE ALKALOID NATURAL PRODUCTS.

By

Mark Chad McMills

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ABSTRACT

FURAN TERMINATED CATIONIC CYCLIZATIONS AND THEIR USE IN SYNTHESIS. APPROACHES TO THE SYNTHESIS OF HELENANOLIDE PSEUDOGUAIANOLIDE, DAPHNANE DITERPENES, AND INDOLIZIDINE ALKALOID NATURAL PRODUCTS.

BY

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In an ongoing investigation of furans as terminators in cationic cyclization, we have examined the use of various thioesters, enones, and α-hydroxy-amides as initiator functions. This approach has been used previously for the successful generation of linearly fused, bridged, and spirocyclic six and seven membered rings present in carbocyclic and azacyclic natural products.

We had hoped to utilize furans in both the cyclization sequence, and as resident functionality to facilitate completion of chosen natural product syntheses. During this study we addressed several questions: 1) could the required cyclization precursors be prepared easily, 2) would furan withstand the conditions needed for cyclization, 3) could the furans be manipulated to provide useful synthetic intermediates, and 4) could these intermediates be transformed into the targeted natural products.

Studies directed toward answering these questions will be presented. We will describe the successful preparation of two bicyclo[5.3.0]decane systems utilizing a 3→2 mode of furan closure, and one linearly fused indolizidine system using a similar type of closure. Currently work is continuing to complete formal total syntheses of compounds such as fastigilin-C, resiniferonol, and elaeokanine A.

FOR MOM, DAD, AND MIKE
THANK YOU

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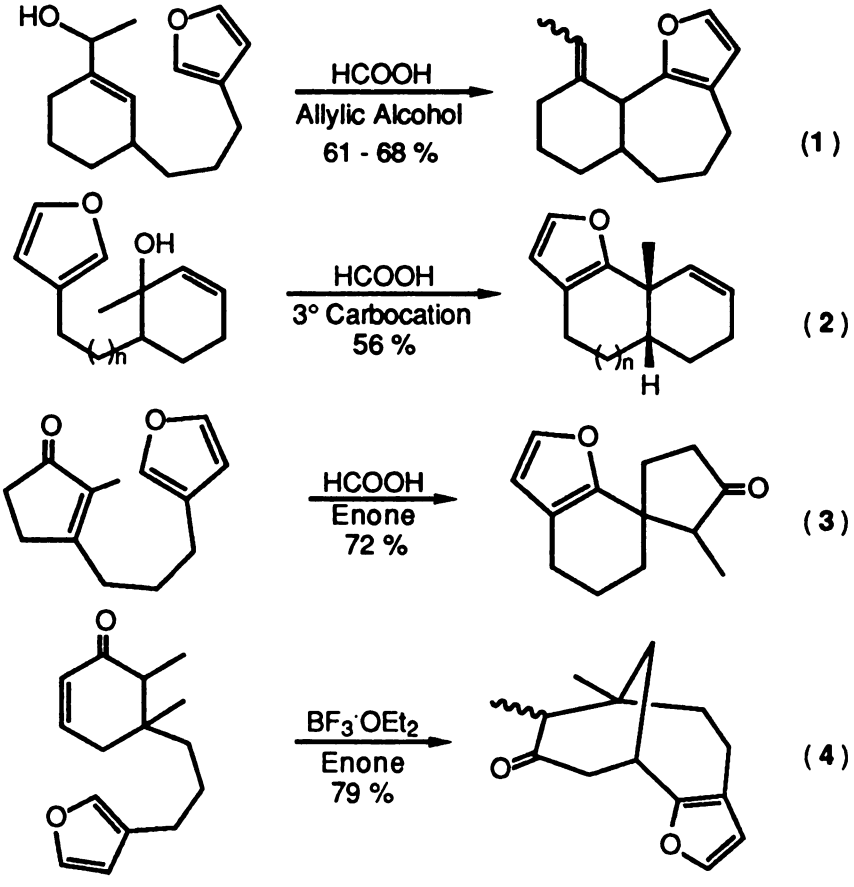
INTRODUCTION

INTRODUCTION

Our research group has been interested in the development of the furan terminated cationic cyclization as a synthetic method. These studies have culminated in the synthesis of spirocyclic-, linearly-fused, and bicyclic alkaloid and terpenoid natural products[1], utilizing both 2-, and 3- substituted furans as terminators[2] in the cyclization process. Epoxides,[1d] allylic alcohols,[1d] enones,[1e] and carbinol amides[1e] have served as initiator functions in these reactions, allowing us to prepare various *5*, *6*, and *7* membered ring containing systems; and the furan moiety has helped establish both regio- and stereochemical control in a number of systems that would otherwise be difficult to handle. Generic (3→2) furan terminated cyclizations are illustrated in Eqs. 1-4.



The introduction of a furan into the newly constructed molecule serves several functions. Initially, furan serves as a regiochemical control element for the introduction of one or two oxygen atoms and functionalized carbon molecules. A fused furan ring can further serve to restrict the freedom of a conformationally mobile system such as a cycloheptyl ring by adding the enforced rigidity of a double bond to the framework. Finally, furan can function as the operational equivalent of a number of 1,4-dioxygenated chains as well as five and six membered rings after additional manipulation (Fig. 1).

Recently, we have successfully concluded the syntheses of several targets that serve as examples of our ongoing research directions. In the case of bridged carbocyclic systems, Herrinton and Tanis[3] have completed the synthesis of Nakafuran 9, a natural fish antifeedant. Furyl Grignard reagent **1** (CuCN) was added in S_N2' fashion to vinyl epoxide **2**, to give allylic alcohol **3** (62%). Oxidation, conjugate addition (MeCu, $BF_3{\cdot}(OEt)_2$)[4], and introduction of an enone double bond (selenation, oxidation) gave compound **5** that serves as the precyclization substrate. Acid catalyzed cationic cyclization then gave an excellent 79% yield of the bicyclo[4.3.1]decane system **6**. The synthesis was completed by Wittig olefination and acid catalyzed double bond migration to give nakafuran 9 (**8**).

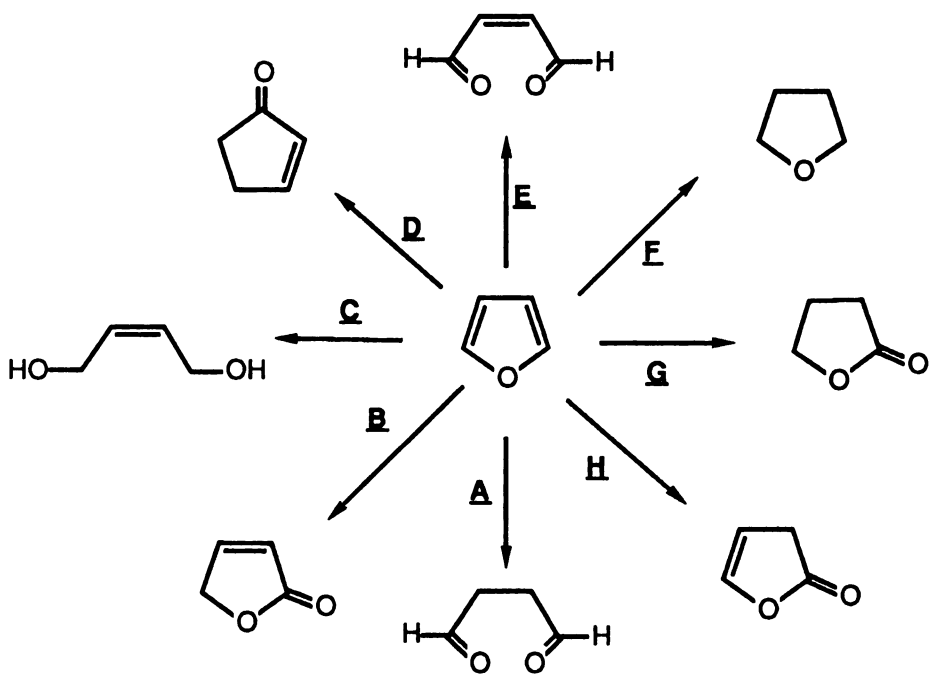
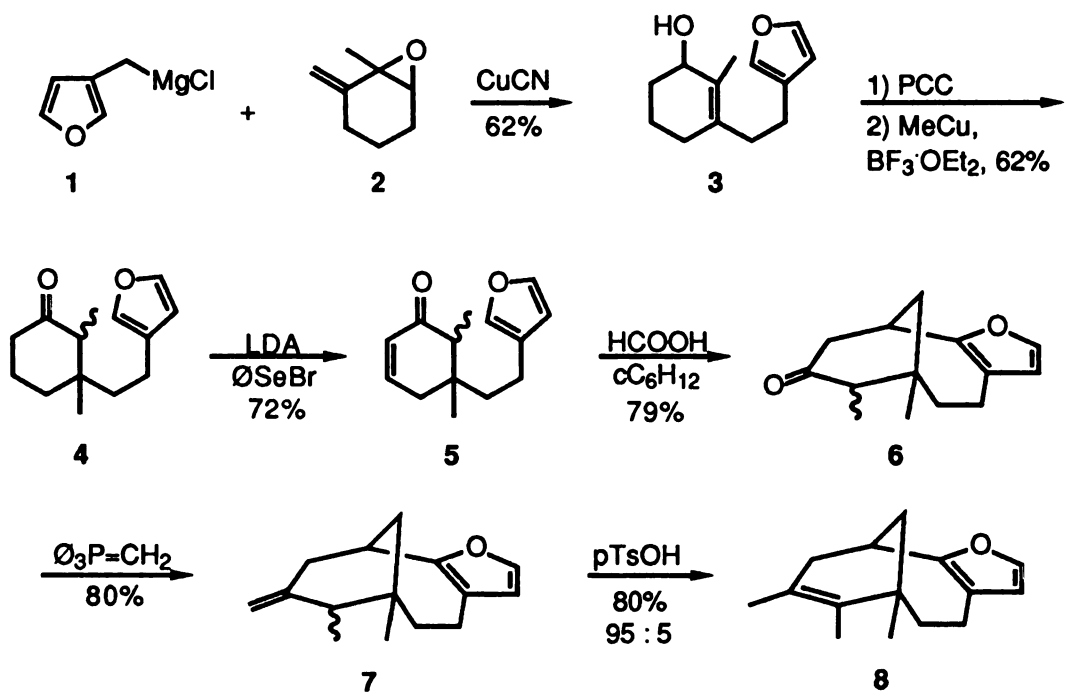
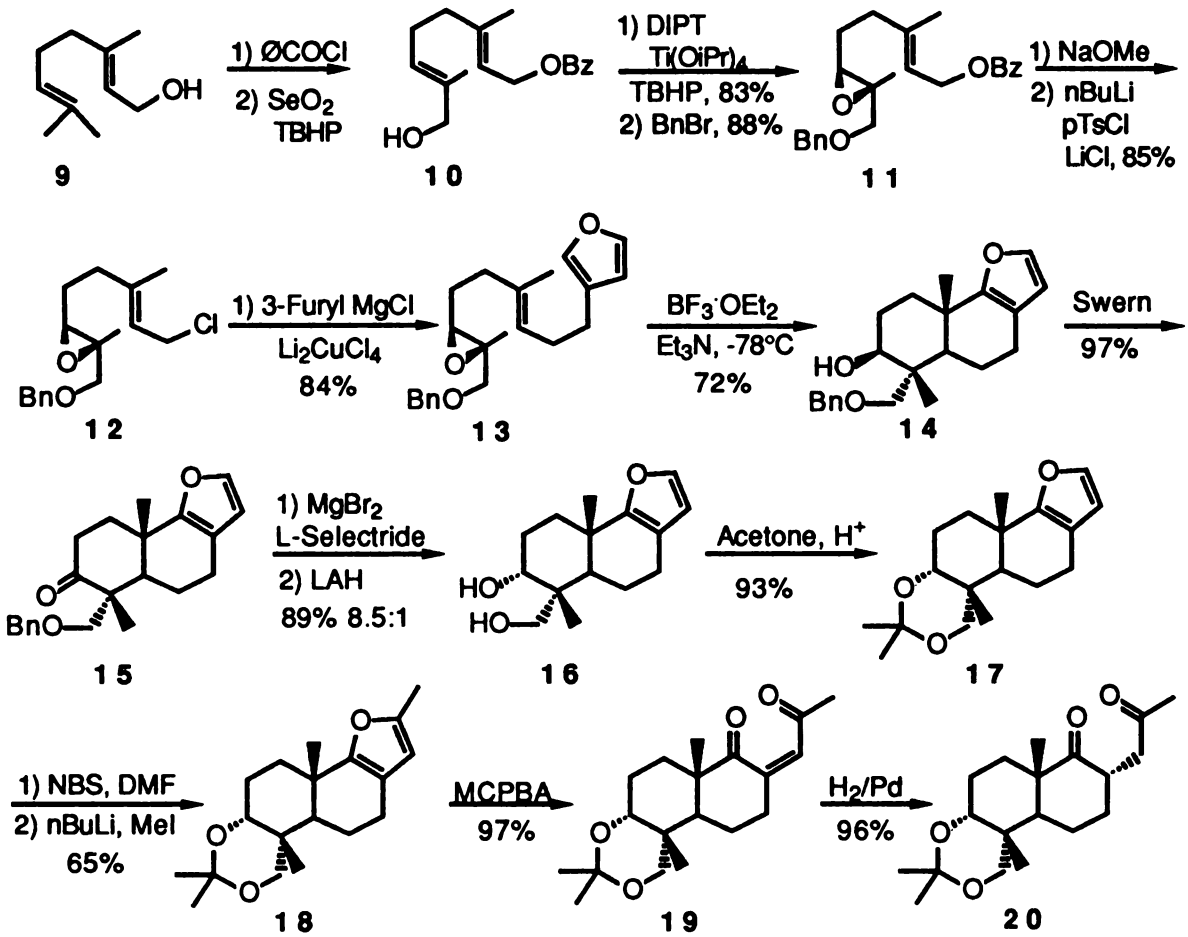


Figure 1: Furan Oxidation States

As an example of the linearly fused terpenes which might be prepared via a furan terminated cyclization, Scheme 2 outlines our formal total synthesis of aphidicolin[5], a diterpene tetraol that has shown considerable activity against both Herpes and leukemia.. Especially interesting in this case, is the fact that the molecule has been synthesized in both racemic and chiral forms, demonstrating that a complete transfer of asymmetry is possible in the furan terminated cationic cyclization. In the event geraniol was converted to chiral epoxide **11** through a Sharpless[6] asymmetric epoxidation, further reactions added a furan ring to give compound **13**. Triethylamine-moderated $BF_3{\cdot}OEt_2$ cyclization gave a excellent (72%) yield of **14**, with no trace of the alternative enantiomer detected. The conversion of **14** to the known aphidicolin precursor **20** is presented in the latter portion of Scheme **2**.



Scheme1: Total Synthesis of Nakafuran 9

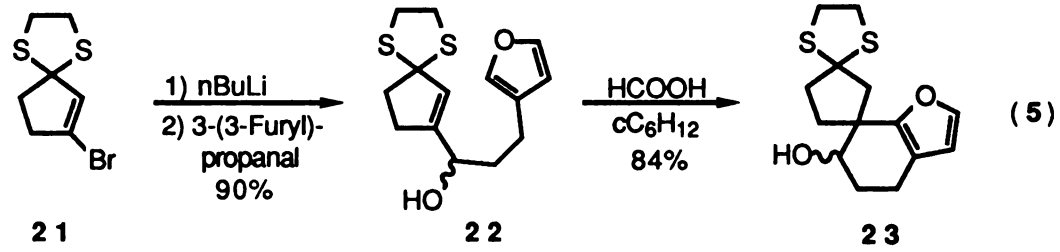


Scheme 2: Formal Total Synthesis of Aphidicolin

Finally, in the case of the spirocyclic carbocycles, an interesting bicyclo-[5.4.0]decane has been prepared by McMills and Tanis[7](Equation **5**). This system evolved, somewhat unexpectedly, from a separate study directed toward the synthesis of simple guaianolides such as estafiatin. Toward that end, thioketal **21** was metallated (nBuLi) and was then added to 3-(3-furyl)ethanal to give alcohol **22** (90%). When this substrate was treated with formic acid, did not cyclize to form the linearly fused compound as anticipated, but instead opened and reclosed the thioketal function, with the furan attacking the 2-position of the double bond to give spirocycle **23** (84%).

These simple examples clearly indicate that furan terminated cationic cyclizations can be employed in the synthesis of a variety of alkaloids and terpenoids. These data when considered together with many examples from our laboratories of the preparation of 7-membered rings suggested the application of this methodology to the synthesis of the functionally and

stereochemically complex bicyclo[5.3.0]decane containing natural products such as the pseudoguaianolides or tigliane/daphnane diterpenes. We reasoned that the inclusion of the furyl 2,3-double bond into the 7-membered ring would provide well defined conformations of the normally flexible and troublesome carbocycle, thus enabling us to resort to standard cyclic methodology for the establishment of additional asymmetric centers in a predictable fashion. To this end, we have chosen to incorporate three different cyclization modes, designated as A, B, and C. With these three simple disconnections and furan placements, a variety of diterpenes, pseudoguaianolide, and tigliane/daphnane diterpenes have become available as synthetic targets. These closures will be discussed in more detail in subsequent sections of this dissertation.



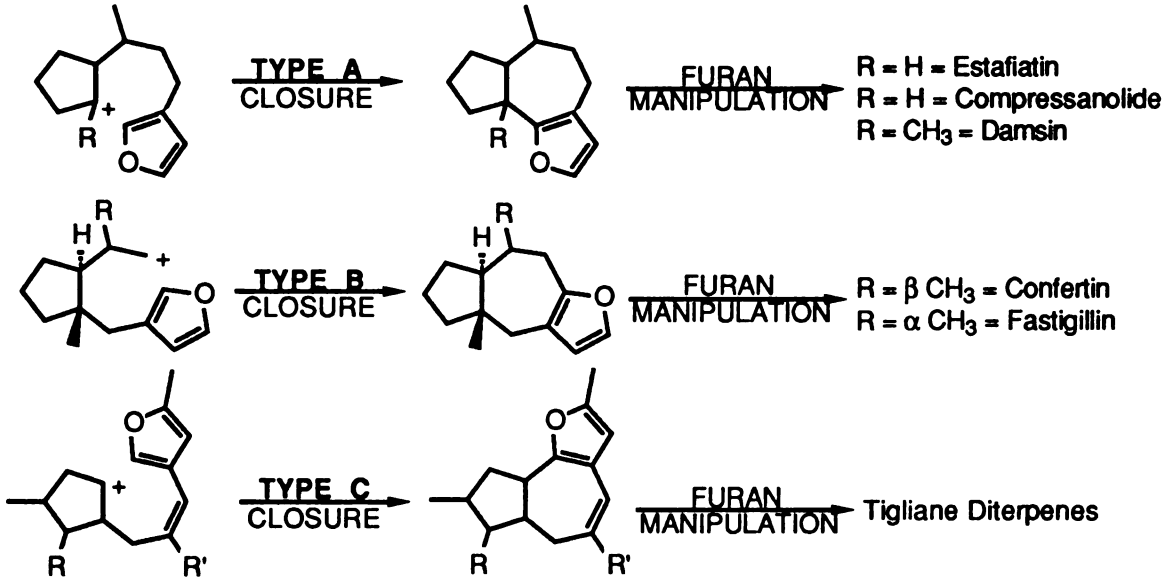


Figure 2: Generalized Cyclization Modes

APPROACHES TO FASTIGILIN-C

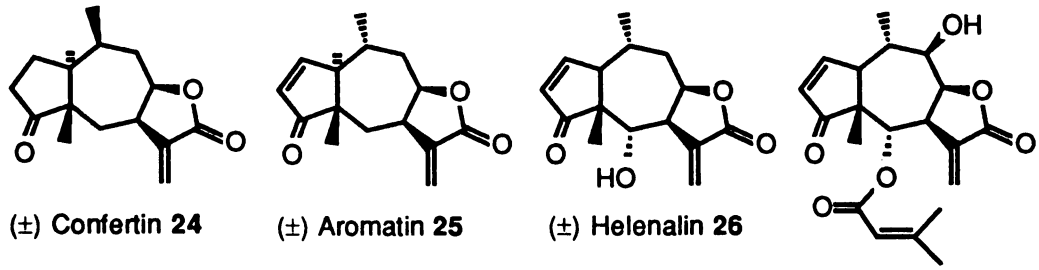
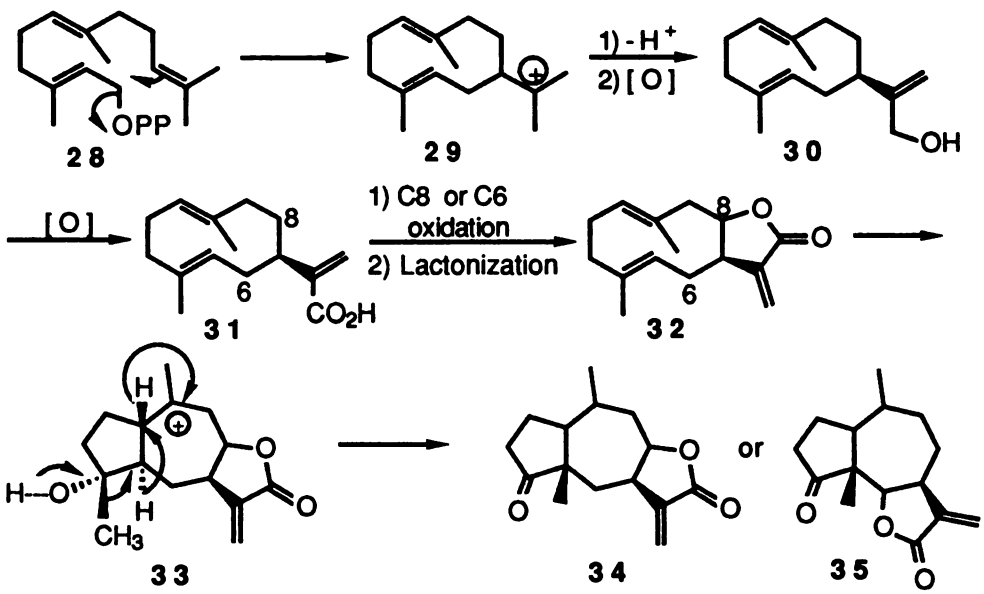


Figure 3: Pseudoguaianolide Natural Products

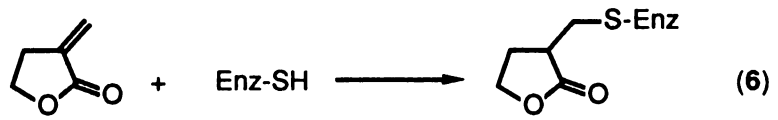
Pseudoguaianolides[8] are a class of natural products that contain a bicyclo-[5.3.0]decane ring system. These natural products are thought to arise from a cascade of intermediates starting with trans, trans farnesyl pyrophosphate.[9] Thus, bond formation initiated by loss of pyrophosphate gives a germacradiene (or triene), and enzymatic oxidation of carbon 6 or 8 with subsequent lactonization generates two possible germacranolides **32,** and its C6 regioisomer. Cation induced cyclization and trapping by water leads to the guaianolides that are the biological precursor of the pseudoguaianolides. Migration of a methyl group from C4 to C5 generates two regiochemically different types of pseudoguaianolides, as seen in Scheme **3.**

Much of the biological activity of the sesquiterpene lactones has been traced to the ability of the α-methylene lactone to act as a Michael acceptor for thiol containing enzymes[10] (see Equation **6**). This inhibits amino acid incorporation into proteins causing a disruption of metabolism at the cellular level. Cytotoxic activity has also been linked to the presence of the α-methylene lactone, but tends to be enhanced by the presence of a conjugated cyclopentenone and hydroxyl groups about the periphery. These compounds are suspected to cause an inhibition of DNA transcription or synthesis.[4]

Contact dermatitis is another problem associated with these compounds[11]. It is thought that a Michael reaction occurs with a skin protein forming an antigen that sensitizes some lymphocytes.[6] This causes an allergic response that can range from very mild to extremely severe. Finally, a number of these sesquiterpene lactones have exhibited both phytotoxic and antimicrobial properties. Hager has postulated that attack of sulfur at an auxin receptor occurs, then, once bound to the protein receptor, the thiol (RSH) is set free.[12] The formation of the sulfur bond then causes irreversible inhibition of plant growth. In many cases, these lactones are stress metabolites (they are formed during periods of stress to a plant example pest attack, drought or overexposure) and act as a chemical defense for the plant.



SCHEME 3: Biosynthetic Pathway Toward the Pseudoguaianolides



In recent years the pseudoguaianolides were discovered to have potent anti-inflammatory and antitumor activity. In arthritis screens, compounds containing α-methylene lactones, α,β-unsaturated cyclopentenones and epoxy-cyclopentanones showed significant activity at levels as low as 2.5

mg/kg/day.[14] Induced pleurisy, anaphylaxis and hypersensitivity were suppressed as well. Studies of the inhibition of lysosomal enzyme activity by derivatives of helenalin were conducted to determine what structural features were necessary for activity.[15] It was found that masking the α-methylene lactone, loss of the hydroxyl at C6, or changing the lactone from cis to trans all resulted in reduced activity. These pseudoguaianolides, applied at 5×10^{-4} M, compare favorably with standard antiinflammatory agents such as salicylates (1×10^{-3} M) and phenylbutazone (1×10^{-4} M).[16]

Helenalin is an active cytotoxic agent for human KB or H. Ep-2 carcinoma cell lines.[17] At a therapeutic level (8 mg/kg), helenalin has shown little toxicity in mice, but at a level of 25 mg/kg some cardiac toxicity has been noted. In the case of P-388 lymphocytic leukemia, the bis ester of helenalin with succinic anhydride has been shown to act by suppressing DNA synthesis as well as inhibition of protein and RNA synthesis.[18] Hall *et al.* have cited the lack of sufficient quantities of the natural products and limited information about their mode of action as reasons why the pseudoguaianolides have not been used in clinical trials.[19] One goal of this study is to develop an efficient route to these compounds and to provide adequate quantities of representative compounds to make possible human studies of the various biological activities.

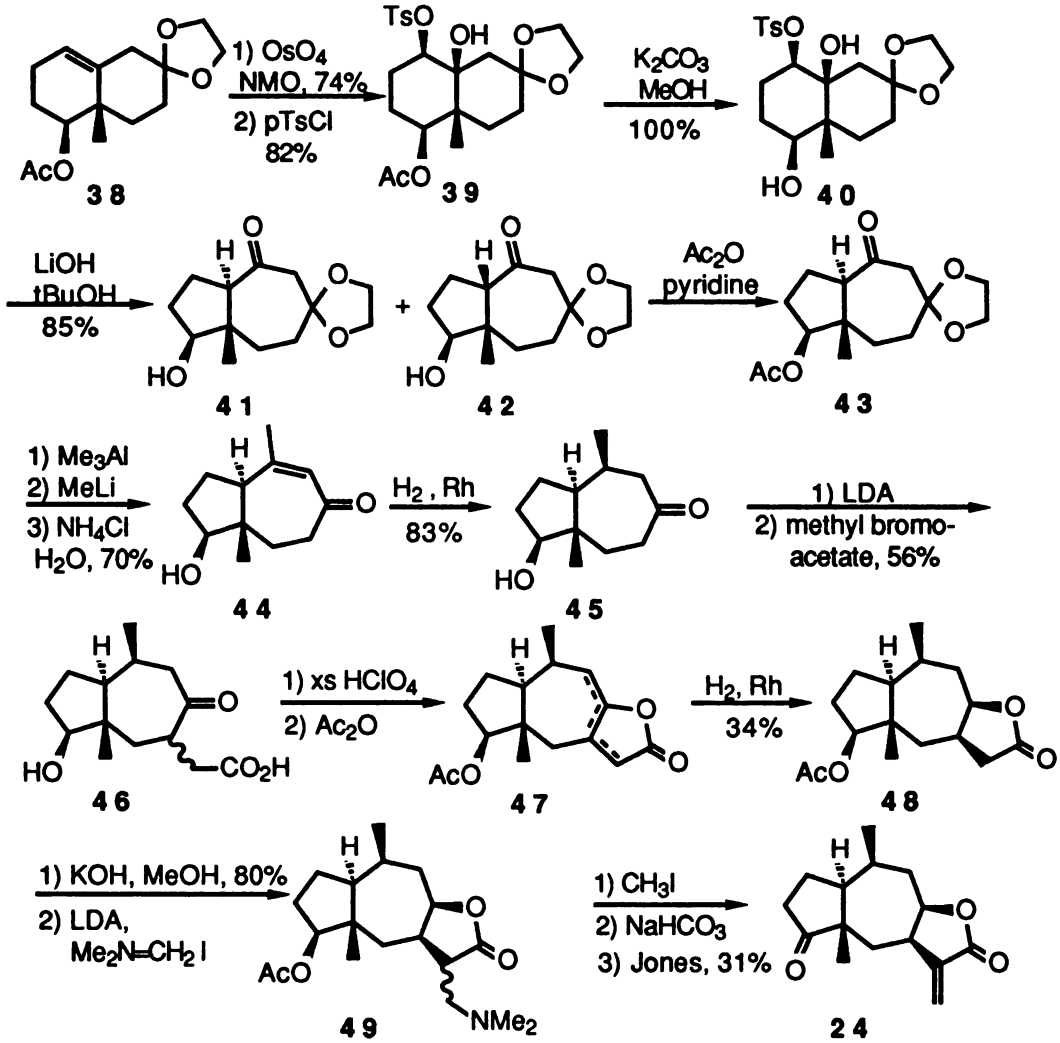
The pseudoguaianolides are grouped in two categories 1) ambrosanolides, with a β-oriented methyl group at C10 and 2) helenanolides, which are biologically more complex with an α-methyl group at C10. The ambrosanolides are illustrated by the compounds mexicanin and confertin. These relatively simple ambrosanolides are contrasted by the more highly functionalized and biologically potent helenanolides such as helenalin and fastigilin-C. Fastigilin-C is currently the only member of this class of compounds to have eluded total synthesis.

Ambrosanolides **Helenanolides**

Figure 4: Generalized Pseudoguaianolides

Many groups have examined the preparation of, or approaches toward the synthesis of representative pseudoguaianolides. Thus, syntheses of confertin, range in overall yields from a high of 10-15% by Wender and Schlessinger[20] to low overall yields of 0.8 - 0.9% by Marshall[21] and Heathcock have been reported. In most cases, ring A has come from substituted methyl cyclopentenone with some notable exceptions. Schultz's ring A was derived from methyl 1,3-cyclopentanedione and Heathcock's ring A from a substituted cyclohexenone. We will describe the preparation of representative pseudoguaianolides in Schemes **4-12**.

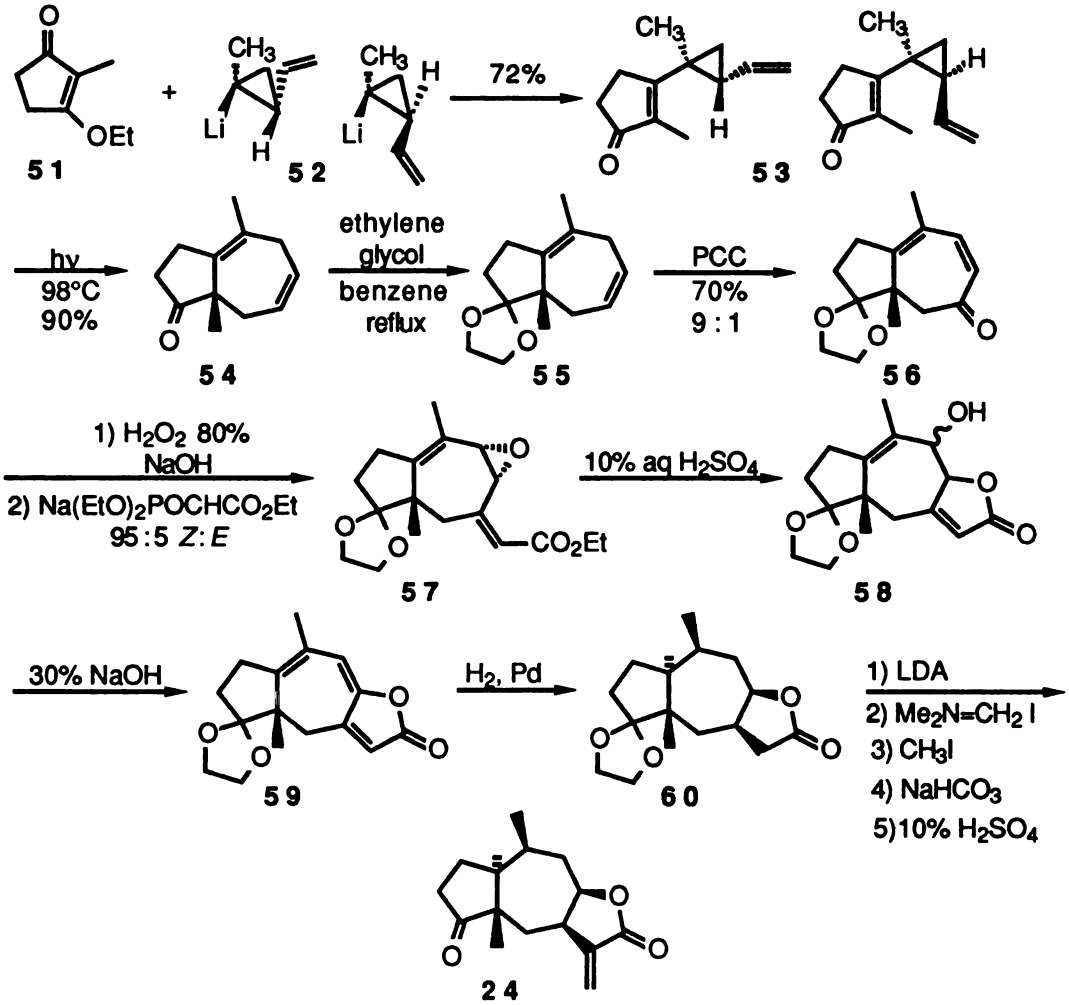
Heathcock[22] (Scheme **4**) begins his approach to confertin **24** from the known ketal acetate **38**. Osmylation from the less bulky β-side (blocked by the dioxolane), tosylation of the secondary alcohol (pTsCl, pyridine) and deprotection of the acetoxy-diol (K_2CO_3, MeOH) gave compound **40**. The resulting diol tosylate was exposed to solvolytic conditions (LiOH, tBuOH, 65°C) to give **41** and **42** epimeric at C1 (85%), in an equilibrium ratio of ~ 4:1. Protection of the free hydroxyl as an acetate and subsequent reaction with Me_3Al, MeLi and quenching with NH_4Cl/H_2O gave enone **44** as the sole product in 70% yield. At this point, Heathcock can diverge with this enone **44** to produce either the helenanolides 10α-CH_3 orientation (Li/NH_3) or the ambrosanolides 10β-CH_3 configuration ($H_2/Rh\text{-}Al_2O_3$). In the event, reduction of enone **44** with $H_2/Rh\text{-}Al_2O_3$ gave **45** (83%), which was enolized (LDA) and the enolate then alkylated with methyl bromoacetate to afford **46** (56%) selectively with C-ring elements in place. Hydrolysis of the ester and subsequent closure (excess $HClO_4$) gave crude butenolide **47** (34%) which was hydrogenated (H_2, Rh/Al_2O_3) to provide butyrolactone **48** (34%). Lactone **49** was then smoothly converted to confertin **24** (31%) as shown.



SCHEME 4: Heathcock's Synthesis of Confertin

Two substantially different synthetic routes toward confertin were taken by Wender and Semmelhack. Wender[23] (Scheme 5) chose a divinyl cyclopropane rearrangement to form the hydroazulene system **54**. The preparation of the substrate suitable for rearrangement began with the addition of lithio cyclopropane **52** to 3-ethoxy-2-methylcyclopentenone followed by hydrolysis the enol ether to give **53** (72%). Irradiation of the divinyl cyclopropane at 98°C resulted in cyclization to form the bicyclo[5.3.0]decane **54** (80%). Dieneone **54** was then protected (ethylene glycol, benzene, reflux) and oxidized (PCC) to give a 9:1 ratio of dieneone **56** (70%) regioisomers. Epoxidation (H_2O_2, NaOH, 70%) and Horner-Emmons olefination ($Na(EtO)_2POCHCO_2Et$, 80%) of the ketone gave the epoxy triene **57**. Finally, compound **57** was subjected to ester hydrolysis (aq. H^+), epoxide

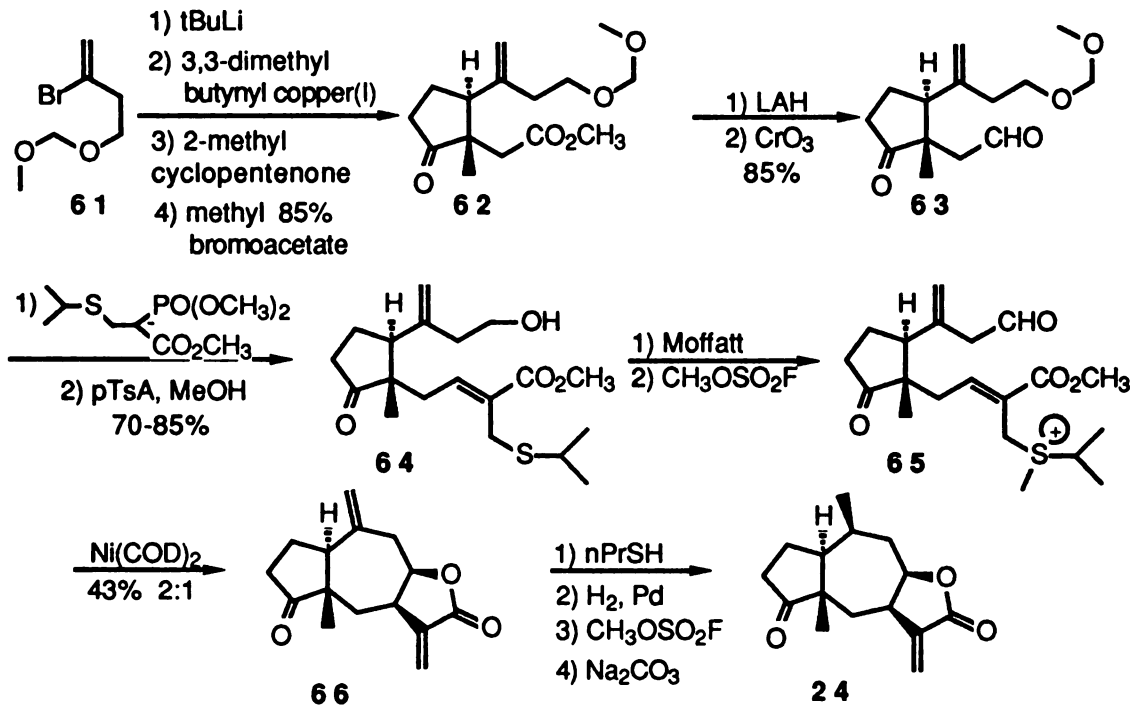
opening (10% H_2SO_4) to form a lactone, followed by dehydration (30% NaOH) to furnish triene-lactone **59**. Hydrogenation (H_2, Pd) established the ring fusion, the C10-CH_3, and butyrolactone stereocenter in the desired sense affording lactone **60**, which was then converted to (±)-confertin by the method of Heathcock.



SCHEME 5: Wender's Synthesis of Confertin

Semmelhack[24] employed yet another interesting variation, a metal promoted cyclization-lactonization, in his successful synthesis of (±)-confertin **24** (Scheme 6). Using a tandem Michael addition/alkylation sequence, cyclopentanone **62** was prepared in 85% yield, as illustrated in Scheme 6. Reduction (LAH) and oxidation (CrO_3) gave aldehyde **63** in 85% yield ; and this was added in Horner-Emmons fashion to the sodium or lithium salt

formed by reaction of sodium or lithium isopropylmercaptide with trimethyl phosphonoacrylate to give α-thiomethyl enoate **64** (70-85%) as a *Z*/*E* mixture (4:1(Na) to 1:8(Li)). Hydrolysis (pTSA, MeOH) of the methoxymethyl protecting group, followed by careful Moffatt oxidation (dicyclohexylcarbodiimide, TFA) of the resulting hydroxyl group generated an aldehyde in a 9:1 isomer ratio, contaminated with some of the opposite olefin stereoisomer. Treatment of the mixture with "Magic Methyl" (CH_3SO_3F) resulted in a sulfur ylide **65**, which was treated with either Zn(0) or Ni(0) to promote cyclization. Zinc (zinc-copper couple) gave a product that was determined to be the α–cis fused lactone (30%), whereas nickel (nickel cyclooctadiene) gave a 2:1 ratio of the β-cis fused lactone (**66**), (±)-confertin, to the α-cis fused lactone in 43% yield. Semmelhack has not yet explained the role of either the double bond geometry or the nature of the metal employed in the stereochemical outcome of the cyclization.

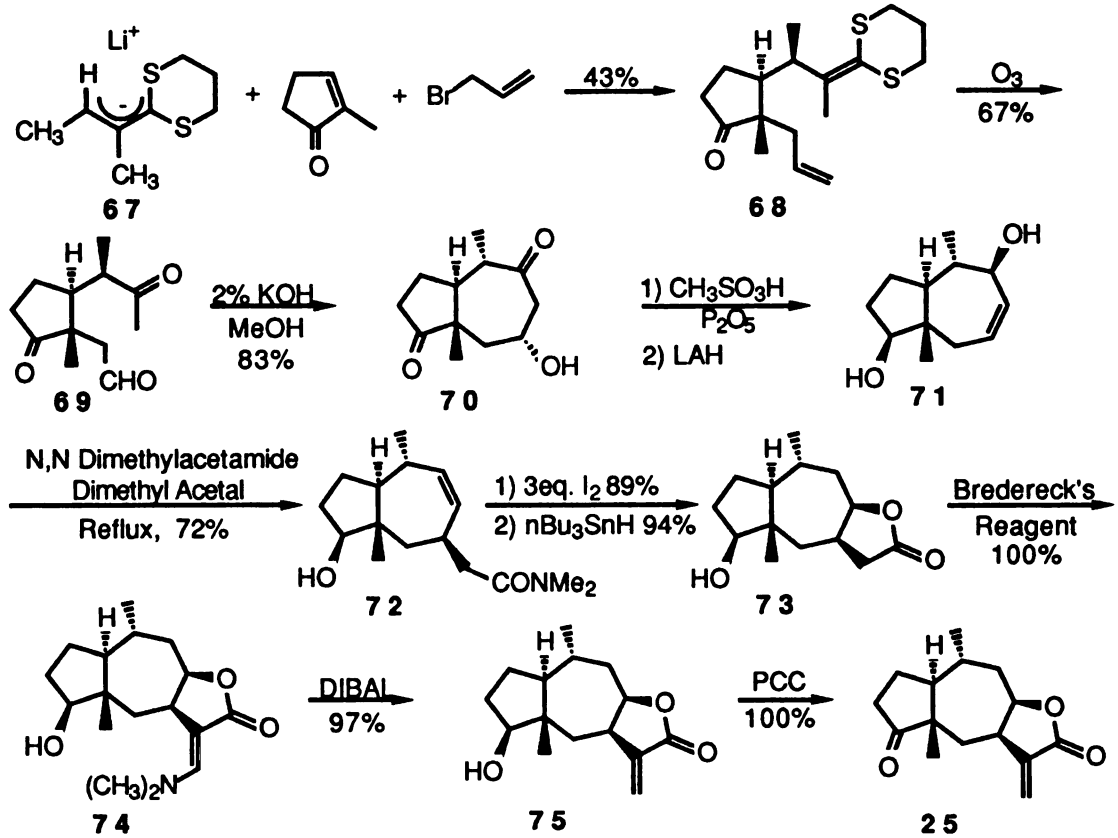


SCHEME 6: Semmelhack's Synthesis of Confertin

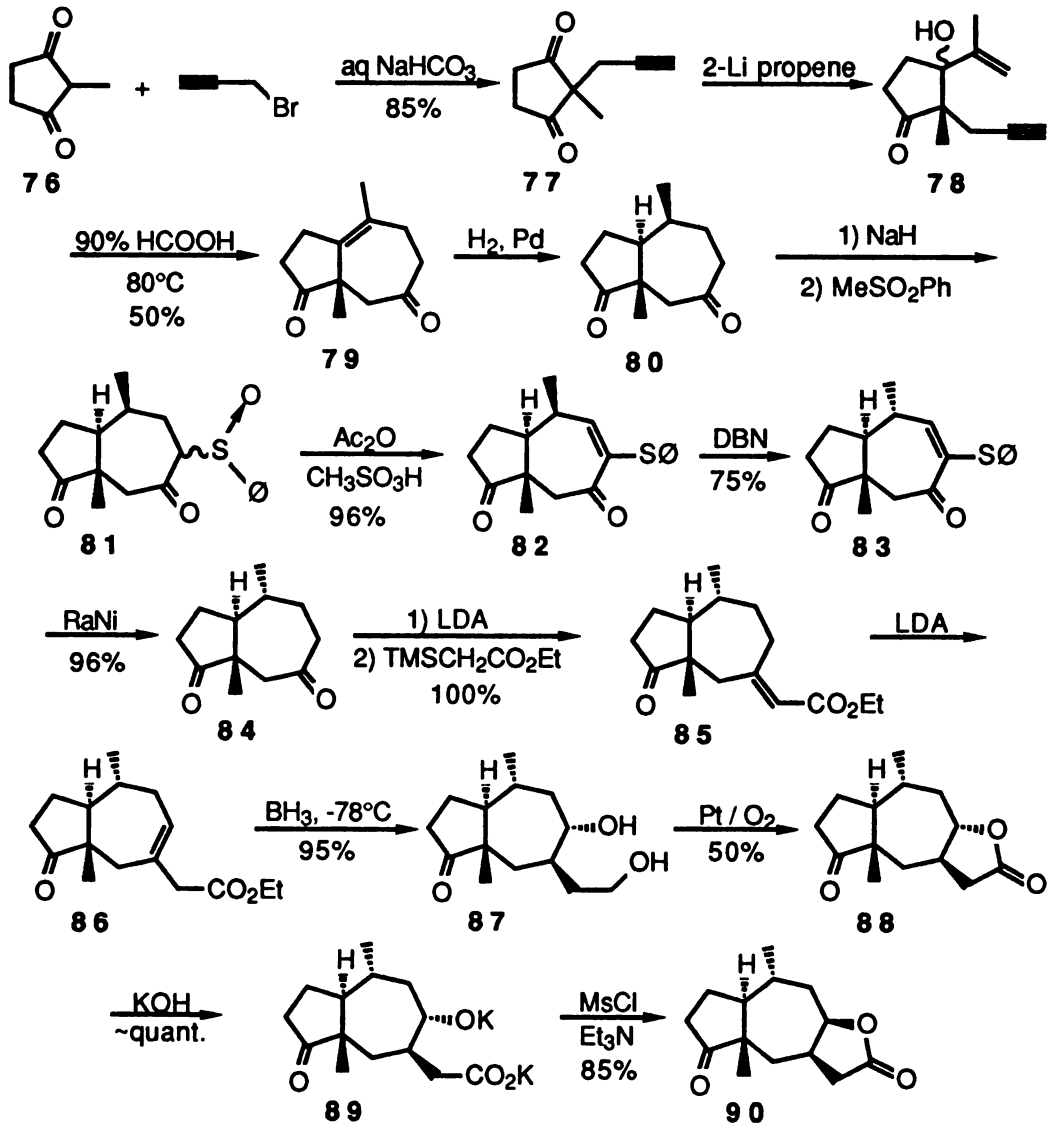
The simple helenanolides, represented by aromatin **25**, have also served as targets for total synthesis. Ziegler's[25] approach to the synthesis of aromatin used dithianylidene anion chemistry, as described in Scheme **7**. Thus, dithianyl anion **67** was added to 2-methyl-cyclopentenone and the resulting

copper enolate (CuI, $P(OMe)_3$) was trapped by reaction with allyl bromide to give compound **68** in 50% yield. Ozonolysis then provided ketones **69** (67%) and its epimer in a 18:1 ratio, and aldol cyclization (2% KOH-MeOH) afforded a single aldol product **70** (85%), in which the C10-CH_3 has epimerized to the favored α-(equatorial) orientation. Dehydration (MeOH-P_2O_5) of 70, followed by reduction (LAH), gave diol **71** (83%), which was ideally suited for the C-ring annulation *via* Claisen technology. The Eschenmoser variant of the Claisen rearrangement ($Me_2NCH_3CH(OMe)_2$) afforded eneamide **72** (72%) after saponification. Iodolactonization (I_2, aq. THF) followed by reductive elimination ($(Bu)_3SnH$) of iodine generates **73**, thus establishing the bicyclo[5.3.0]decane ring system. Ziegler completed the synthesis of (±) aromatin with an interesting elaboration of the C-ring to form the α-methylene butyrolactone. Reaction of lactone 73 with bis(dimethyl-amino)methoxymethane (Bredereck's Reagent) gave the related vinylogous carbamate which provided (±)-aromatin after reduction (DIBAL), acidification (NH_4Cl), and oxidation (PCC) to the 4-one product. Ziegler has also completed a synthesis of (±) confertin from compound **72** *via* iodine elimination (DBN) and hydrogenation (H_2, Pd) of the resulting olefin. The latter reduction gave an excellent yield of the β-methyl product.

Lansbury[26] has also completed a synthesis of (±)-aromatin as described in Scheme **8**. Propargylation of 2-methyl-1,3-cyclopentanedione gave **77** (85%), which added propenyl lithium to afford compound **78**. Cyclization of **78** by treatment with formic acid (90% HCOOH, 80°C) yielded dione **79**. Compound **79** was reduced (H_2, Pd), providing the undesired β-methyl stereochemistry, a situation that was remedied, but at the cost of a number of steps, as illustrated in (Scheme **8**).[27] With the desired C10 α-methyl ketone **84** in hand, Lansbury then added the elements of the C-ring butyrolactone by first forming the α,β-unsaturated ester **85** (100%) *via* Petersen olefination, followed by double bond migration to the 7,8-position by kinetic-controlled enolate protonation. Reduction of both the double bond and ester functions by diborane gave diol **87** (95%) after alkaline peroxide treatment. The C-ring was then formed by a Pt/O_2 oxidation giving lactone **88** (50%), which led to (±)-aromatin, as described in Scheme **8**.



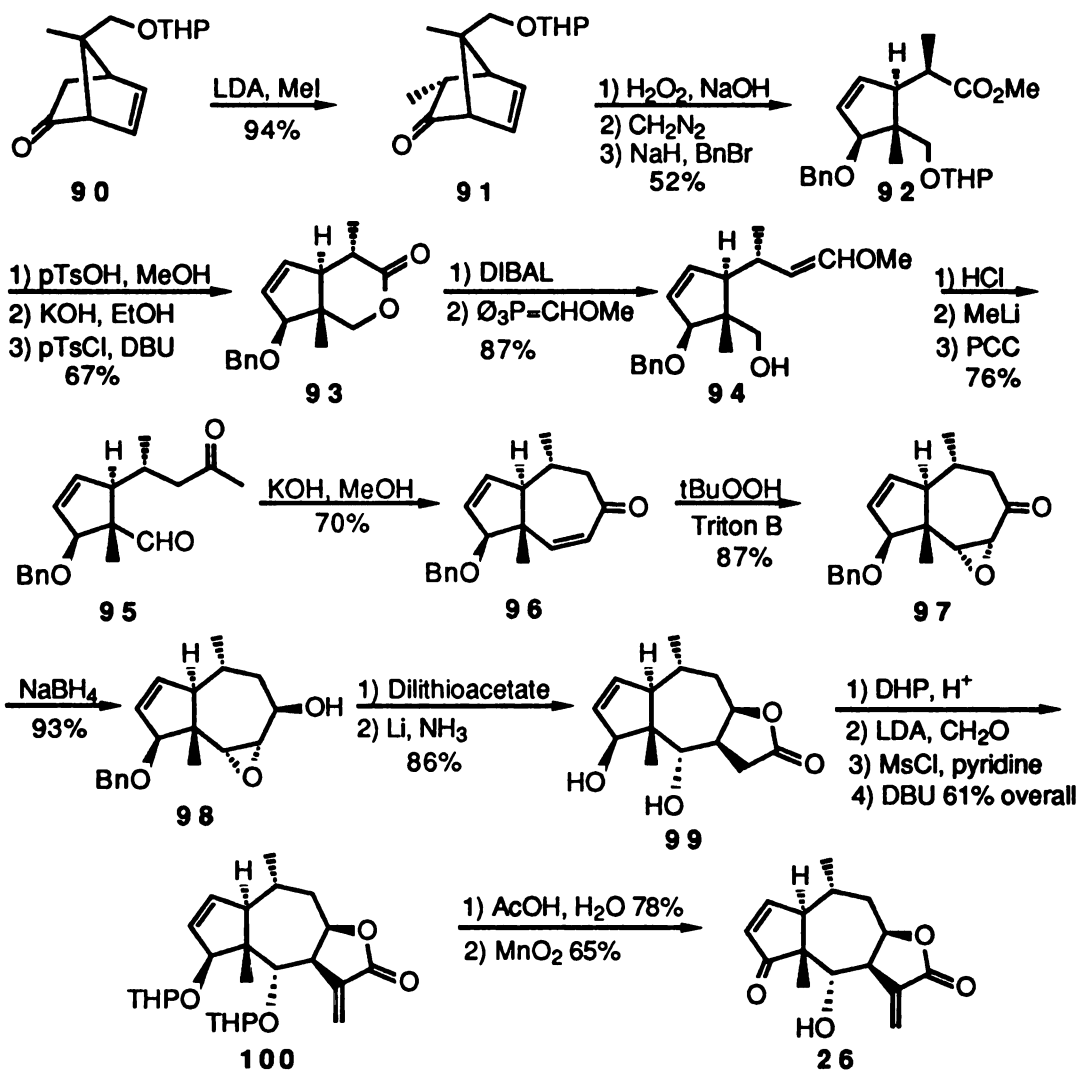
SCHEME 7: Ziegler's Synthesis of Aromatin



SCHEME 8: Lansbury's Synthesis of Aromatin

The final examples of pseudoguaianolide syntheses discussed here are directed toward the more highly oxygenated helenanolides, such as helenalin, and fastigilin-C. As might be expected for these more functionalized ring systems, the number of syntheses reported decreases as the complexity of functionality and stereochemistry increase. Helenalin has been synthesized by Grieco and Schlessinger. Fastigilin-C has not yet yielded to total synthesis, however, a synthesis of 2,3-dihydrofastigilin was recently reported by Lansbury.

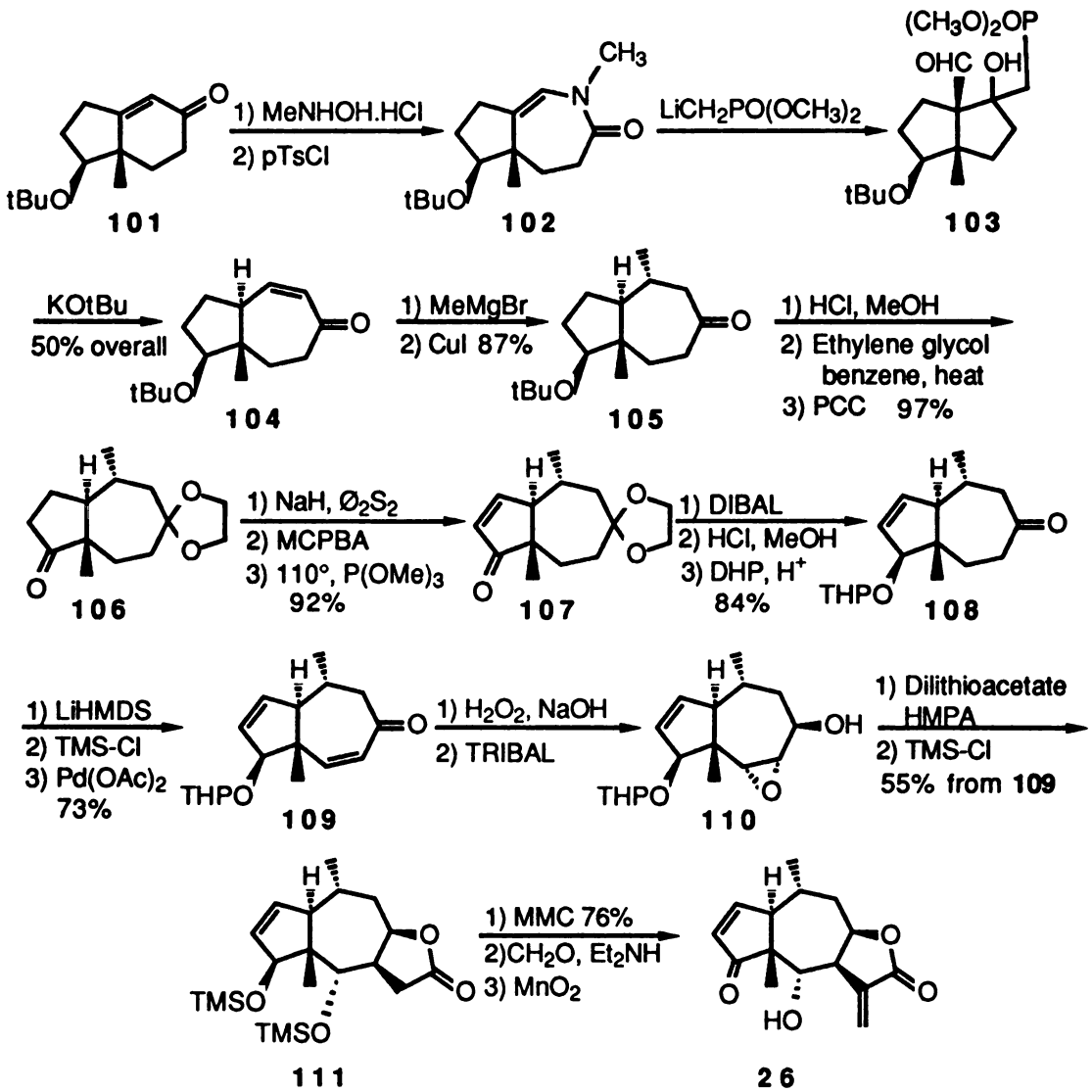
Grieco[28] began his synthesis of (±) helenalin **26** (Scheme **9**) in a fashion very similar to his prior pseudoguaianolide preparations from rigid bicyclic precursors. The known bicyclo[2.2.1]-heptanone **90** was alkylated (LDA, MeI) to give exclusively the endo methylated ketone **91** (94%). A base catalyzed Baeyer-Villiger oxidation (H_2O_2,OH^-) and subsequent lactone opening gave **92** after esterification (CH_2N_2, 86%). These steps unmasked the A-ring as a cyclopentanol, having the desired ring fusion stereochemistry; however the C10-CH_3 has the ambrosanolide configuration. This latter concern was readily corrected by an equilibrium-driven epimerization favoring the desired C10-α-CH_3 (helenanolide) orientation. Toward that end, **92** was converted to the desired lactone **93** in a series of five steps as drawn. Reduction of **93** (DIBAL) and Wittig olefination ($Ø_3P$=$CHOCH_3$) gave an enol ether, which led to keto-aldehyde **95** after hydrolysis, MeLi addition, and oxidation (PCC, 45% over 5 steps). Aldol condensation (KOH, MeOH) and dehydration (pTsOH) then gave enone **96** (70%), which was epoxidized (tBuOOH, Triton B, 87%) and reduced ($NaBH_4$, 99%) to give alcohol **98**. The final stages of this helenalin synthesis involved dilithioacetate addition to the epoxide, removal of the C4 oxygen benzyl protecting group (Li, NH_3) and acidic quenching to give lactone **99** (86%). This was smoothly converted to the target compound as shown in Scheme **9**.



SCHEME 9: Grieco Synthesis of Helenalin

In the Schlessinger synthesis of helenalin[29] an epoxy alcohol intermediate (**110**) very similar to that described by Grieco, was prepared by a completely different procedure. The known enone **101** was converted to lactam **102** using the Barton rearrangement (MeNHOH·HCl, 40°C, pTsCl) . Addition of lithio dimethyl methylphosphonate to lactam **102** occurred with subsequent ring opening to a metallated cyclopentyl enamine that gave aldehyde **103** after hydrolytic workup. Retroaldol fragmentation of aldehyde **103** on treatment with KOtBu generated a Horner-Emmons intermediate which closed to enone **104**, after intramolecular capture of the aldehyde. Cuprate addition (MeMgBr, CuI) to enone **104** then introduced the C10-CH_3 from the desired and less sterically encumbered α face leading to **105** (67%). To complete the

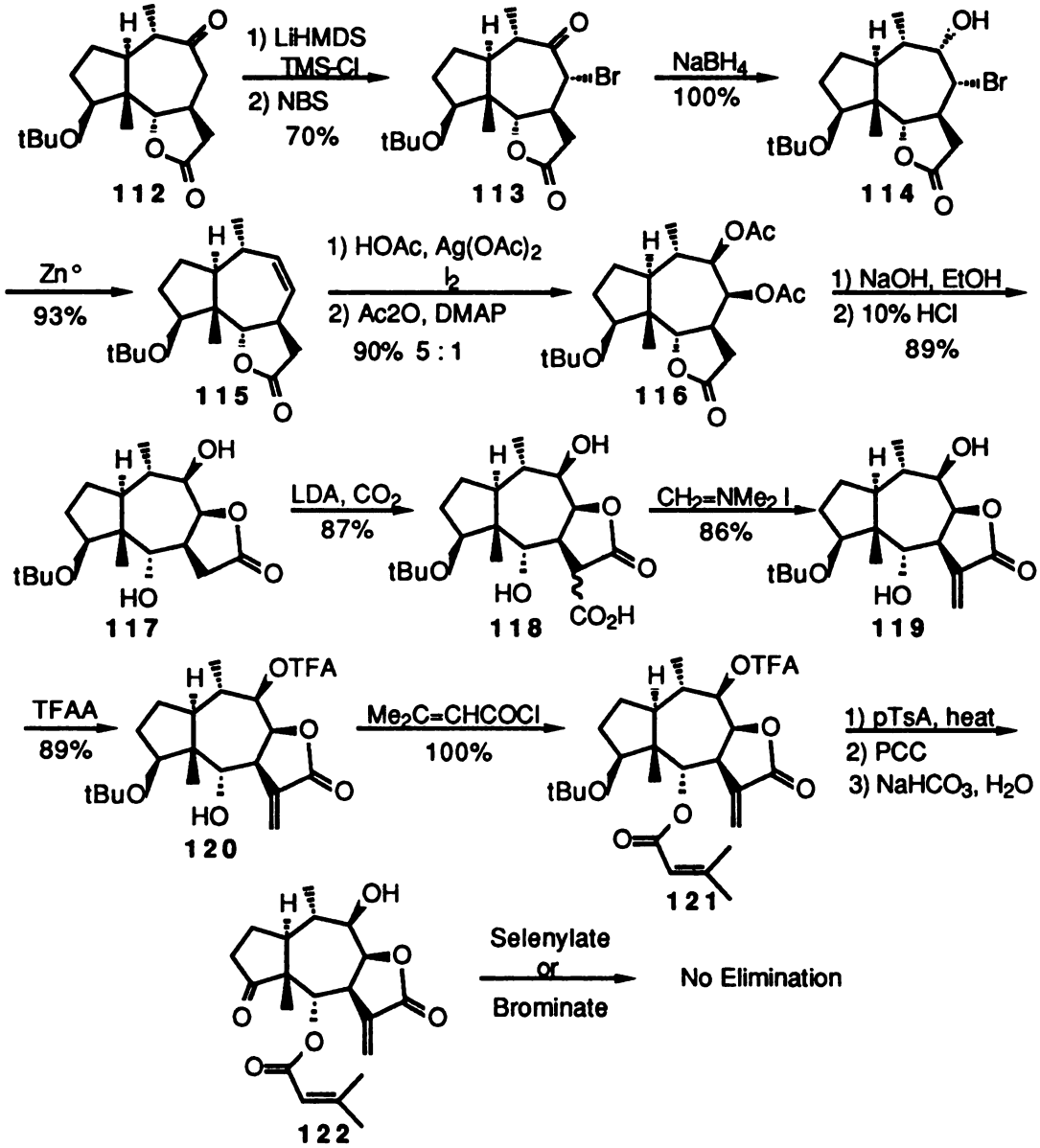
synthesis of known intermediate **109**, Schlessinger was then faced with the task of introducing two double bonds at the 2,3 and 6,7 positions as well as manipulating of the oxidation states at C4 and C8. Toward that end, ketone **105** was deprotected (H^+), the C8 ketone was blocked as the corresponding dioxolane (ethylene glycol, pTsOH), and the C4-one was introduced by oxidation (PCC). As described in Scheme **10**, ketone **106** was converted to the A-ring enone; this was reduced, the resulting alcohol protected as a THP ether, and the Δ6,7-double bond was introduced *via* Saegusa oxidation of the silyl enolether after hydrolysis of the dioxolane. The remainder of Schlessinger's synthesis followed that of Grieco to afford (±)-helenalin **26**.



SCHEME 10:Schlessinger's Synthesis of Helenalin

Fastigilin-C **27**, one of the most complex of the pseudoguaianolides is functionalized at all seven carbons about the B-ring. As a result of this factor, and two peculiarities noted during Lansbury's[30] attempted synthesis of **27**, fastigilin-C has resisted total synthesis to date. The efforts of Lansbury, which comprised routes A and B are described in Schemes **11** and **12** respectively.

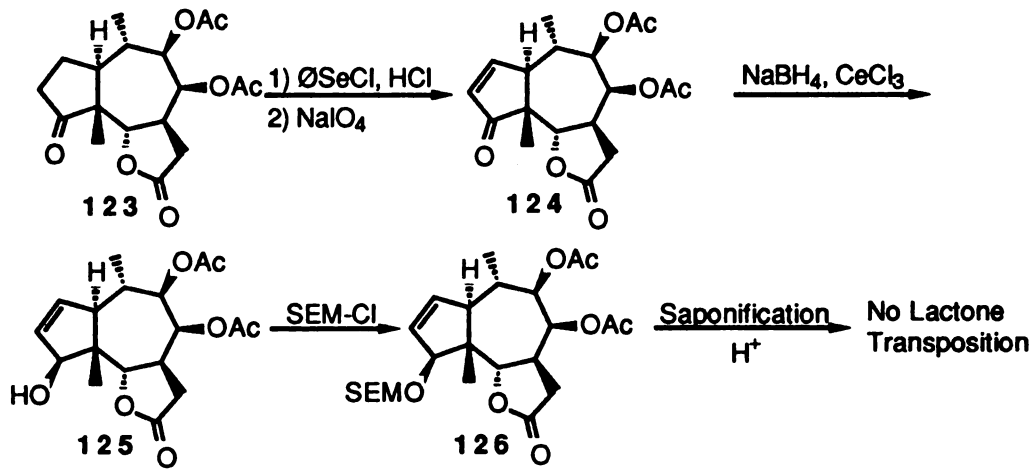
Route A begins with the bromination (LiHMDS, NBS) of the enol silyl ether derived from ketone **112** to give **113**, followed by reduction ($NaBH_4$) of the C9 ketone to give alcohol **114**, with the incorrect stereochemistry at C9 for fastigilin-C. Therefore the hydroxyl group was eliminated (zinc) to form olefin **115** (90%), and a "Wet" Prevost reaction (HOAc, H_2O, $Ag(OAc)_2$, I_2) was employed to give a 5:1 ratio of the 8β,9β diacetate (Ac_2O, DMAP) **116** in 90% yield to the related 8α,9α diacetate. Saponification (aq. NaOH) of **116** followed by acid treatment and heat afforded a 9:1 mixture of the 9β-hydroxy-7,8 cis lactone **117** (89%). With all stereochemical aspects of fastigilin correctly established in diol lactone **117**, Lansbury simply needed to introduce the Δ 2,3 ene-4-one double bond and functionalize both the C6 alcohol and the lactone methylene carbon. Toward that end, Lansbury examined route B the introduction of the Δ 2,3 double bond at an earlier stage prior to the B-ring elaboration. As seen in Scheme **12**, keto diacetate **123** was selenylated by the method of Grieco (HCl, PhSeCl), the selenide oxidized, eliminated, and the C4 ketone converted to the 4β-SEM ether **126** (a. $NaBH_4$, $CeCl_3$, b. SEM-Cl). At this stage, Lansbury was unable to transpose the lactone, therefore, he chose to return to the nearly completed fastigilin skeleton and introduce the enone as the final step for the completion the synthesis.



SCHEME 11: Lansbury's 2,3-Dihydrofastigilin-C

Instead Lansbury chose to further examine route A to attempt to functionalize the completed fastigilin ring precursor (see Scheme **11**). α-methylation of lactone **117** (LDA, CO_2, 87%), then alkylation with Eschenmoser salt (CH_2=NMe_2I) of the carboxylactone gave α-methylene butyrolactone **119** (86%). Methylene lactone **119** was selectively converted to the diester (C9-OH, TFAA, pyridine, 89%) and when heated to reflux with β,β dimethylacryloyl chloride gave the senecoiate ester **121** (100%). Hydrolysis of the C4 ether (pTsA) and oxidation (PCC) gave 2,3-dihydrofastigilin-9-

trifluoroacetate **122** which resisted all attempts at introduction of the Δ2,3 double bond. The mild conditions necessary to ensure survival of the resident functionality (C1,C5 trans orientation) and the steric hindrance provided by the axial 5β-CH_3 and 6α-ester conspire to prevent C-3 functionalization. Thus the synthesis of (±)-**27** remains unfinished.



SCHEME 12: Lansbury's Unsuccessful Lactone Transposition

Our interest centered upon the synthesis of fastigilin-C **27** via our previously established furan terminated cationic cyclization methodology. We reasoned that with proper masking of the resident functionality in a more robust form, and incorporation of the butyrolactone in latent form as a furan, that we would be able to overcome the the functionalization and conformational problems encountered by Lansbury. One potential retro-synthetic approach to fastigilin-C is presented in Figure **5** (route **A**). The crucial steps in this proposed sequence are the furan terminated acylium ion initiated cyclization which establishes the 7-membered B-ring and the three component coupling which establishes the cyclization substrate. Our concern with the latter were twofold; i) what equivalent of a 2-metallated acrylate would add to 2-methylcyclopentenone, and ii) could we expect any control in the development of the C6 oxygen bond?

Marino[31] has demonstrated the utility of the anion prepared from 2-bromoacrolein in conjugate addition sequences, however, we were unable to detect even trace amounts of products which correspond to 1,4 addition after quenching with H^+, TMS-Cl, or 3-furaldehyde (eq. **7**), therefore, the route was abandoned.

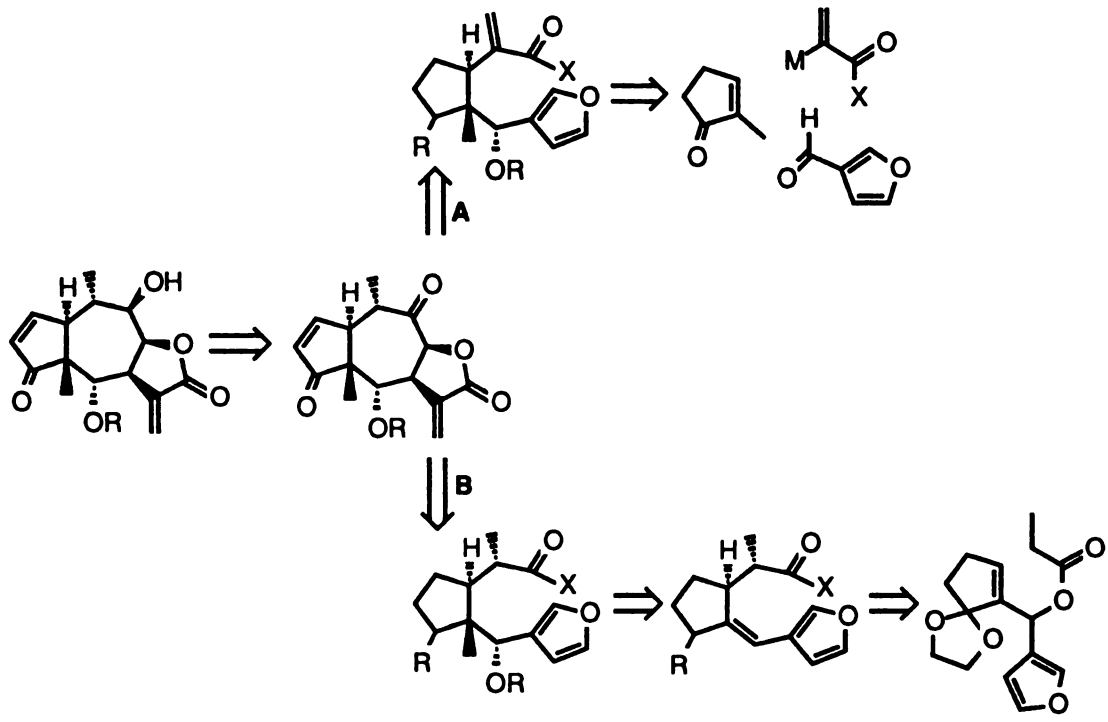
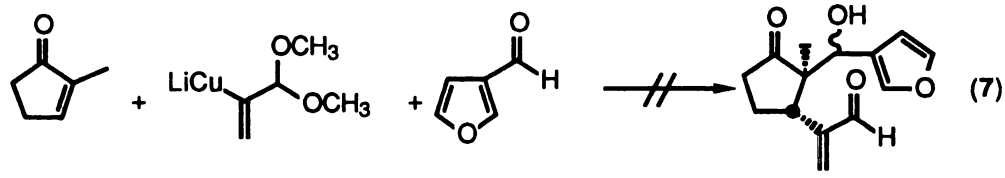


Figure 5 : Possible Retrosynthesis for Fastigilin-C



(7)

Another alternative which was considered was postulated from the retrosynthetic analysis presented in Figure 5 (route **B**). We examined a route which would establish the desired cyclization substrates via an Ireland[32] type enolate Claisen rearrangement. Some precedent for this type of construction was found in the work of Burke.[33] Important questions to be answered in this approach were i) will the depicted rearrangement occur through the cyclopentyl unit or the furyl moiety, ii) what will be the selectivity at the 2 methyl bearing centers, and iii) can the C5-CH_3 and the C6-OH be added with the desired stereochemistry?

Toward those ends, we constructed a model system as outlined in Equations **8** and **9**. Metallation of 2-bromocyclopentenone-ethylene ketal (nBuLi) and quenching with $(CH_2O)_n$ by the procedure of Smith[34], afforded α-hydroxymethyl-ketal **128** (70%), which was acylated with propionyl chloride to give propionate **129** (96%). Enolization of **129** under standard Ireland conditions (LDA, THF, -78°C) followed by silylation with TBDMS-Cl provided the *E*-enolsilyl ether[35] which was warmed to room temperature. We obtained a 90% yield of esters in a *ca.* 10:1 ratio, with the stereochemistry anticipated to be as predicted by literature precedent.

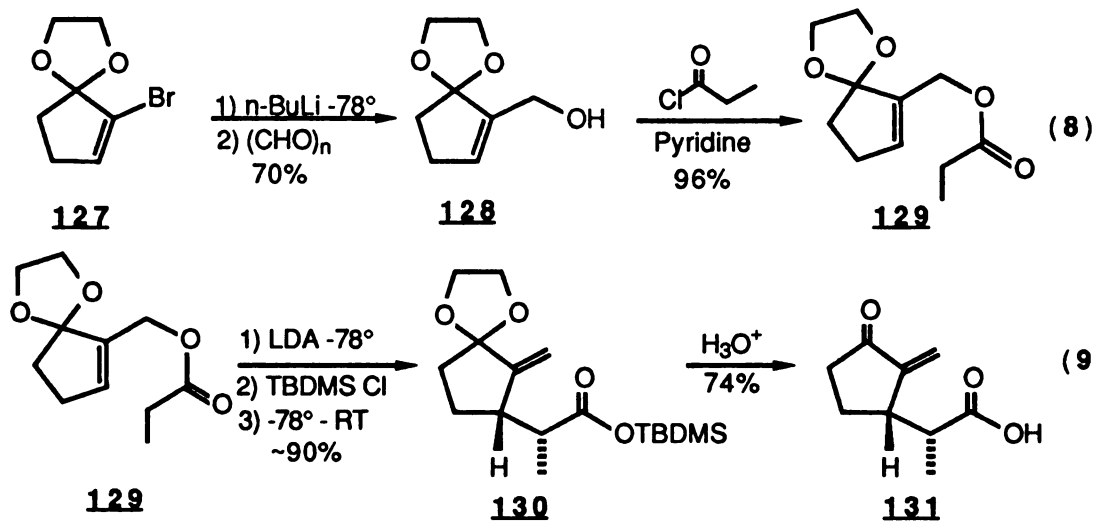
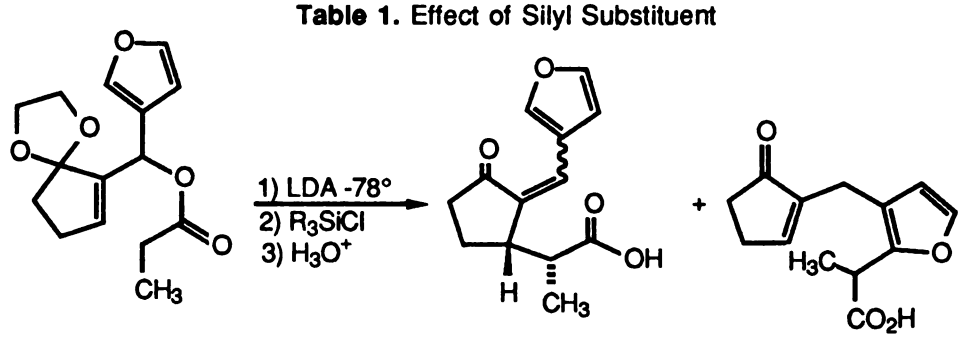


Table 1. Effect of Silyl Substituent

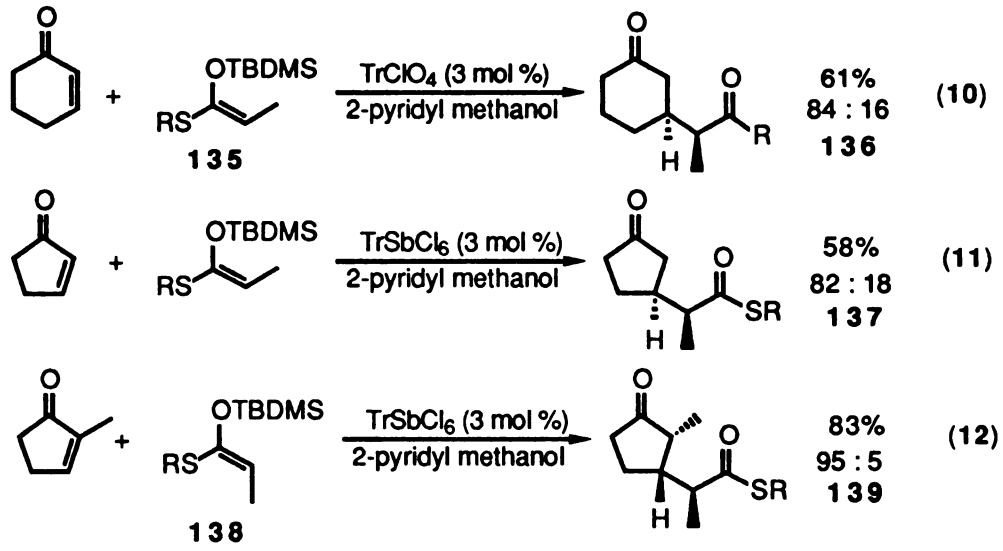


R_3SiCl	Yield	133/134
t-BuMe$_2$	69%	95:5
(Me)$_3$	79%	75:25
(i-Pr)$_3$	73%	20:80

With that information in hand, we next examined a system where furan had been incorporated. Our hydroxy methyl component required an additional furan to be placed at the hydroxymethyl carbon. Therefore we substituted 3-furaldehyde for formaldehyde in the cuprate reaction (**127**, nBuLi, CuI) of vinyl anion formed to give an alcohol (89%). The alcohol was esterified (propionyl chloride, pyridine) to give **132** in a 95% chromatographed yield. We then subjected propionate **132** to the enolate Claisen conditions (Table **1**) used in our model system (LDA, -78°C, TBDMS-Cl, RT) and we were pleased to find, upon hydrolysis, (5% aq HCl) a 69% yield of a two component mixture in a 95:5 ratio. The major product was found to be the expected mono-substituted furan acid **133**, the minor product was determined to be a disubstituted furan **134**, a product that arose from an ester enolate Claisen reaction with one of the double bonds of the furan instead of the cyclopentenyl double bond.[36] We discovered that the nature of the substituents on the silylating reagent had a profound effect (Table **1**) upon the course of the reaction.

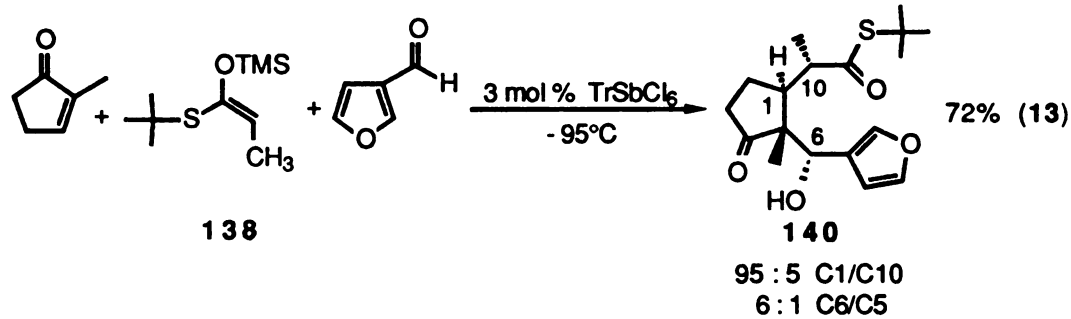
Our next task was to modify the enone and in the process introduce the C5-CH_3 and the C6-OH groups. We examined a number of sequences including enone reduction and alkylation, epoxidation and epoxide opening, and were frustrated by our inability to introduce the CH_3 correctly with either the absence or the presence of the OH. These difficulties, and an interesting report by Mukaiyama, caused us again to modify our approach.

While we were struggling with our attempts to introduce the C5-CH_3 and the C6 oxygen to the enolate Claisen product, we took note of a series of reports by Mukaiyama[37] which described a trityl cation catalyzed addition of ketene acetals to enones, including cycloalkenones. Mukaiyama reported good yields of either *syn* or *anti* (eq **10,11**) products as a function of substrates and reaction conditions. Of greater importance was the report of the addition of enolsilyl ethers of t-butylthiopropionate to 2-methylcyclopentenone to give predominantly the *trans* arrangement (eq **12**) about cyclopentane ring, and also afforded the correct relative stereochemistry at C10, C1, C5. The utility of the thioester moiety for cationic processes was also appreciated for our projected furan terminated ring closure.



Given Mukaiyama's success in securing a number of centers needed for the preparation of fastigilin-C, we decided to examine this approach as an alternative to the troublesome Claisen functionalization. Toward that end, t-butyl thiopropionate (available from Columbia Organics) was deprotonated according to Gennari (LDA, -78°C) and trapped (TMS-Cl) to form the relatively stable thio silyloxy enol ether **136**.[38] Alternatively, we also prepared **136** by treating the thioester with TMSOTF (RT).[39] In each of these cases we obtained the desired ketene acetal in *ca.* 80% yield as a 95:5 ratio of *Z* to *E* olefin isomers, as determined by gas chromatography and comparison of our data with that of Gennari. The other components for the three component Michael addition-Aldol condensation, 2-methylcyclopentenone and 3-furaldehyde are commercially available in research quantities. With the reagents in hand, we studied the experimental sequence utilizing the following protocol: to 2-methylcyclopentenone in dry CH_2Cl_2 cooled to -95°C was added the distilled ketene acetal followed by 3-5 mole% of Ph_3CSbCl_6 ($TrSbCl_6$), and then finally 3-furaldehyde in CH_2Cl_2 was added dropwise (Equation **13**). During our study of this sequence, we examined the variation of time intervals between additions upon the outcome of the reaction and discovered that timing of the aldehyde addition is most crucial. The addition of 3-furaldehyde 20-30 minutes after the Michael addition components have been added led to a 72% yield of a mixture of compounds which exhibited >95:5 NMR ratio of the *trans* to *cis* C10-C1 stereochemistry, and an aldol ratio (C5-C6) of ~4-6:1 (CH_3, 0.82 ppm), these products were also accompanied by *ca.*

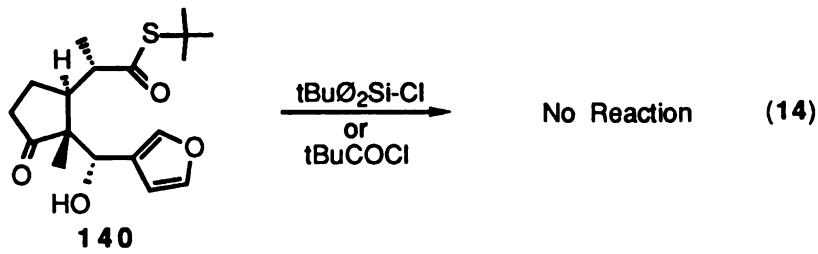
1% of what appeared to be a lactone. The initial Michael stereochemistry was also examined by addition of the thio silyloxy enol ether to 2-methylcyclopentenone and then quenching of the resulting enolate (H_2O) to give two products in a 95:5 ratio as determined by ^1H NMR and GC. The Michael addition and aldol ratios were nearly identical to those reported by Mukaiyama, however the relatively poor aldol (*ca.* 6:1) selectivity observed was the cause of some concern as it appeared that we would have to carry a complicated mixture some distance into the sequence before we might consider rectifying the C-O stereochemistry. This mixture would add complexity to the ^1H NMR spectrum and complicate our analysis of subsequent reactions. Regardless, we opted to continue with the mixture as we were unable to improve the aldol stereochemistry beyond 6:1, and next examined the crucial cyclization.

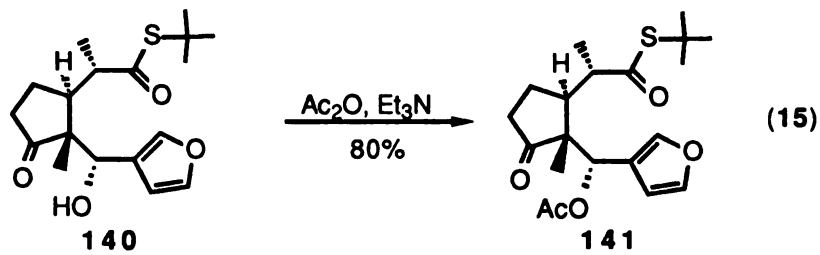


138 **140**

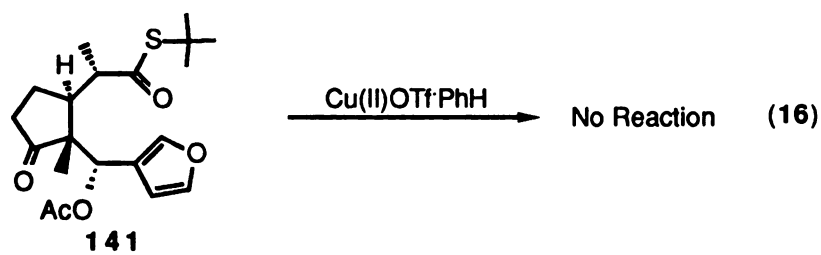
95 : 5 C1/C10
6 : 1 C6/C5

To prepare for cyclization, the alcohol produced from the tandem Michael addition 3-furaldehyde aldol condensation was protected to eliminate the possibility of a lactone being formed, or a retroaldol decomposition. We had decided to try three protecting groups, with a possibility of fine tuning the reaction with either size or type of protective reagent. Attempted protection with both t-butyl diphenylsilyl chloride[40] and pivaloyl chloride[41] failed, with no trace of silylated or acylated products detected (Equation **14**). Acetylation (AcCl or Ac_2O, Et_3N)[42] did not appear (TLC) to be productive , however, when this reaction was monitored by GC, we discovered that the desired acetate had indeed been formed (80%, eq **15**).



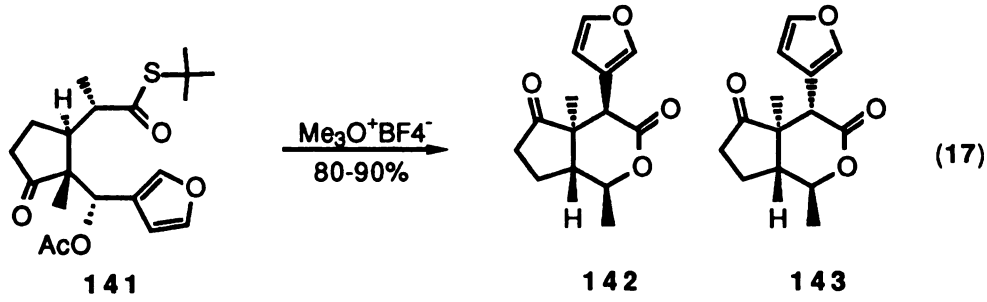


With our cyclization precursor **141** in hand, conditions were needed to cyclize the furyl thioester. It was thought that three different reagents for cyclization might be effective based on literature precedent, they were Cu(II)OTf·PhH, $Me_3{}^+OBF_4{}^-$, and $Hg(CF_3CO_2)_2$. Our first attempts were done using Cu(II)OTf·PhH as the acylation catalyst using the work of Kozikowski[35] as a model. Kozikowski[43] found that seleno esters could be induced to acylate furan, pyrrole or thiophene intermolecularly in the presence of Cu(II)-OTf·PhH (in 64-100% isolated yields). Upon treatment of compound **141** with 1.2 eq. of Cu(II)OTf·PhH no change in TLC was observed, and after workup, the starting material was recovered unchanged. Similar results were obtained with heating or reaction times of up to 24 hours.



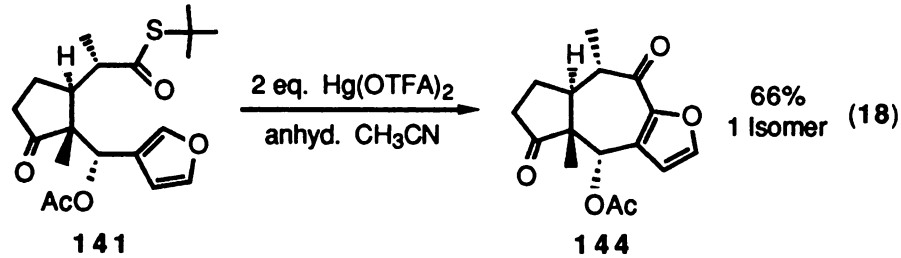
Our second effort involved the methylation of sulfur utilizing Meerwein's reagent ($Me_3O^+BF_4{}^-$). Upon addition of $Me_3O^+BF_4{}^-$ to a dichloromethane solution of **141**, there was an immediate change in the TLC and two spots of

lower R_f were detected. After work up, it was found that we had not cyclized through furan acylation, but instead had formed the diastereomeric lactones **142** and **143** in a 4-6:1 ratio (aldol center) in good chemical yield (80-90%).

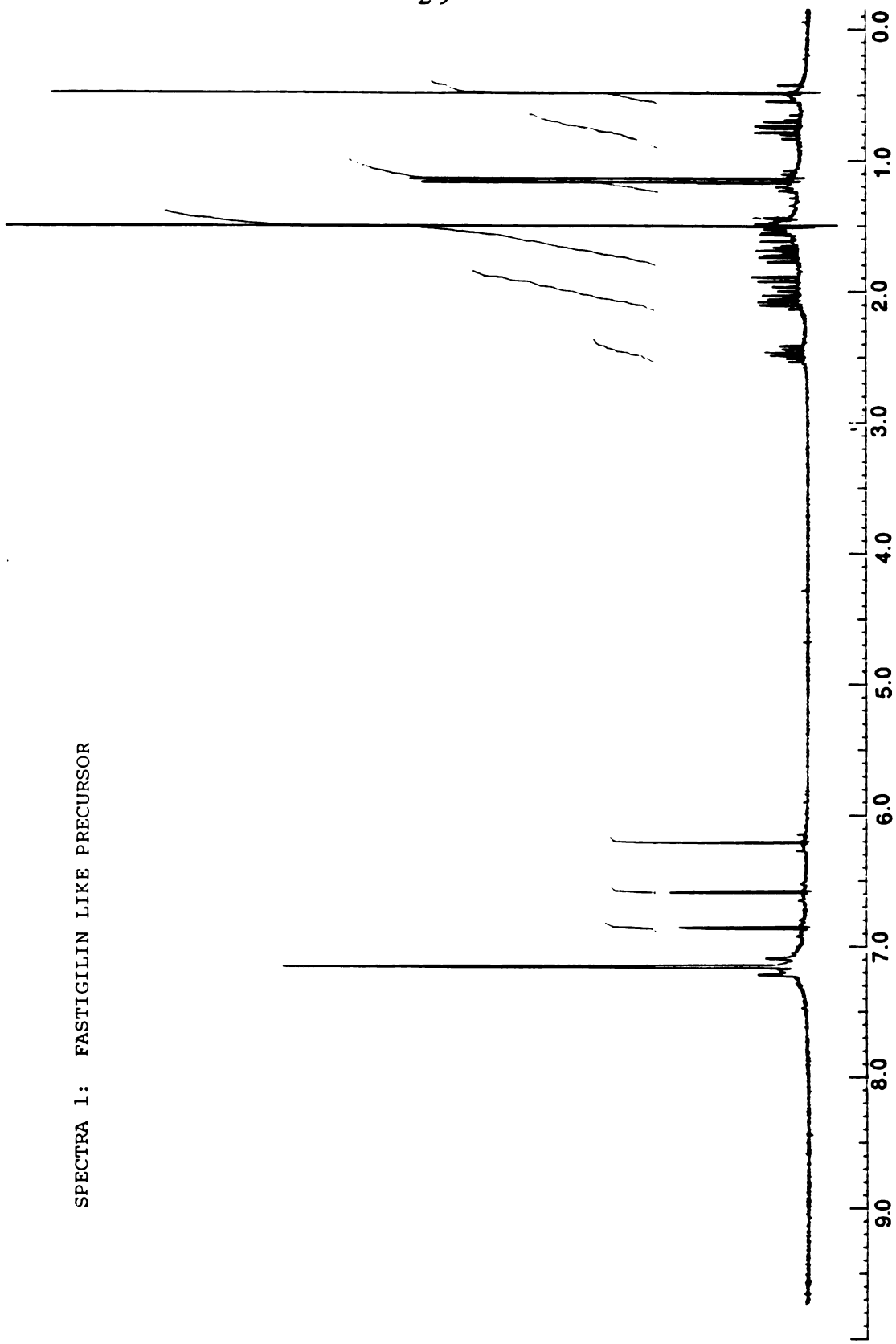


141 **142** **143** (17)

With our options becoming few, we chose to use a potent thiophile to initiate cyclization. Based on the work of Masamune[44], we decided to look at various thiophilic metal complexes such as $Ag(CF_3CO_2)_2$, $AgBF_4$, and $Hg(CF_3CO_2)_2$. Our first attempt involved mercuric trifluoroacetate (2 eq.) in dry acetonitrile (Equation **18**). Upon addition of the mercury salt there was a change in color to a greenish hue, then a white precipitate formed. Thin layer chromatography showed a new spot had formed that was <u>not</u> the same R_f as either the starting material or the lactones (**142,143**) observed previously. After workup, we isolated a 61% yield of a white - yellow solid, mp 158.5-160 °C (uncorrected). The NMR of the product produced a typical proton doublet pattern (δ=6.87, 6.58, both a d, J=1.71Hz) for the two furan protons of a 2,3 disubstituted compound. The ^1H NMR also revealed a doublet pattern for the C10 methyl (1.15ppm, J=6.85 Hz), a singlet for the C5 angular methyl (0.49 ppm) and a singlet for the methine at C6 (6.19 ppm). The ^1H NMR and GC seemed to indicate that we may have obtained a single isomer in which the minor aldol product seems to have disappeared. One explanation would be the selective destruction of one isomer possibly by retroaldol.

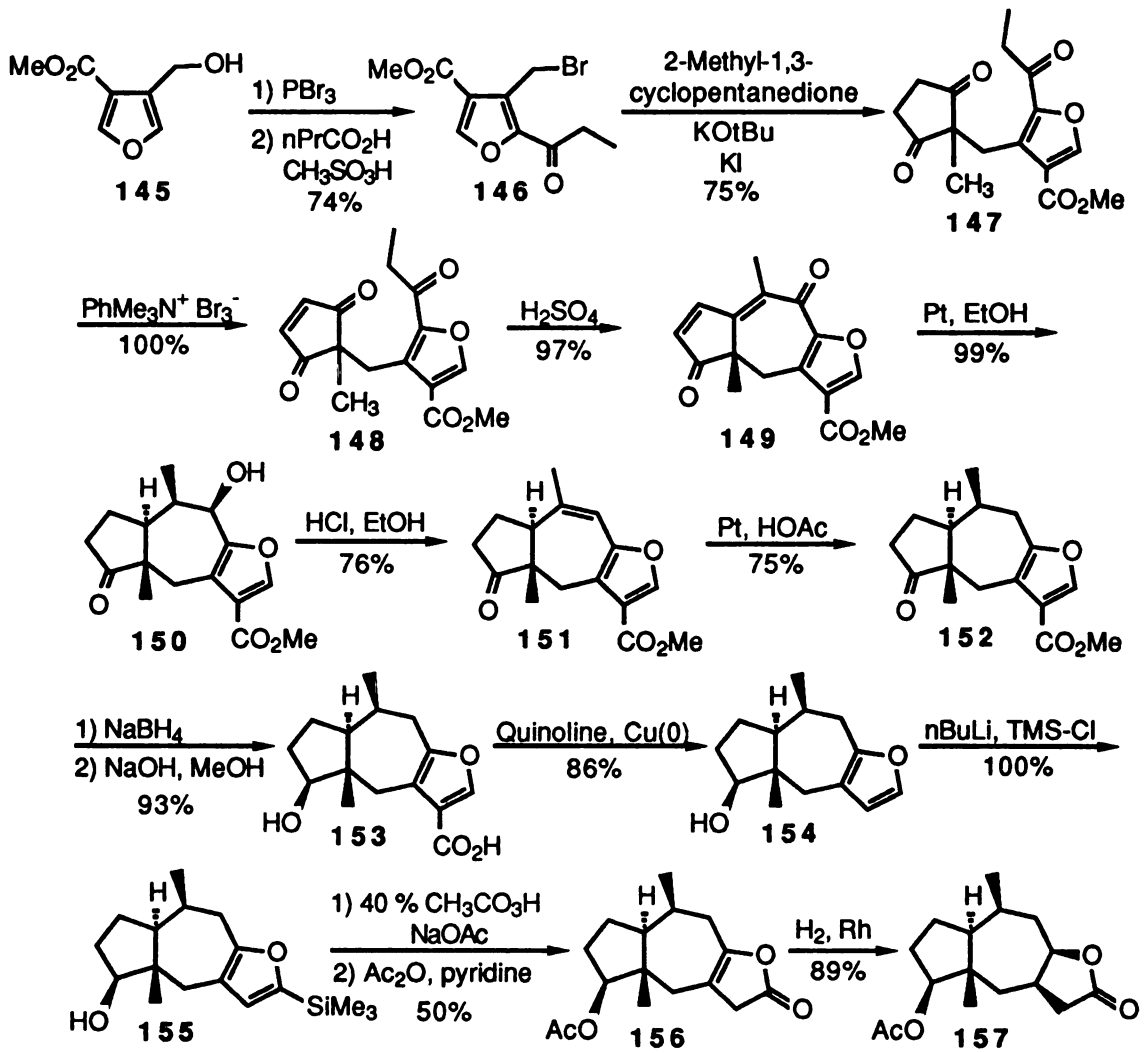


141 **144** (18)



SPECTRA 1: FASTIGILIN LIKE PRECURSOR

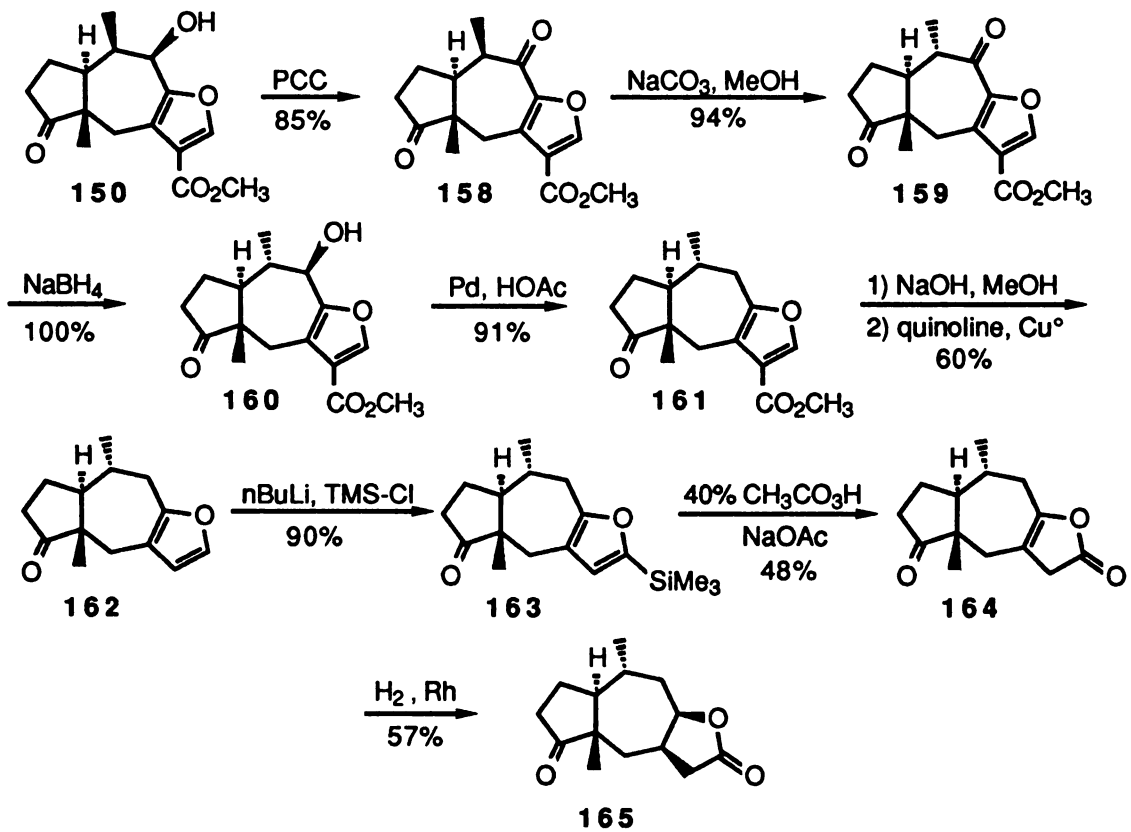
High resolution mass spectrometry, ^{13}C NMR, and FT-IR all confirm the presence of the cyclized bicyclo[5.3.0]decane product. Spectroscopic studies of the products are continuing (COSY[45], NOESY[46], HOHAHA[47] ^1H NMR) to determine the exact stereochemistry of the compound formed. Crystals have been obtained, but as yet the structure has not been elucidated by x-ray crystallography.



SCHEME 13: Schultz's Synthesis of Confertin

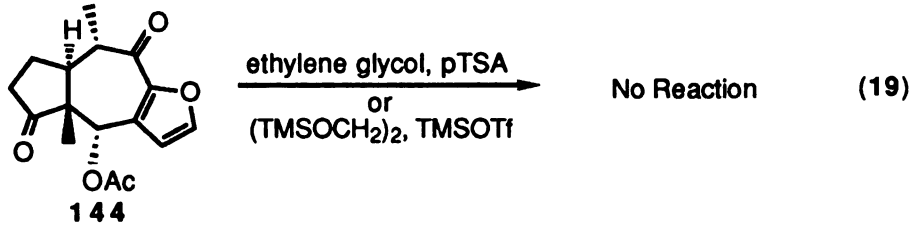
With compound **144** in hand, we were in a position to complete a total synthesis of fastigilin C and/or aromatin, confertin and helenalin. Aromatin and helenalin appeared as particularly desirable targets since Schultz[48] and his group had completed formal total syntheses of both confertin and

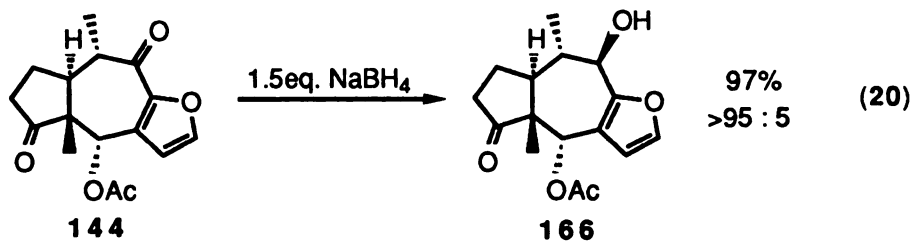
aromatin from a common furan intermediate **150** (Scheme **13**). More importantly, Schultz completed his syntheses of aromatin/confertin with a furan oxidation to obtain the butyrolactone needed in these systems, similar to a process we had envisioned to complete our synthetic effort.



SCHEME 14: Schultz's Synthesis of Aromatin

Intending to complete a synthesis of fastigilin-C, our first goal was the protection of C4 carbonyl as the ethylene ketal. Unfortunately, thermodynamic (ethylene glycol/benzene/reflux) as well as kinetic ($(TMSOCH_2)_2$, TMSOTf, -78 °C) conditions for ketalization[49] gave no reaction (Equation **19**). Needing to differentiate the C4 and C9 carbonyls, we attempted a sodium borohydride reduction. Using 1.5 eq. of $NaBH_4$ gave what appears to be a single isomer of alcohol **166** (97%) in which the "conjugated" C=O has been reduced to the exclusion of the more hindered C4 C=O (eq. **20**).





A comparison of alcohol **166** to a related compound (**160**) prepared by Schultz, we found the coupling constant of the doublet for C9 methine proton (9.69 Hz), was in accord with that found by Schultz (J=9.4 Hz.). Schultz attributed the coupling constant to a 180° dihedral angle between the two protons. An inspection of Dreiding models clearly showed two distinct conformations in which hydride attack could occur. In conformation **A**, the seven membered ring was nearly chair-like making the β-face accessible to hydride attack giving a product epimeric to Schultz's. If, on the other hand, the ground state conformation looks more boat like as in **B**, then only the α-face is accessible to hydride attack giving the β alcohol. Since our coupling constant of the C9 hydrogen was so similar to that of Schultz, we tentatively concluded that our assignment for the position of the alcohol is β. In addition, we have performed MM2[50] calculations on structure **166** and have arrived at a minimized structure with a C9-C10 dihedral angle of *ca.* 170°, in relatively good agreement with that derived from NMR data.

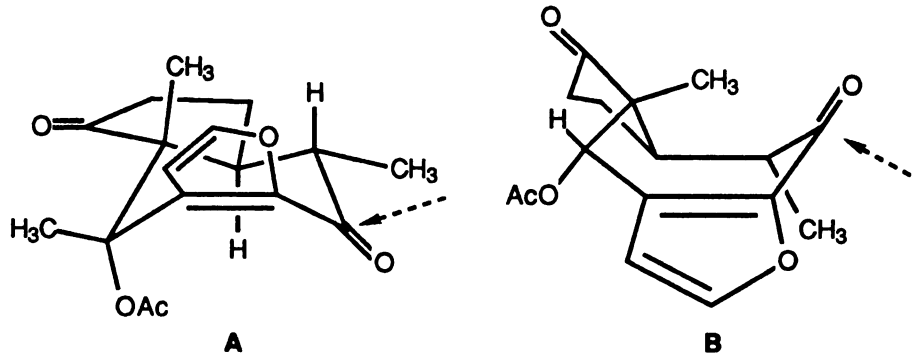
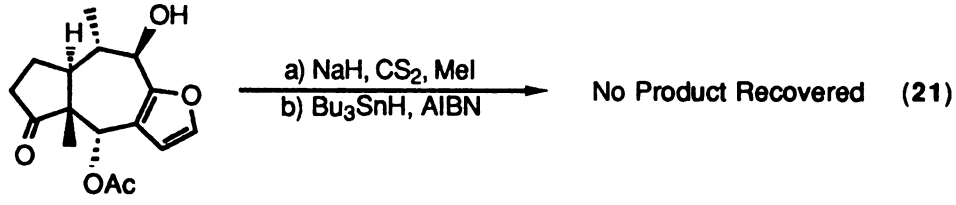
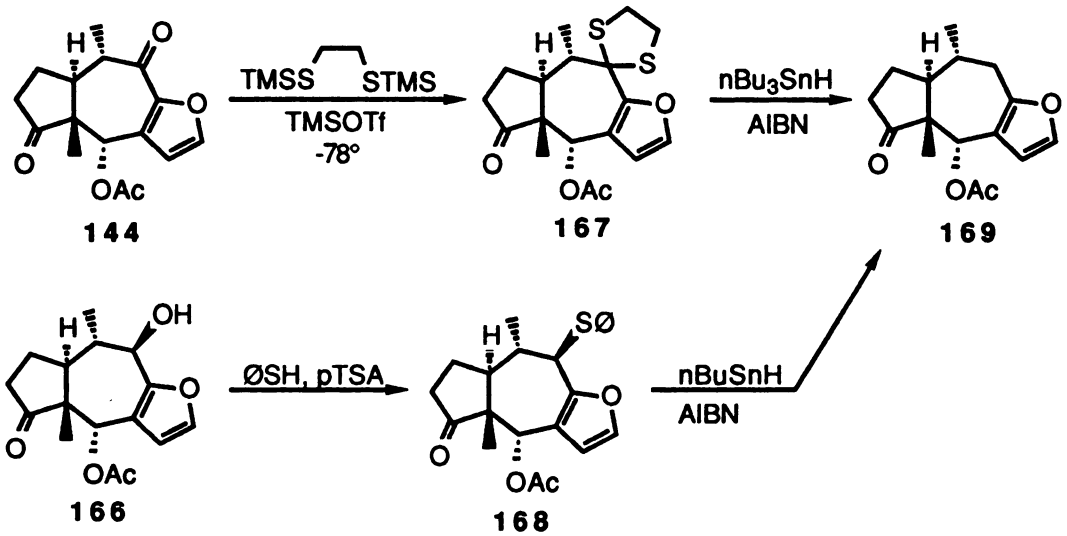


Figure 6: Stereochemistry of Ketone Reduction

With mono-protected diol **166** in hand, we turned our attention to the synthesis of aromatin, and helenalin. In order to prepare these compounds, we examined the possible methods of deoxygenating the C6 and C9 positions for aromatin, and remove the C9 oxygen to arrive at helenalin. We have investigated various Barton[51] deoxygenation methods (NaH, CS_2, nBu_3SnH) to remove these oxygens and have met with little success, these include attempts to reductively remove each alcohol separately (including various Barton methods and halogenation of the secondary alcohols) and a bis reduction (2 eq. NaH, 15 eq. CS_2) from the keto diol derived from **166** (Equation **21**).

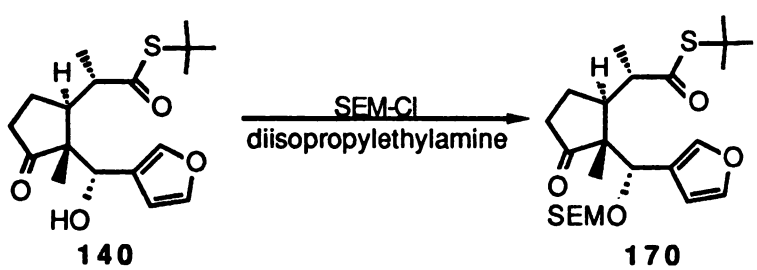


Two possible approaches toward aromatin and/or helenalin are currently under study. The first requires the selective formation of either the dithioketal **167** as indicated in Scheme 15, or formation of thiophenyl compound **168**. The thioketal and/or C9-SPh compounds could be reduced (Ra-Ni, and Bu_3SnH respectively) to afford the deoxy furan **169** (Scheme **15**). This mono-acetoxy furan might then be converted to helenalin in a manner similar to that employed by Schultz during his synthesis of aromatin.

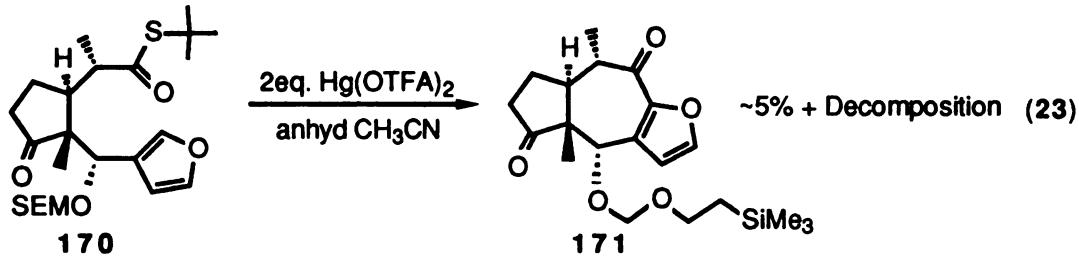


Scheme 15: Future Plans

The second approach requires the synthesis of a cyclization precursor with a different group protecting the C6 oxygen. Manipulation at this stage is a requirement as we have found that altering the C6-OH protecting function is very difficult post cyclization, as the C6 oxygen becomes too hindered for replacement by any other protecting group. We have completed a pilot study in which alcohol **140** was protected as the SEM-ether[52] (SEM-Cl, diisopropylamine) in 97% yield (eq **21**). When subjected to 2 eq. of $Hg(CF_3CO_2)_2$, no cyclized product was seen and after 24 hour exposure to Hg(II), the TLC showed predominantly starting material and/or deprotected alcohol. It seems that SEM is not stable to the reaction conditions. We are in the process of employing either MEM (methyloxyethoxymethyl)[53] or MOM (methoxy-methyl)[54] functions as protection for the C6-O during the cyclization. Should these techniques succeed, then we might have a compound that can withstand reductive (Barton) or oxidative conditions anticipated during assaults on helenalin and/or aromatin.

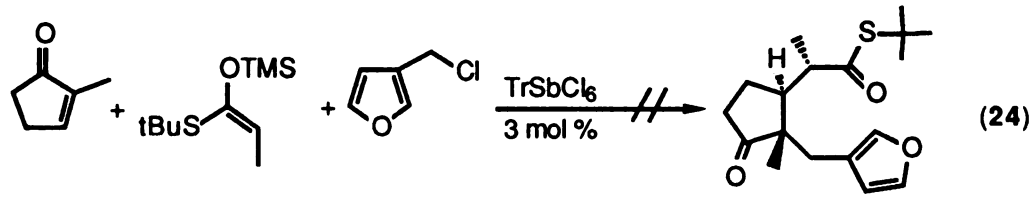


86% (22)



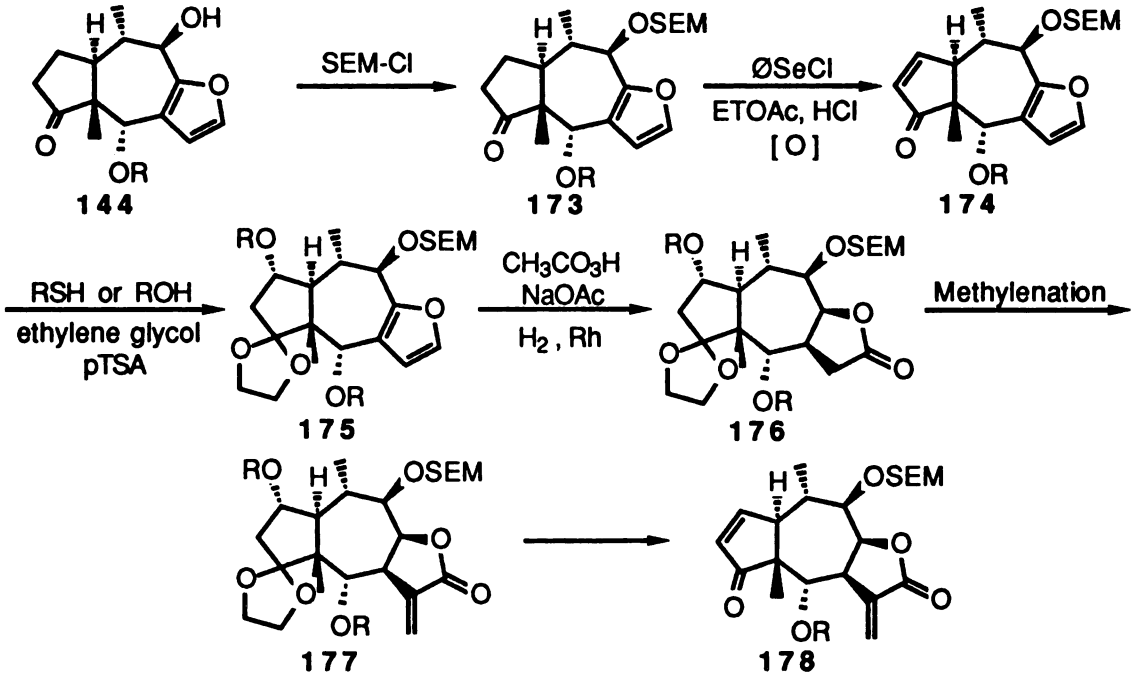
Another possibility was to enter the product manifold without the C6 oxygen, thus avoiding the question of oxygen removal for the preparation of aromatin. This might be accomplished if we could replace 3-furaldehyde in the initial Michael-Aldol reaction with 3-halomethyl furan, thus converting the process to a Michael addition-enolate alkylation. As was previously mentioned, the initial Michael addition of the thiopropionate enol ether to 2-methyl cyclopentenone was smoothly accomplished and the cyclopentyl enol ether was isolated and subjected to Mukaiyama[55] reaction conditions for silyl enol ether alkylation ($TiCl_4$).

Our initial electrophile for reaction with thiosilyloxy enol ether (**138**) was 3-chloromethyl furan (3-furylmethanol, MsCl, collidine, LiCl) (**179**). Unfortunately we observed only the product of a Michael reaction without any further alkylation. Our assumption was that the chloro compound may not be sufficiently electrophilic to react with silylenol ether (**138**). Currently, we are synthesizing the bromomethylfuran compound to form the protected bicyclo[5.3.0]decane ring system of aromatin or confertin.



A major portion of our remaining work will focus on the total synthesis of fastigilin-C, which includes, manipulation of the A ring to generate an eliminatable group for formation of the enone once the furan has been oxidized and reduced to the butyrolactone. This question of enone formation was a key problem in Lansbury's synthetic scheme, however we anticipate that our intermediates should not suffer these problems as the rigidity

introduced into the B-ring by the furyl moiety should lessen the interactions of the axial groups at C5 and C6 which Lansbury felt were the source of his difficulties.



SCHEME 16: Completion of Fastigilin-C

EXPERIMENTAL

EXPERIMENTAL SECTION

General. Tetrahydrofuran (THF) and benzene were dried by distillation under argon from sodium benzophenone ketyl; methylene chloride (CH_2Cl_2), triethylamine, methanesulfonyl chloride (mesyl chloride), pyridine, boron trifluoride etherate ($BF_3{\cdot}OEt_2$), hexamethylphosphorus triamide (HMPA), chlorotrimethylsilane (TMS-Cl), and diisopropylamine were dried under argon by distillation from calcium hydride. Formic acid (98%) was purchased from Fluka and used as received. All lithium reagents were purchased from Aldrich Chemical used as a known molarity. Petroleum ether refers to 35-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Columbia Chemical and used as received. All other reagents were used as received unless otherwise stated; all reactions were performed under argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 167 and Nicolet IR-44 Fourier Transform spectrometers with polystyrene as standard.

Proton magnetic resonance spectra (^1H or ^{13}C NMR) were recorded on a Varian T-60 at 60 MHz, a Varian FT-80 at 80 MHz, a Bruker WM-250 spectrometer at 250 MHz, a Bruker WM-300 at 300 MHz, or a Bruker WM-500 at 500 MHz as mentioned in dueteriochloroform or deuteriobenzene. Chemical shifts are reported in parts per million (δ scale) from residual proton resonance. Data are reported as follows: chemical shifts (multiplicity: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, a = apparent), coupling constant (Hz), integration.

Electron impact (EI-MS, 70 or 25ev) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. High Resolution Mass Spectra (HR-MS) were recorded at the Michigan State University Regional Mass Spectroscopy Facility (NIH), Department of Biochemistry.

Gas Chromatograms were obtained on a Hewlett Packard 5770A using a 35 meter capillary column containing methyl silicone. Parameters were as follows; Injector =250°C, Detector =350°C, Column =100-220°C @ 10°/min

Flash column chromatography was performed according to the method of Still[55] et. al. using Merck silica gel and eluted with solvents mentioned. The column outer diameter (OD) is listed in millimeters.

Mukaiyama Michael Addition/Aldol Adduct **140**

To a solution of thiosilylenol ether **137** (1.67g, 7.66 mmol) in CH_2Cl_2 (10 ml) at -95°C was added 2-methylcyclopentenone (0.797 ml, 8.12 mmol) and trityl hexachloroantimonate (0.221g, 0.383 mmol, 5 mol%). After stirring for 20-30 min. at -95°C (time is critical in the addition of the aldehyde, longer time periods cause destruction of the Michael product and substantially lowered yields), 3-furaldehyde (0.636 ml, 0.706g, 7.35 mmol) in CH_2Cl_2 (2 ml) is added dropwise over 10 min. The solution was stirred at -95°C for 12 hrs., quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 x 25 ml), the organic phases combined, washed with brine (2 x 50 ml), dried over $MgSO_4$, and evaporated *in vacuo*. The residual oil obtained was chromatographed (flash technique, SiO2, 230-400 mesh, 270g, 50 mm O.D., ether/hexane, 1:1) and gave two fractions, **140** (1.88g, 72.6%) and an unwanted lactone product, **142** (0.19g).

^{1}H NMR (250 MHz, C_6D_6) δ = 7.79 (m, 1H), 7.06 (m, 1H), 6.43 (m, 1H), 4.73 (d, J=10.8 Hz, 1H), 4.11 (d, J=10.8 Hz, 1H), 2.71 (m, 1H), 2.66 (m, 1H), 2.35 (m, 1H), 1.38 (s, 3H), 1.30 (s, 9H), 0.82 (d, J=6.4 Hz, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 225.38, 203.80, 142.93, 141.75, 126.58, 109.86, 71.83, 55.45, 49.77, 48.21, 43.57, 42.11, 38.11, 29.51, 23.71, 16.40.
IR (neat) 3496, 2967, 2927, 2877, 1739, 1682, 1476, 1374, 1277, 1159, 1078, 965, 800, 738 cm^{-1}.
EI-MS (70eV) m/e = 338 (M^+), 264 (0.27), 248 (1.45), 214 (1.48), 185 (6.05), 146 (11.42), 125 (19.66), 97 (72.20), 96 (32.54), 95 (38.03), 90 (14.98), 83 (32.77), 69 (16.24), 57 (100), 55 (68.93), 41 (64.02).
HR-MS m/e = 338.1552 calculated 338.1549 found
GC = 6.72 minutes, 6.96 minutes ~4:1 ratio

Acetylated Cyclopentanone **141**

To a solution of aldol alcohol **140** (1.02g, 3.02 mmol) in CH_2Cl_2 (40 ml) was added triethylamine (2.11 ml, 15.05 mmol), DMAP (0.03g, catalytic) and acetic anhydride (0.712 ml, 7.54 mmol) dropwise. After stirring at RT for 12 hrs., the solution was quenched carefully with sat. $NaHCO_3$ (15 ml dropwise), extracted with CH_2Cl_2 (4 x 15 ml), the organic phases combined, dried over $MgSO_4$, and evaporated *in vacuo*. Chromatography (flash technique, SiO_2, 140g, 40 mm O.D., ether/hexane, 1:1) of the resulting orange viscous oil gave acetylated product **141** (0.923g, 80.3%) and a product that arose from retroaldol (11.0%).

^{1}H NMR (250 MHz, C_6D_6) δ = 7.81 (m, 1H), 7.01 (t, J=1.73 Hz, 1H), 6.55 (m, 1H), 6.09 (s, 1H), 2.76-2.34 (m, 3H), 1.95-1.31 (m, 3H), 1.68 (s, 3H), 1.49 (s, 9H), 1.07 (s, 3H), 0.85 (d, J=9.86 Hz, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 217.55, 203.98, 169.25, 143.04, 142.61, 122.52, 110.50, 70.83, 54.40, 49.43, 48.42, 43.13, 38.57, 31.84, 29.72, 23.25, 22.92, 20.51, 17.27, 15.59.
IR (neat) 2968, 2927, 2903, 1746, 1702, 1676, 1456, 1366, 1234, 1162, 1080, 1023, 967, 957, 752 cm^{-1}.
CI-MS (CH_4) m/e = 380 (M^+, 18.5), 338 (16.8), 321 (29.5), 293 (6.6), 265 (100), 249 (17.5), 231 (5), 203 (3.3), 166 (2.4), 139 (2.5), 97 (2.2), 57 (3.1).
HR-MS = 380.1657 calculated, 380.1655 found
GC = 13.40 minutes, 13.46 minutes, ~4:1 ratio

Formation of Lactones **142** and **143**

To a solution of the acetylated thioester **141** (0.025g, 0.065 mmol) in CH_2Cl_2 (4 ml) was added trimethyl oxonium tetrafluoroborate (0.011g, 0.0723 mmol). After stirring at RT (4 hrs.), the solution was quenched with sat. $NaHCO_3$ (2 ml), extracted with CH_2Cl_2 (3 x 5 ml), dried over Na_2SO_4, and concentrated *in vacuo*.. Chromatography of the residue (flash technique, SiO_2, 230-400 mesh, 3g, 10 mm O.D., ether/hexane, 1:1) gave two fractions of **142** (0.014g, 93%) and **143** (0.001g, 6%) which were presumed to be lactones.

142: ^{1}H NMR (250 MHz, C_6D_6) δ = 7.39 (m, 1H), 7.05 (t, J=1.66 Hz, 1H), 6.46 (m, 1H), 4.40 (s, 1H), 2.03 (dq, J=8.6 Hz, 5.63 Hz, 1H), 1.86-1.52 (m, 2H), 1.38-1.11 (m, 2H), 0.97 (d, J=8.6 Hz, 3H), 0.70 (m, 1H), 1.60 (s, 3H).

143: ^{1}H NMR (250 MHz, C_6D_6) δ = 7.26 (m, 1H), 6.93 (t, J=1.77 Hz, 1H), 6.22 (m, 1H), 4.10 (s, 1H), 2.01 (m, 1H), 1.73 (m, 1H), 1.4-0.96 (m, 4H), 0.96 (d, J=7.5 Hz, 3H), 0.83 (s, 3H).

Hexahydro-6α-acetoxy-5β,10α-Dimethyl-4,8-Dioxoazuleno-[7,8]-furan **144**

To a solution of acetylated thioester **141** (8.66g, 22.79 mmol) in anhydrous acetonitrite (90 ml) was added mercuric trifluoroacetate (19.44g, 45.58 mmol) in several portions. The solution changed from a water white to green, then finally forming a white precipitate. The solution was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, the organic phases combined, washed with brine (3 x 20 ml), dried over $MgSO_4$, and concentrated *in vacuo*. The solid recovered was chromatographed (flash technique, SiO_2, 230-400 mesh, 400g, 60 mm O.D., ether/hexane, 3.5:1) and gave 4.37g (66.1%) of cyclized furan **144** as a white crystalline solid. mp = 158.5-160°C uncorrected.

^{1}H NMR (500 MHz, C_6D_6) δ = 6.87 (d, J=1.71 Hz, 1H), 6.58 (d, J=1.71 Hz, 1H), 6.19 (s, 1H), 2.47 (dt, J=11.58, 6.33 Hz, 1H), 2.07 (dq, J=9.24, 6.85 Hz, 1H), 1.94 (dd, J=16.43, 8.01 Hz, 1H), 1.69 (ddd, J=14.21, 12.34, 8.13 Hz, 1H), 1.60-1.40 (m, 1H), 1.50 (s, 3H), 1.15 (d, J=6.85 Hz, 3H), 0.75 (ddd, J=16.45, 9.24, 8.13 Hz, 1H), 0.49 (s, 3H).

^{13}C NMR (62.95 MHz, C_6D_6) δ = 217.06, 189.25, 168.96, 149.15, 146.70, 127.32, 115.29, 70.34, 53.84, 45.65, 41.01, 36.91, 24.80, 21.19, 14.80, 14.46.

IR (neat) 2990, 2943, 2877, 1750, 1662, 1488, 1415, 1370, 1225, 1058, 1015, 976, 892 cm^{-1}.

EI-MS (70eV) m/e = 248 (6.63), 247 (19.78), 215 (4.33), 165 (4.05), 124 (5.89), 97 (10.58), 95 (5.03), 91 (8.04), 77 (8.97), 55 (19.66), 43 (100).

HR-MS = 290.1154 calculated, 290.1132 found

GC = 11.63 minutes, >97:3 one compound

Hexahydro-6α-acetoxy-8β-hydroxy-5β,10α-Dimethyl-4-oxoazuleno-[7,8]-furan **166**

To a solution of cyclized furan **144** (0.248g, 0.855 mmol) in methanol (10 ml) was added $NaBH_4$ (0.048g, 1.28 mmol) in one portion. The reaction (12 hrs.) was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 x 15ml), washed with brine (2 x 10 ml), the organic fractions combined, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting solid was chromatographed (flash technique, SiO_2, 230-400 mesh, 25g, 2.0 mm O.D., ether/hexane, 5:1) and gave 0.241g (96.7%) of a single alcohol product **166**.

^{1}H NMR (250 MHz, C_6D_6) δ = 6.87 (m, 1H), 6.65 (d, J=1.79 Hz, 1H), 6.09 (s, 1H), 4.19 (d, J=9.69 Hz, 1H), 2.23 (dq, J=8.75, 6.14 Hz, 1H), 1.98 (dd, J=18.27, 9.00 Hz, 1H), 1.80-1.43 (m, 5H), 1.51 (s, 3H), 1.06 (d, J=6.48, 3H), 0.57 (s, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 217.84, 169.15, 153.17, 140.21, 115.91, 115.36, 73.98, 70.45, 53.63, 42.33, 38.17, 36.16, 24.01, 20.36, 16.10, 15.58.
IR (neat) 3224, 2972, 2924, 1743, 1701, 1464, 1458. 1373, 1236, 1124, 1080, 1016, 1003, 983, 937, 893, 748, 611 cm^{-1}.
EI-MS (25eV) m/e = 232 (35.63), 175 (10.92), 161 (19.20), 159 (13.05), 147 (23.34), 126 (17.94), 124 (14.05), 97 (16.69), 69 (18.19), 44 (17.57), 43 (100).
GC = 11.08 minutes, 11.47 minutes, 96:4 ratio

Hexahydro-6α-hydroxy-5β,10α-Dimethyl-4,8-Dioxoazuleno-[7,8]-furan

To a solution of cyclized furan **144** (0.200g, 0.689 mmol) in methanol/water (15 ml/1 ml) was added K_2CO_3 (0.100g, 0.724 mmol). After stirring for 5 hrs., the reaction was quenched (15 ml H_2O), extracted with CH_2Cl_2 (4 x 10 ml), the organic phases combined, dried over $MgSO_4$, and concentrated *in vacuo*. The solid obtained was chromatographed (flash technique, SiO2, 230-400 mesh, 20g, 20 mm O.D., ether/hexane, 5:1) and gave 0.170g (99.4%) of a white solid **166A**.

^{1}H NMR (250 MHz, C_6D_6) δ = 7.11 (d, J=1.70 Hz, 1H), 6.31 (d, J=1.70 Hz, 1H), 4.84 (bs, 1H), 3.80 (m, 1H), 2.76 (dt, J=11.86, 6.32 Hz, 1H), 2.26-1.84 (m, 2H), 1.57 (dd, J=4.05, 2.13 Hz, 1H), 1.19 (d, J=6.91 Hz, 3H), 1.89 (adq, J=9.19, 3.30 Hz, 1H), 0.59 (s, 3H).

^{13}C NMR (62.95 MHz, C_6D_6) δ = 220.42, 190.70, 157.28, 146.96, 131.99, 114.71, 69.39, 55.29, 45.97, 39.57, 38.10, 25.10, 15.17, 14.90.

IR (neat) 3445, 2974, 2936, 2880, 1741, 1701, 1653, 1487, 1417, 1278, 1263, 1122, 1060, 974, 794 cm^{-1}.

EI-MS (25eV) m/e = 163 (0.22), 135 (1.36), 127 (1.39), 124 (1.80), 115 (2.02), 100 (5.46), 97 (12.94), 96 (17.61), 86 (19.06), 84 (33.36), 67 (25.00), 60 (17.96), 58 (70.16), 51 (30.61), 49 (100).

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APPROACHES TO RESINIFERONOL

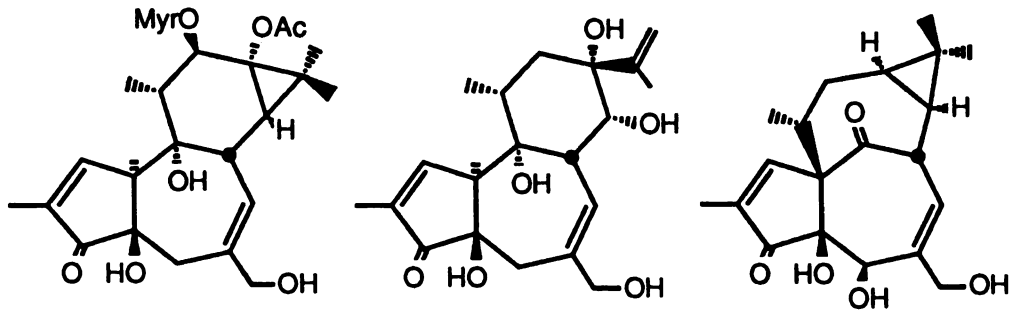


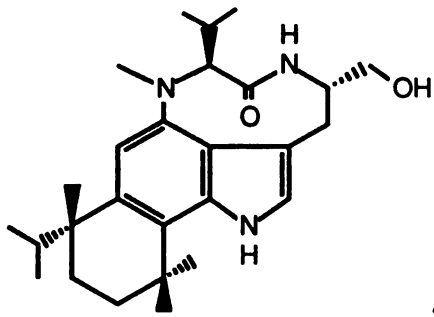
Figure 1: Tigliane, Daphnane, and Ingenane Natural Products

Tigliane,[1] daphnane,[2] and ingenane[3] diterpenes such as phorbol **1**, resiniferonol **2**, and ingenol **3** are examples of compounds known as tumor promoters.[4] Administration of a subthreshold dosage of a potent carcinogen such as 7,12-dimethylbenz[a]anthracene followed by application of the tumor promoter results in numerous papillomas and squamous carcinomas when applied to the skin of mice.[5] Phorbol itself is not a carcinogen, but seems to amplify the effect of a carcinogen, thus increasing the risk of cancer development. Recently, a similar two step carcinogenic mechanism has been delineated to account for human carcinogenesis.[6]

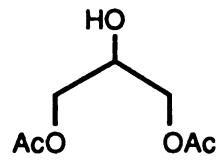
Phorbol has been shown to exhibit activity at concentrations comparable to that of mammalian hormones, and therefore has been suggested to mimic one of these hormones in enzyme binding and activation. Protein kinase C has been implicated as a major receptor for phorbol, and is thought to be responsible for hormonal signal transduction in cells.[7]

The conformations of some tumor promoters such as phorbol, resiniferonol, ingenol, and teleocidin have been correlated by Wender[8] in terms of heterocyclic electron density to attempt to explain the similar responses from such dissimilar compounds. Oxygen functionality at C-4, C-9,

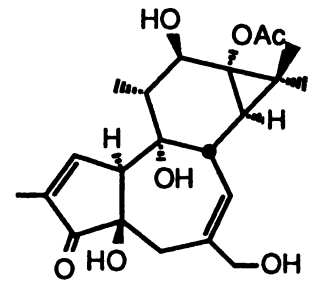
and C-20 of phorbol have been related to the indole nitrogen N-1, benzylamine nitrogen N-13, and hydroxyl at C-24 of teleocidin. The lipophilic side chain of phorbol myristate acetate can also be correlated to the cyclohexyl carbocycle portion of teleocidin. A similar argument has been made for the activity of ingenol. The C-4 hydroxyl, C-20 hydroxyl, and C-9 ketone compare favorably to the areas of high electron density in both PMA and teleocidin. A possible note of support comes from the fact that 4α phorbol, which exhibits a vastly modified conformation in the region occupied by the A-ring, is completely inactive as a tumor promoter. A comparison of the structures of both phorbol epimers reveals very little difference in structure except for the region about the hydroxyl group. These compounds have further been modeled with respect to diacyl glycerols, the endogenous substrates for protein kinase C, which these promoters presumably mimic.[9] A natural extension for these hypotheses would be the synthesis of analogs that compare favorably in conformation and relative heteroatom placement and electron density to PMA and other promoters. Wender[10] has designed several new compounds that appear to have structural features necessary for binding and activation. The basic requirements are as follows: 1) a rigid structure to hold the pharmacophore in the correct spatial arrangement, and 2) place heteroatoms at positions similar to those of PMA, DAG and teleocidin. The rigid template was available from an aromatic nucleus, and the use of nitrogen or oxygen with the appropriate spacer atoms should form a compound that might show similar activity to the natural substrates. Toward that end, Wender has synthesized a trisubstituted benzene (Figure 3) with heteroatoms in good agreement with their model. The decyl group on nitrogen serves as the mimic of the the lipophilic ester subunit contained in PMA and teleocidin. The substrates were tested using a protein kinase C binding assay and were found to bind to PKC receptors. Although binding affinity was less than that of PMA, it was shown to be within an order of magnitude of the endogenous diacyl glycerol activators.



Teleocidin **4**



Diacylglycerol **5**



Phorbol **6**

Figure 2: PKC Promoters

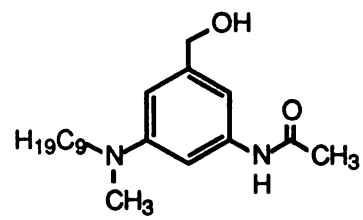
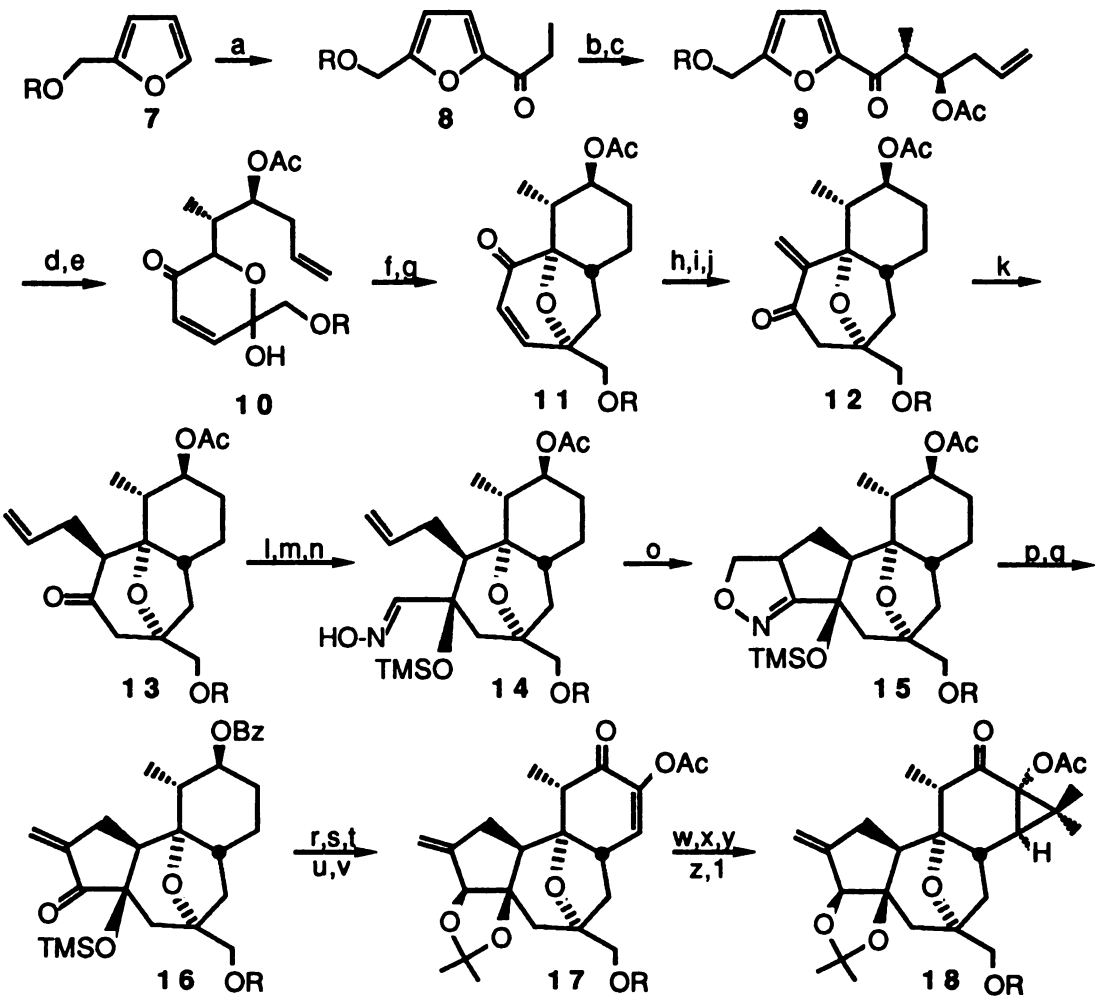


Figure 3: Synthetic Pharmacophore

Wender's[11] group has embarked on a program directed toward the total synthesis of phorbol, resiniferonol, and ingenol from a bicyclic BC ring structure. Wender assumed that tiglianes and daphnanes arose directly from a biological cascade of intermediates, whereas the ingenanes might be realized from a rearrangement of the C ring which might provide a biosynthetic approach to the ingenanes. Reducing the problem to that of the synthesis of a bicyclic B,C-ring is a worthwhile synthetic problem, however it is an oversimplification because of the flexibility of the bicyclo[5.4.0]undecane ring. A relative lack of control of the of the conformations available to the bicyclo[5.3.0]undecane nucleus serve to magnify the difficulty of this problem as it renders the usually reliable cyclic control of peripheral stereochemistry useless. Wender chose to relieve this difficulty by adding an oxygen bridge that would substantially reduce the degrees of freedom available to **1**. Wender has now nearly completed two different syntheses of phorbol shown in Scheme **1**[12] and **2**. Starting with 2-furylmethanol, the alcohol was protected as its TBS ether, and the side chain added at the five position for formation of the C ring after metallation (n-BuLi) and addition of the furyl lithium to lithium propanoate. An aldol reaction was then used to increase the chain length, and engender the correct relative stereochemistry at the secondary methyl bearing center of the future C-ring. The aldol was protected

(AcCl), the ketone reduced ($NaBH_4$), and the furan was oxidized to afford the desired pyrone **10**. The stage is now set for the crucial [5+2] cyclization of the olefinic terminus to the derived pyrilium ion. In the event, **10** was acetylated and base induced pyrilium formation resulted in the formation of the highly functionalized rigid tricycle **11** (89%). The A-ring was then appended as follows; the enone was reduced (H_2 / Pd), the product ketone treated with $Ph_3P{=}CH_2$, allylic oxidation (SeO_2) and oxidation of the C-4 alcohol then furnished the desired exomethylene ketone **12**. Two carbons, comprising C3 and C4, were then added *via* higher order vinyl cuprate addition (**13**). The A-ring carbonyl and angular OH are deftly introduced as a TMS-cyanohydrin from the addition of TMSCN to the ketone at C5. Oxime formation and oxidation formed the nitrile oxide resulting in a [3+2] cycloaddition with the available double bond to give **15**. Reduction (Ra-Ni) of the N-O bond, hydrolysis of the imine, and base induced elimination (DBU) of the resulting hydroxy compound completed the A,B,C-ring containing tricyclic system (**16**). The synthesis was completed by functionalization of the C ring and addition of the dimethylcyclopropane. The Wender group concluded this approach with an acetonide formation, deprotection, oxidation, phenyl sulfide addition, acetoxylation, and elimination to form the α-acetoxyenone **17**. Sulfur ylide addition then yielded the completed tetracyclic phorbol model (**18**). Rings A,B, and C were formed in 14% overall yield, averaging 90% for each individual step.

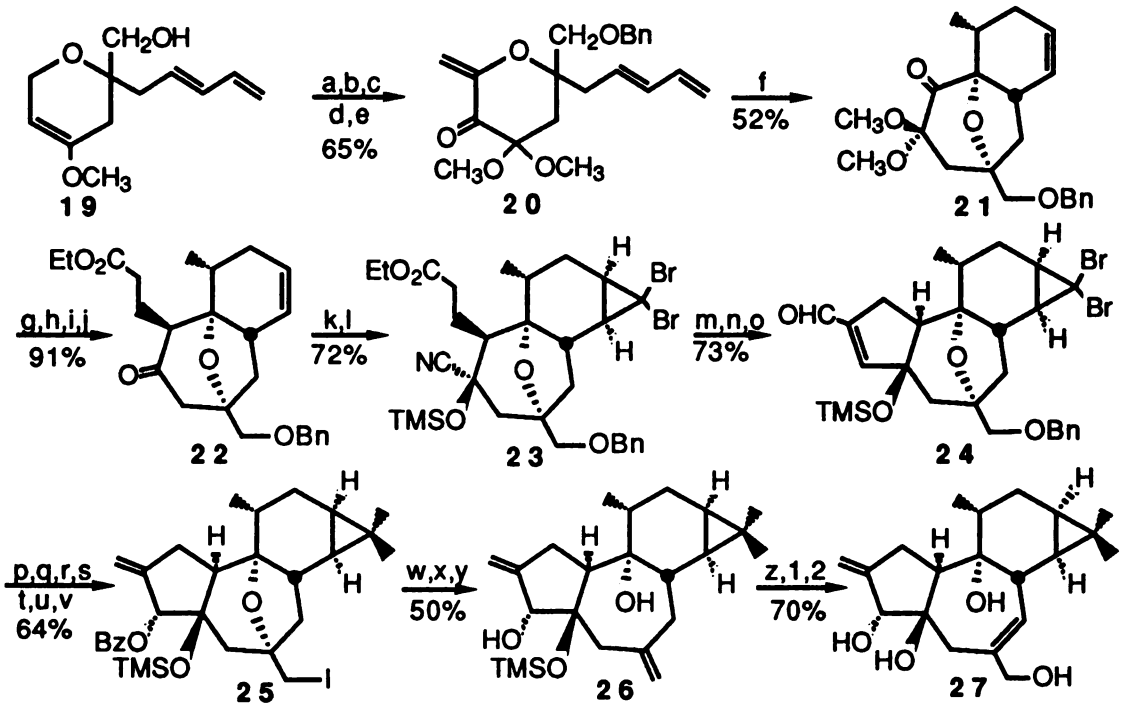


a) TBSCl, RCO_2Li b) $LiN(TMS)_2$, RCHO c) AcCl d) $NaBH_4$ e) MCPBA f) Ac_2O g) DBU h) H_2, Pd h) Ph_3PCH_2 i) SeO_2 j) MnO_2 k) $(vinyl)_2CuCNLi_2$ l) TMSCN, ZnI_2 m) DIBAL n) $HONH_2.HCl$ o) Bleach p) RaNi, H_2 q) Bz_2O r) DBU s) DIBAL t) R_4NF u) C_3H_5OMe v) DIBAL w) PCC x) LDA, $PhSSO_2Ph$ y) $Pb(OAc)_4$ z) MCPBA, heat 1) Ar_2SCMe_2

Scheme 1: Wender's First Generation Phorbol Route

Wender[13] has published a second route to phorbol using a formal [4+2] Diels-Alder approach. This synthesis began with a hetero Diels-Alder reaction giving a dihydropyran that formed the basis of ring B. Treatment of the Diels-Alder adduct with LDA and 1-bromo-2,4-pentadiene added the sidechain that formed the bulk of the C ring. Selective oxidation of the methoxy enolether (MCPBA, MeOH), followed by Swern oxidation of the resulting epimeric alcohols, gave a monoprotected 1,2-diketone. Exo-methylenation *via* aldol condensation with acetaldehyde proved difficult, but with the addition of lithium bromide, the reaction proceeded smoothly to give the requisite ketoalcohol. The alcohols were then dehydrated (MsCl,

DBU) by elimination to give trieneone **20** required for Diels-Alder cyclization. Compound **20** was heated in xylene at 145°C to give compound **21** exclusively, in 52% yield for the four steps. The exo selectivity in this cyclization is thought to result from steric congestion of the C-4 methoxy group in the endo transition state. Introduction of the A- and D-rings began with the transposition of the ketone from C-10 to C-4 in a fashion similar to the previous synthesis (Scheme 1). In this case, instead of a cuprate addition, a second hetero Diels-Alder was used to form a single ortho lactone which upon protonation provided ketoester **22**. At this juncture, the C ring olefin was cyclopropanated ($PhHgCBr_2$), and then a reduction/oxidation (DIBAL, Swern), aldol sequence was used to obtain the A-ring. To finish the sequence required more A ring manipulation, and finally oxidation (SeO_2), elimination ($SOCl_2$), addition to complete the approach as outlined in Scheme **2**.



a) MCPBA b) Swern c) $LiN(TMS)_2$, CH_3CHO d) MsCl, Et_3N e) DBU f) 145°C, xylene g) $Ph_3P{=}CH_2$ h) $(CO_2H)_2$
i) $CH_2{=}C(OTBS)OEt$, ZnI_2 j) HF k) $PhHgCBr_3$, 80°C l) TMSCN, ZnI_2 m) DIBAL n) Swern o) $Bn_2NH_2CF_3CO_2$
p) DIBAL q) $Me_2CuCNLi_2$, MeI r) $NO_2PhSeCN$, H_2O_2 s) Bz_2O t) ZnI_2, TMSCN u) Tf_2O v) Bu_4NI w) t-BuLi
x) TMS-Im y) SeO_2 z) $SOCl_2$ 1) KOAc, AgOAC 2) TBAF

Scheme 2: Wender's Second Generation Phorbol Synthesis

Our strategy for the synthesis of tigliane and daphnane natural products differs from that of Wender in that our initial goal was the synthesis of an A,

B-ring system with a functional equivalent of a cyclohexenone present to form the C-ring. As has been previously described, a furan can function as the operational equivalent of a wide variety of a number of useful organic residues, including a six-membered ring. This equivalence, and the proximity of this residue to the A-B ring fusion suggested the application of a furan terminated cationic cyclization sequence to generate a furan containing bicyclo[5.3.0]decane nucleus **30** (Figure 4). This analysis allowed us to dissect the 7-membered B ring at the cyclopentanone **31**. We might further simplify **32** by disconnecting the side chain in a "normal" polarity sense affording the hypothetical cyclopentanone-2-nucleophile-3-electrophile and a residue comprised of an allylic electrophile and furyl nucleophile.

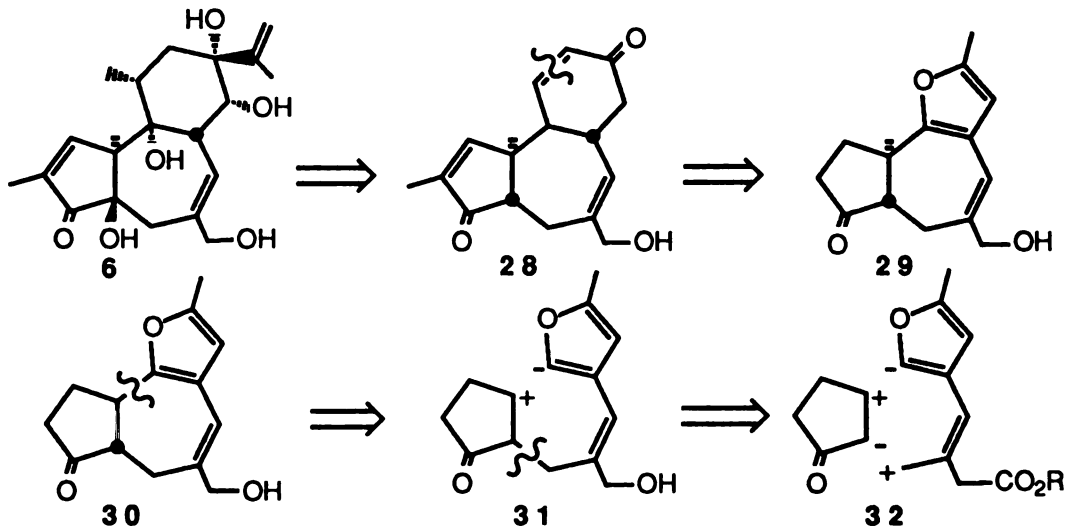


Figure 4: First Generation Retrosynthetic Analysis

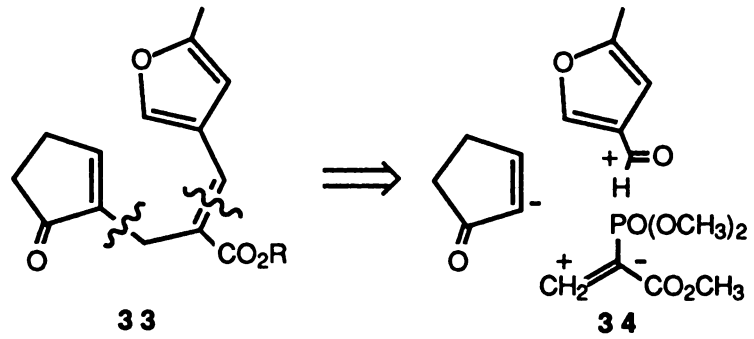
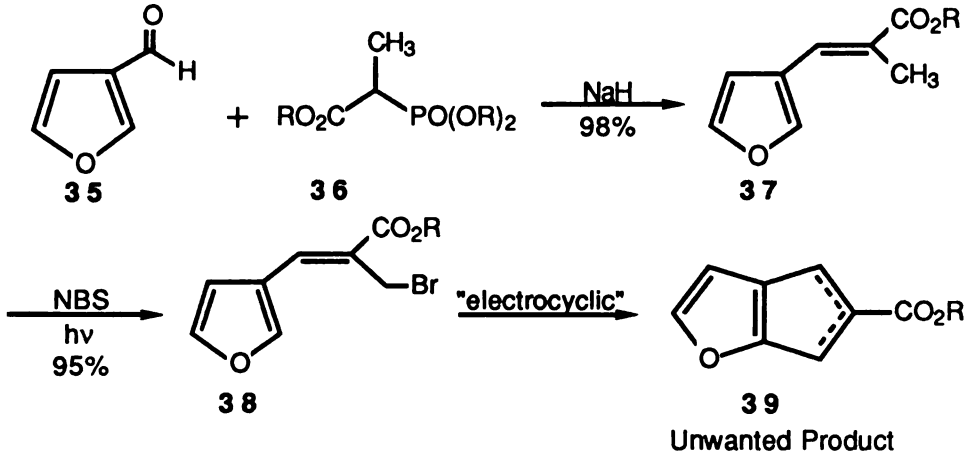


Figure 5: Second Generation Retrosynthetic Analysis

With this analysis accomplished, we examined our "intermediates" in order to insure the bond formations occur in the forward direction for the desired sequence. This was readily achieved *via* the reaction of a cyclopentanoid carbanion, possessing an incipient electrophilic β-carbon (2-lithio-2-cyclopentenone ethylene ketal) with a furan containing allylic halide. The latter component (1-ethyl-2-bromomethyl-(E)-3-(5-methyl)-3-furyl acrylate) would then possess the furyl carbanion in latent form as the neutral furan. The furyl acrylate might then be realized as outlined in the lower portion of Scheme 3. Our initial effort began with a two component alkylative sequence that would provide the desired furylacrylate **38**. Furan **37** was easily prepared by the reaction of 3-furaldehyde with methyl phosphonopropionate to give **37** in 98%. Bromination[14] with NBS in carbon tetrachloride (hv) provided **38** in 95% yield. We were in a position to study the coupling of **38** with 2-lithiocyclopentenone ethylene ketal. In the event, **41** (Li, Scheme 4) prepared by the procedure of Smith[15], was treated with bromide **38** under a wide variety of reaction conditions, to no avail. We were unable to observe even trace amounts of the desired **31**, but instead we obtained a lone furan containing product **39**, the results of an undesired (likely electrocyclic) cyclization. We also discovered that bromide **38** gives **39** on prolonged storage.

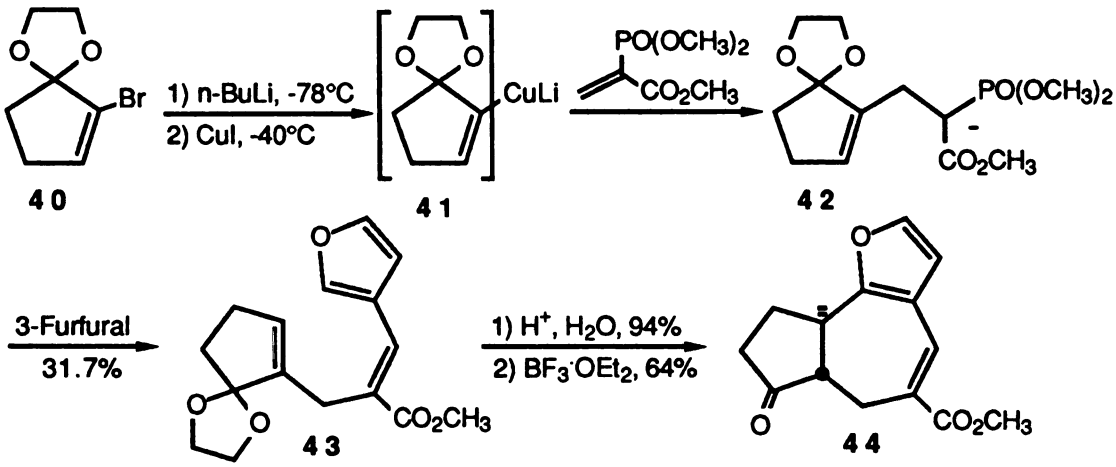


SCHEME 3: 1st Generation Phorbol Precursor

We were then forced to look at possible alternative routes to secure the requisite cyclization precursor. One attractive alternative involved a one pot, three component coupling of an anion derived from Smith's protected

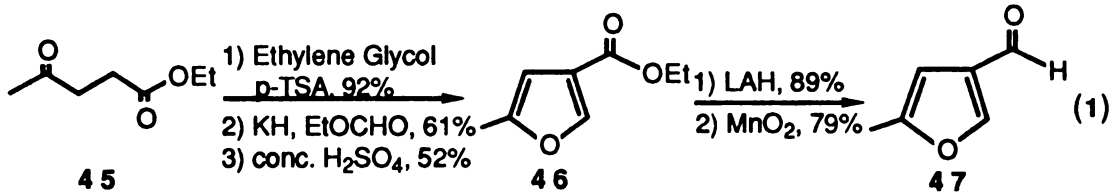
bromoenone with trimethyl phosphonoacrylate[16] to give a Horner-Emmons like intermediate that could be quenched with 3-furaldehyde to give adduct **43**. This type of system would follow from our second generation retrosynthetic disconnections (Figure 5).

This possibility was realized when **41**, prepared by lithium-halogen exchange of bromoenone **40** was treated with CuI to form a cuprate. The cuprate was exposed to trimethylphosphonoacrylate at -78°C and the mixture was quenched with 3-furaldehyde to give **43** (32%). After workup, we obtained a 6:1 ratio of the *cis* to *trans* compounds **43**. Hydrolysis of the resulting ketal yielded an enone in nearly quantitative yield. With the enone in hand, we then examined the crucial cyclization sequence. The desired closure was effected by $BF_3{\cdot}OEt_2$[17] (Scheme 4) in dichloromethane to give the tricycle in a 64% unoptimized yield.



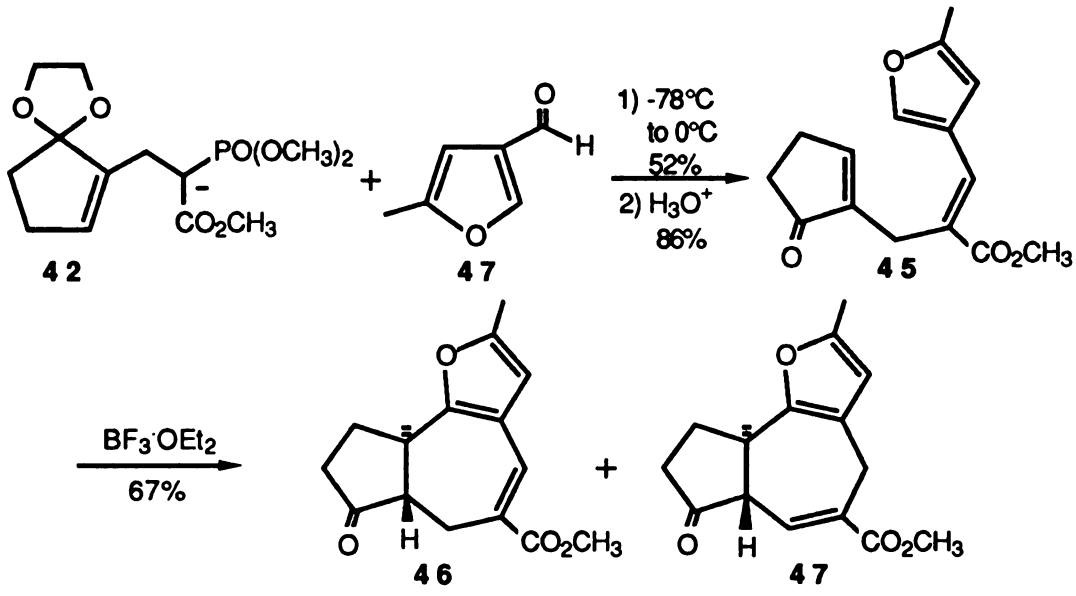
SCHEME 4: First Generation Desmethyl Phorbol

Having demonstrated the viability of the reaction, we elected to undertake the preparation of the cyclization intermediate possessing the furyl-C5-CH_3 needed to build the C-ring. We began this endeavor with the preparation of 2-methyl-3-furaldehyde. Synthesis of the disubstituted furan was found to be more difficult than anticipated despite (scant) literature precedent.[18] The ketone of ethyl levulinate was protected as its dioxolane, which was then coupled with ethyl formate *via* the corresponding potassium enolate. The crude α-formyl ketone was then treated with acid (conc. H_2SO_4) to give the furan in a reproducible but disappointing 29% overall yield.



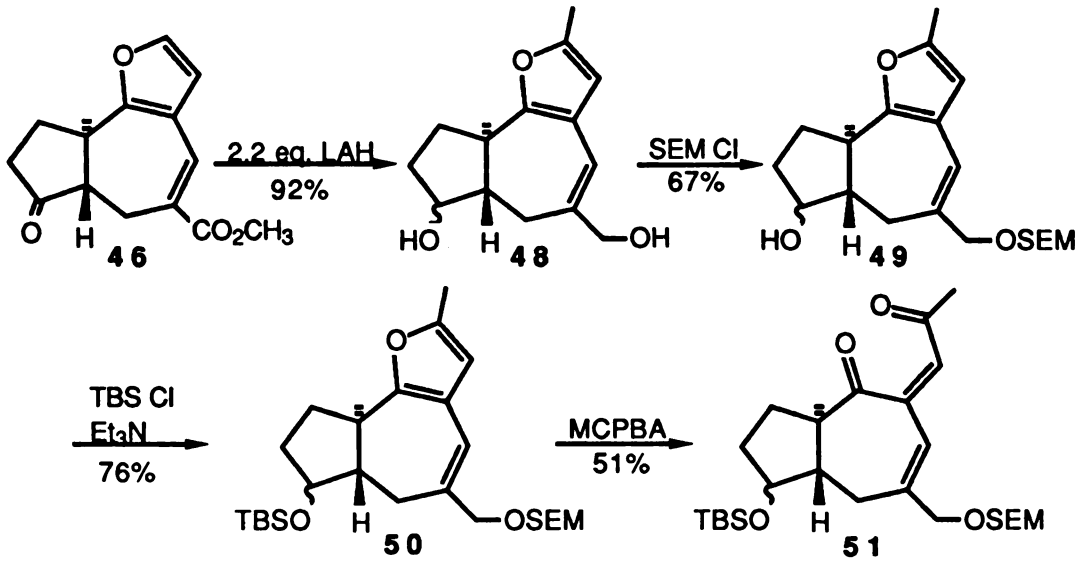
The synthetic route utilized in the preparation of **44** was then applied to furaldehyde **47**. To the anion derived from the protected cyclopentenone **40** (Scheme 5) was added a stoichiometric amount of CuI[19] to form the lower order cuprate (-78°C→-45°C→-78°C), the use of catalytic amounts of copper led to drastically lower yields. Trimethylphosphonoacrylate[20] (THF, -78°C) was added to the preformed cuprate via a chilled cannula and the resulting solution was warmed to -20°C, then to 0°C, followed by quenching with 5-methyl-3-furaldehyde. This procedure resulted in an increase of our yields of **45** from 35% to a reproducible 50-60%. The only difficulty with this procedure was that the olefin was obtained with poorer stereoselectivity (3-4:1 vs 6-8:1) in the Wittig olefination than previously observed. The addition product was deprotected (5% aq. HCl, 86%) and enone **45** was cyclized with $BF_3{\cdot}OEt_2$ (1.0 eq.) to afford the desired bicyclo[5.3.0]decane product **46** (60-70%).

An analysis of the ^1H NMR allowed us to determine that **46** was in fact a mixture of 2 olefin regioisomers **46** and **47** which were nearly inseparable by TLC. However, careful flash chromatography provided both compounds, and we determined that along with the expected product **46**, there was a second compound with the double bond in the C6-C7 position instead of the desired C7-C8 position. The NMR clearly showed the vinyl proton as a doublet (δ= 7.62 ppm,J=1.86 Hz) instead of a singlet (7.58 ppm) for **46**. Olefin **47** also exhibited a doublet of doublets (3.89 ppm, J=21.3, 1.56 Hz) that was not present in compound **46**. This second product was obtained as a 1:3-8 mixture (**47/48**) with **46**, as determined by gas chromatographic analysis. Although this outcome was initially disconcerting we could in principle utilize this byproduct. We might isomerize the double bond to the C7-C8 position by rhodium[21] or acid[22] catalysis, or secondly the double bond could be hydrogenated and reintroduced in a manner similar to that employed by Wender.[23]



SCHEME 5: Synthesis of Methyl Phorbol Adduct

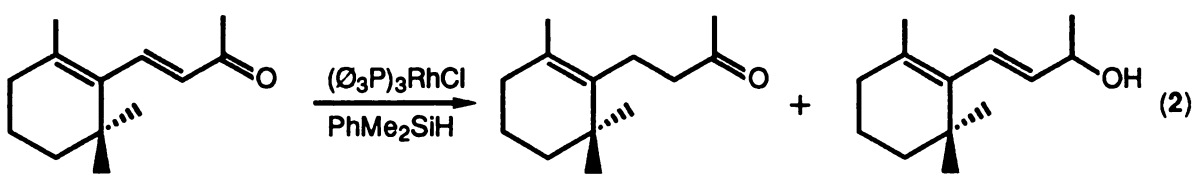
With the isolated tricycle **46** in hand, we needed to oxidatively open the furan to an ene-dione and selectively manipulate a compound containing three ketone carbonyls. We felt that we could indeed selectively protect a side chain ketone in preference to the 7-membered ring carbonyl, however the A-ring ketone added an undesired degree of complexity to the scheme. Therefore, we elected to eliminate this problem by reducing the various carbonyls (LAH, 92%). We protected the primary allylic alcohol as a SEM ether[24] (SEM-Cl, 67%, Scheme 6) **49**, and the more hindered A-ring secondary alcohol was then masked as the corresponding TBDMS ether[25] (TBS-Cl, 76%) **50**. With the potentially problematic ketones masked and the ester reduced, the furan might be oxidized[26] to furnish a dione after ene-dione reduction. In the event, the furyl compound was treated with 1.2 equivalents of MCPBA (aq. $NaHCO_3$), to give, after workup, the desired ene-dione **51** in 51% yield. The relatively unstable enedione, produced above, should afford the more stable dione upon selective reduction. Initially, we attempted hydrogenation with Lindlars catalyst ($Pd/Pb/CaCO_3$)[27], but no reduction was observed. We then attempted reduction over Adams catalyst (Pt_2O)[28], but recovered only a fully reduced tetrahydrofuran as the sole product.



SCHEME 6: Furan Manipulation

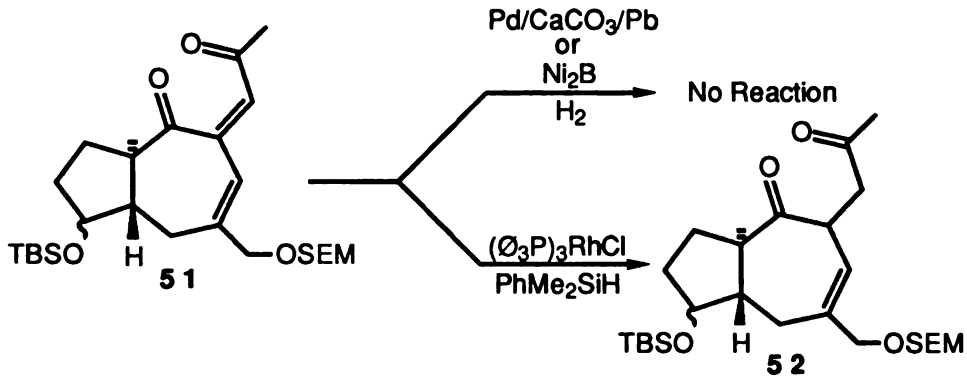
Ojima[29] (Equation 2) has found that hydrosilylation of α,β-unsaturated carbonyls occured using dimethylphenylsilane and Wilkinsons catalyst ($(Ph_3P)_3RhCl$) leading to 1,4 reduction of the olefin with little over reduction. He has also found that the same conditions will reduce the α,β-unsaturated double bond of an enone in preference to the δ,γ-double bond. It has been proposed that silane attacks rhodium, then forms an η^2 complex to the ketone, silicon migration to oxygen and addition of rhodium to carbon then occured. Once the α-(siloxyallyl)rhodium hydride was formed, there was an isomerization to the γ-(siloxyallyl)rhodium hydride accompanied by a hydride shift to form the 1,4 adduct. On an extremely small scale (Scheme 7), this was in fact what was seen. Mixing the enedione, Wilkinsons catalyst, and dimethylphenyl-silane in benzene resulted in conjugate reduction.

Ojima Example



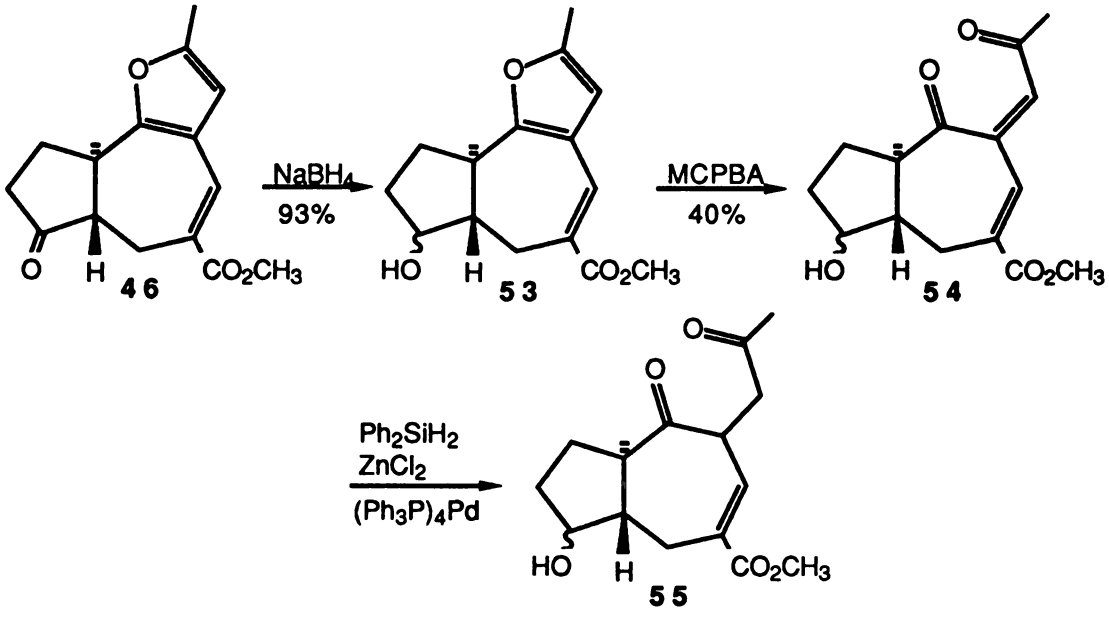
91 9

94% Overall Yield



SCHEME 7: Attempted Ene-Dione Hydrogenation

Concurrent with the ene-dione reduction mentioned above, we examined the elaboration of a furan-containing bicyclo[5.3.0]decane in which the ene-oate had not been reduced to an allylic alcohol. We studied the borohydride reduction of **46** to give 93% (Scheme 8) of a single alcohol **53**, which was not protected. Oxidation of the furan was accomplished using 1.2 eq. of MCPBA in a two phase mixture with sodium bicarbonate as a buffer. Ene dione **54** was isolated in 40% yield with a recovery of 58% starting material. Prolonged exposure to the peracid caused a destruction of both starting material and product probably due to multiple sites of unsaturation available for oxidation.

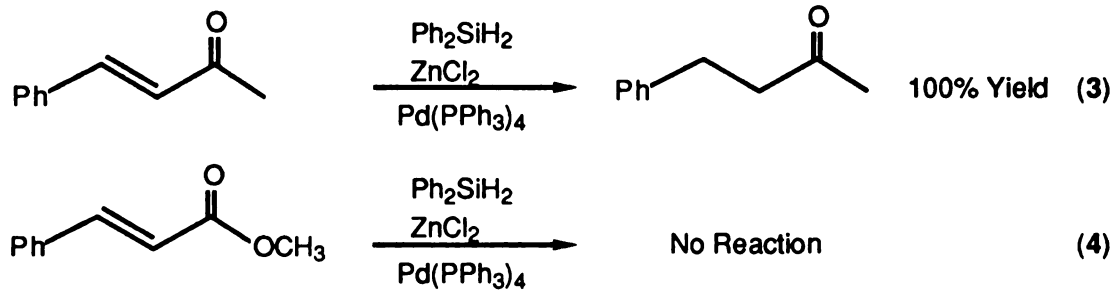


SCHEME 8: Current Monoreduced Furan Sequence

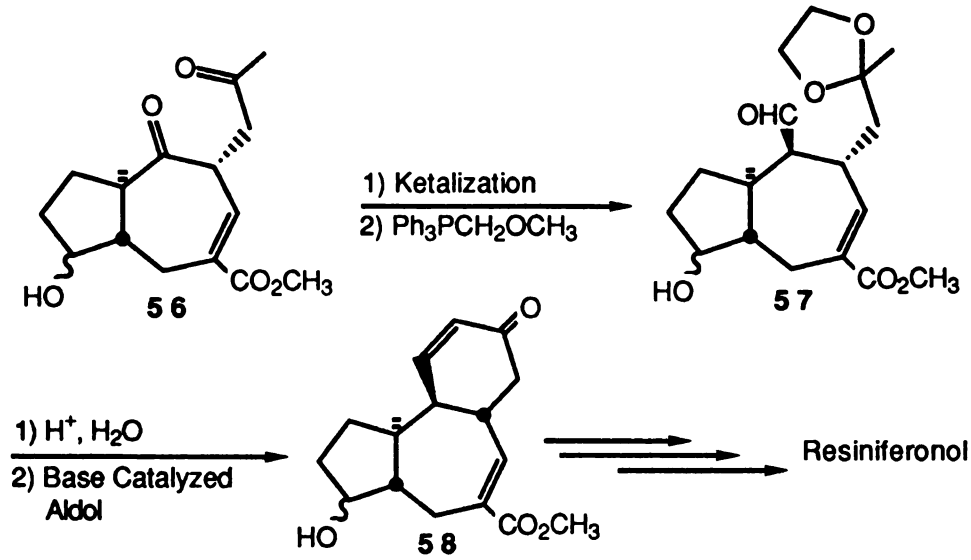
Keinan[30] has reported a variation of Ojima's hydrosilylation that will reduce an α,β-unsaturated ketone or aldehyde without reducing an α,β

unsaturated ester, using a soluble palladium catalyst with zinc chloride and diphenylsilane. Hydride addition at the β-carbon occured from the less hindered face forming a palladium enolate then quenching with water. Zinc chloride is reported to act not merely as an acid, but as some sort of "Zn-H" or "Zn-H-Si" species that transfered hydride to palladium. We are currently exploring the possible uses of this reation to maintain oxygen functionality in various oxidation states throughout the molecule.

Keinan Example



The C-ring construction can then be completed after selective protection and addition of a one carbon aldehyde equivalent and aldol-cyclodehydration. Compound **58** once obtained and oxygenated at C-5 and C-10 might enable us to search for any competitive binding with protein kinase C. We expect our intermediate to be flexible enough for analog synthesis as well as serving as an advanced intermediate for the preparation of the less complex resiniferonol.



SCHEME 9: Future Synthetic Strategy

EXPERIMENTAL

EXPERIMENTAL

Formation of Diol **46**.

To a solution of **46** (0.0683g, 0.262 mmol) in anhydrous ether (5 ml) was added LAH (0.119g, 0.263 ml, 0.315 mmol, 1.0 M) over 5 min. The mixture was quenched with sat. $NaHCO_3$ (5 ml) and NaOH (1 ml, 2N), extracted with CH_2Cl_2 (3 x 15 ml), EtOAc (1 x 15 ml), the organic phases combined, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (silica gel, 230-400 mesh, 6g, 10 mm O.D., Et_2O/Acetone, 5:1) using the flash technique, and gave 0.056g (92%) of diol **48**.

^{1}H NMR (250 MHz, $(CD_3)_2CO$) δ = 6.13 (m, 1H), 5.81 (m, 1H), 4.38 (dt, J=7.12, 3.55 Hz, 1H), 4.05 (bs, 2H), 3.96 (bs, 1H), 2.65 (dd, J=10.65, 2.1 Hz, 1H), 2.52 (dd, J=10.3, 1.02 Hz, 1H), 2.16 (bs, 3H), 2.28-1.41 (m, 7H).
IR (neat) 3445, 2948, 2920, 2862, 1592, 1441, 1238, 1218, 1140, 1133, 1018, 984, 772, 685 cm^{-1}.
EI-MS (70eV) m/e = 235 (M^++1, 10.71), 234 (M^+, 70.89), 233 (M^+-1, 19.61), 203 (53.32), 175 (27.60), 159 (15.46), 145 (14.03), 131 (15.01), 123 (21.34), 122 (100), 121 (71.34), 109 (28.36), 108 (21.57), 43 (40.35).

Monoprotected SEM Ether **49**.

To a solution of diol **48** (0.056g, 0.239 mmol) and diisopropylethylamine (0.0708 ml, 0.406 mmol) in CH_2Cl_2 (10 ml) was added SEM-Cl (silyl ethoxy methyl chloride) (0.0508 ml, 0.287 mmol)) dropwise over 5 min. The solution was stirred overnight, quenched with sat. NH_4Cl (8 ml), extracted with CH_2Cl_2 (3 x 15 ml), the organic phase combined, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography on silica gel (230-400 mesh, 6g, 10 mm O.D., Et_2O/Hexane, 1:1) gave SEM protected **49** as a light yellow oil (0.0581g, 66.8%).

^{1}H NMR (250 MHz, C6D6) δ = 6.39 (m, 1H), 5.82 (m, 1H), 4.68 (m, 2H), 4.11 (m, 3H), 3.62 (m, 3H), 2.70 (m, 2H), 2.25-1.75 (m, 6H), 2.03 (bs, 3H), 0.98 (m, 2H), -0.2 (m, 9H)

IR (neat) 3442, 2993, 2924, 2870, 1595, 1327, 1152, 1048, 1020, 946, 855, 740, 688 cm^{-1}.

Diprotected SEM, TBDMS Ether **50**.

To a solution of the SEM-protected compound **49** (0.058g, 0.159 mmol) in dimethylformamide (5 ml) was added imidazole (0.0238g, 0.350 mmol) and TBDMS-Cl (t-Butyldimethylsilyl chloride) (0.033g, 0.223 mmol) in one portion. After stirring overnight, the solution was quenched with sat. NH_4Cl (10 ml), extracted with CH_2Cl_2 (3 x 20 ml), the organic phases combined, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (silica gel, 230-400 mesh, 6g, 10 mm O.D., Hexane/Ether, 15:1) of the resulting oil gave 0.058g (76.3%) of diprotected compound **50** using the flash technique.

^{1}H NMR (250 MHz, C_6D_6) δ = 6.51 (bs, 1H), 5.73 (bs, 1H), 4.71 (s, 2H), 4.19 (s, 2H), 3.72 (dd, J=11.9, 10.3 Hz, 2H), 3.05 (m, 1H), 2.70 (d, J=19.5 Hz, 1H), 2.25-1.33 (m, 3H), 2.01 (s, 3H), 0.99 (dd, J=11.9, 10.3 Hz, 2H), 0.92 (s, 9H), 0.03 (s, 3H), -0.02 (s, 12H).

IR (neat) 2957, 2900, 2893, 1590, 1435, 1330, 1267, 1242, 1148, 1052, 991, 820, 698 cm^{-1}.

EI-MS (25eV) m/e = 479 (M^++1, 2.04), 478 (M^+, 6.49), 420 (3.12), 347 (3.08), 332 (4.69), 331 (14.16), 330 (21.35), 273 (9.33), 199 (21.16), 198 (29.59), 197 (27.27), 183 (11.51), 172 (7.20), 75 (100), 73 (34.71).

Formation of Ene-Dione **51**.

To a solution of diprotected furan **50** (0.044g, 0.092 mmol) in CH_2Cl_2 (5 ml) at 0°C was added MCPBA (0.0186g, 0.092 mmol, 85%) in one portion. The reaction was warmed to RT and stirred for 2 hrs. The reaction was quenched by the addition of sat. $NaHCO_3$ (5 ml), extracted with CH_2Cl_2 (3 x 10 ml), the organic layers combined, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (flash technique, SiO_2, 230-400 mesh, 5g, 10 mm O.D., ether/hexane, 1:1) of the resulting oil gave 0.023g (51.1%) of ene-dione **51**.

^{1}H NMR (250 MHz, C_6D_6) δ = 6.23 (bs, 1H), 5.54 (s, 1H), 4.61 (s, 2H), 3.97 (bs, 2H), 3.67 (m, 2H), 3.41 (m, 1H), 2.34 (d, J=20.52 Hz, 1H), 2.81-1.42 (m, 7H), 1.73 (s, 3H), 1.01 (m, 2H), 0.91 (s, 9H), 0.02 (s, 3H), -0.02 (s, 12H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 204.13, 196.40, 155.25, 150.36, 123.35, 121.03, 94.59, 80.06, 75.59, 71.65, 65.54, 51.77, 45.45, 43.63, 32.93, 29.72, 25.99, 19.81, 18.25, -1.28, -4.62.
IR (neat) 2940, 2884, 1700, 1695, 1630, 1445, 1365, 1050, 943, 733 cm^{-1}.
EI-MS (25eV) m/e = 476 (M+-18, 3.96), 437 (14.60), 379 (19.06), 328 (11.47), 295 (11.39), 289 (42.33), 261 (9.90), 215 (8.83), 197 (21.20), 196 (23.10), 171 (16.09), 147 (12.79), 103 (15.43), 75 (60.73), 73 (100).

Monoreduced Ester **53**.

To a solution of **46** (0.244g, 0.938 mmol) in MeOH (15 ml) was added $NaBH_4$ (0.053g, 1.408 mmol) in one portion and stirred (RT) for 4 hrs. The reaction was quenched with sat. aq. $NaHCO_3$ (10 ml), extracted with CH_2Cl_2 (3 x 25 ml), the organic phases combined, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (silica gel, 230-400 mesh, 25g, 20 mm O.D., EtOAc/hexane, 1:1) of the resulting oil gave 0.228g (92.6%) of compound **53** using the flash technique.

^{1}H NMR (250 MHz, C_6D_6) δ = 7.67 (s, 1H), 5.65 (q, J=1.15 Hz, 1H), 4.04 (dt, J=8.71, 5.06 Hz, 1H), 3.78-3.5 (m, 3H), 3.51 (s, 3H), 2.90 (m, 1H), 2.12-1.33 (m, 5H), 1.92 (s, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 168.62, 158.77, 150.84, 132.49, 129.99, 117.58, 107.87, 75.17, 51.63, 44.41, 40.68, 29.98, 29.46, 22.54, 13.08.
IR (neat) 3420, 2951, 2905, 2862, 1704, 1699, 1694, 1682, 1435, 1261, 1249, 1132, 1103, 948, 786 cm^{-1}.
EI-MS (70eV) m/e = 263 (M^++1, 2.38), 262 (M^+, 12.35), 229 (8.37), 216 (8.37), 203 (12.77), 185 (13.18), 145 (16.51), 115 (20.31), 91 (16.57), 77 (10.33), 59 (12.65), 57 (23.69), 55 (23.28), 43 (100).

minor ^{1}H - trans compound δ = 7.71 (s, 1H), 5.62 (m, 1H), 3.49 (s, 3H).

Formation of Ene-Dione **54**.

To a solution of **53** (0.1043g, 0.398 mmol) in CH_2Cl_2 (8 ml) and sat. aq. $NaHCO_3$ (2 ml) was added MCPBA (0.080g, 0.469 mmol, 85%) in one portion. The mixture was stirred 2 hr., cast into CH_2Cl_2/Aq. $NaHCO_3$ (20 ml each), extracted (CH_2Cl_2, 3 x 20 ml), the organic phases combined, tested with starch iodine paper, dried over $MgSO_4$, and concentrated *in vacuo*. Column chromatography (silica gel, 230-400 mesh, 10g, 10 mm O.D., Et_2O/hexane, 5:1) of the resulting oil gave two fractions **53** (0.056g) and **54** (0.044g, 40%). Fraction **53** corresponded to starting material.

^{1}H NMR (250 MHz, C_6D_6) δ = 7.09 (s, 1H), 5.44 (s, 1H), 3.71 (q, J=3.55 Hz, 1H), 3.63-3.15 (m, 3H), 3.42 (s, 3H), 2.68 (m, 1H), 2.32-1.96 (m, 2H), 1.69 (s, 3H), 1.65-1.28 (m, 3H).

^{13}C NMR (62.95 MHz, C_6D_6) δ = 204.79, 196.89, 167.25, 151.73, 139.59, 136.87, 135.06, 131.48, 75.12, 52.27, 52.01, 46.51, 33.99, 29.60, 24.63, 21.58.

IR (neat) 2920, 2900, 2875, 1705, 1695, 1690, 1620, 1455, 1390, 1194, 1093, 1015, 906, 855, 732 cm^{-1}.

EI-MS (25eV) m/e = 260 (M^+-18, 2.66), 228 (5.79), 219 (5.94), 203 (8.81), 200 (7.15), 149 (10.79), 129 (8.27), 111 (9.62), 97 (13.01), 85 (18.97), 83 (17.52), 71 (26.48), 57 (46.18), 44 (31.88), 43 (100).

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APPROACHES TO ELEAOKANINE A

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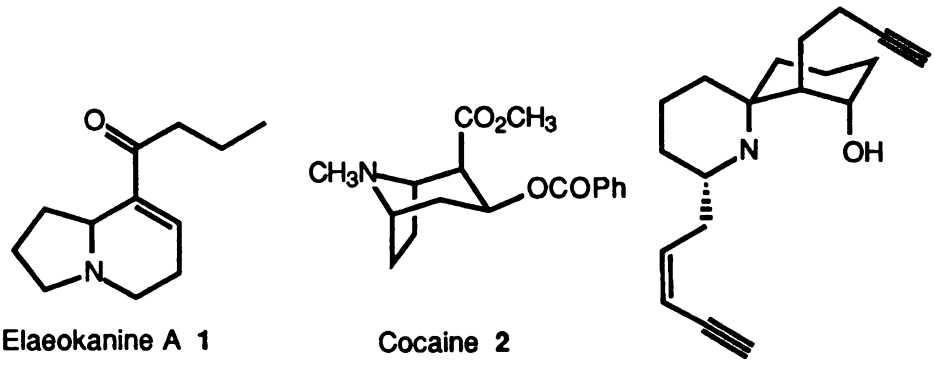


Elaeokanine A **1** Cocaine **2** Histrionicotoxin **3**

Figure 1: Alkaloid Natural Products

As an extension of our work with carbocyclic furan terminated cationic cyclization, we surmised that the use of a nitrogen containing cyclization initiator might allow access to a large array of fused-, bridged-, and spirocyclic alkaloids. After considering either an iminium or N-acyliminium ion as the initiating function, we elected to examine the utility of the more reactive N-acyliminium ion[1] for the task alluded to above. Some important reasons for selecting an N-acyliminium ions as the initiator of choice include: 1) ease of formation from readily available starting materials, 2) formation of a relatively unreactive amide after cyclization, and 3) generally require less reactive terminators for successful reactions. An additional consideration was the extensive literature precedent for the use of this function, notably in the pioneering work of Speckamp[2], and then observed in the efforts of Evans[3], Hart[4], and Chamberlin[5] among others. These workers have applied N-acyliminium ion cyclizations to the construction of a wide variety of structurally diverse alkaloids including perhydrohistrionicotoxin[6], gephyrotoxin[7], and eleaokanine A.[8]

Iminium Ion **A** N-Acyliminium Ion **B**

Figure 2: Iminium and N-acyliminium Ion Structures

Another attractive feature of the N-acyliminium ion as a cyclization initiator is the diversity of precursors which will give rise to the same reactive intermediates. For example, in the early 1900's, Tscherniac[9a] and Einhorn[9b] exposed α–OH-amides to H_2SO_4 in benzene to obtain an α-Ph-amide. This compound resulted from the attack of neutral benzene, as a latent nucleophile, onto the reactive N-acyliminium ion which resulted from dehydration (H_2SO_4) of the α-OH-amide. Although potentially useful, this technique suffered from relatively low yields in intermolecular processes. Since that time there have been many new methods to generate an N-acyliminium ion[10]. The current method of choice is facile monoreduction of a cyclic imide, then protonation and elimination (H_2O) of the α-hydroxyamide or the generation of related α-alkoxy-amide and elimination of the elements of ROH to form the desired N-acyliminium ion.[11] This reaction intermediate was then captured by an internally held nucleophile in a facile intramolecular process. Speckamp[12] has extensively studied the mono-reduction of cyclic imides ($NaBH_4$) in ethanol to give the corresponding α-alkoxy-lactam. This protocol was adopted by Speckamp to circumvent a nagging problem, overreduction to the ω-OH-amide. Capture as the α-OR-lactam ether prevents carbinol-amide opening and subsequent amido-aldehyde reduction. However the α-OR-lactam thus formed, although very useful, cannot be employed universally. Chamberlin[13] solved the problem of overreduction with a simple modification, treatment of the imide in methanol with an excess of $NaBH_4$ at -4°C, which cleanly reduced the imide. This discovery has opened the door for studies of the cyclization under solvolytic as well as acidic conditions. Chamberlin[14] has reported successful cyclizations of the α-OH-lactam after treatment with MsCl and triethylamine followed by capture of the N-acyliminium ion produced after expulsion of the excellent leaving group MsO^-.

A multitude of possible outcomes await the derived N-acyliminium ion upon electrophilic attack, with the majority being either destructive or unproductive. In order to maximize the production of the desired cyclization products we must consider 1) enamide formation, 2) enamide dimerization 3) regiochemical ambiguities, and 4) questionable stereochemical control. Enamide formation can be a major pathway in any acid initiated N-acyliminium ion reaction. The selection of reaction conditions and the relative rate of deprotonation versus cyclization govern the outcome. One might consider this path reasonable as the enamide should be the operational equivalent of the N-acyliminium ion after the addition of a proton. Many workers have discovered that the conditions needed to add H^+ to the enamide are indeed much harsher than utilized with the α-OH or α-OR-lactam and can often lead to destruction of the starting material or the product. Should the enamide pathway be the reaction of choice, then we must concern ourselves with the possibility of irreversible enamide dimerization (see Figure 3).[15]

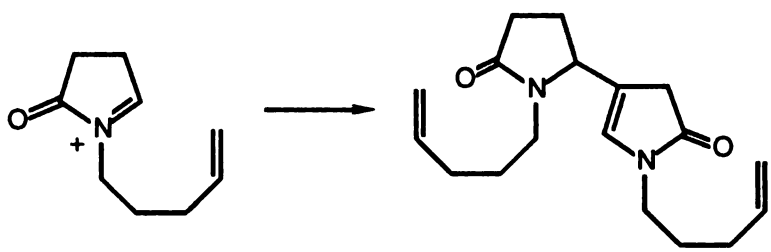


Figure 3: Eneamide Dimerization

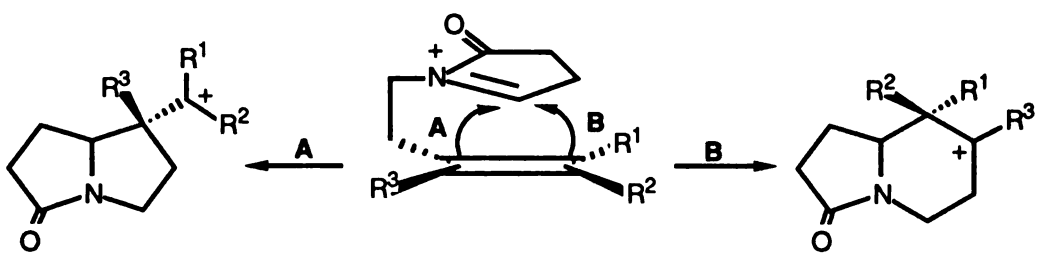


Figure 4 : Regiochemical Outcome of Acyliminium Ion Closure

Regiochemical problems are numerous, for example, in a study by Speckamp[16] of unsubstituted olefin and alkyne terminators which can afford either 6-endo, or 5-exo products he obtains both 5-exo and 6-endo products (Figure 4). In most unsubstituted cases, the formation of the six membered

ring is prevalent, however terminator design is crucial to obtain the product desired.

Overman[17] has shown that substitution of the olefin with sulfur or silicon directed the cyclization as in Figure 5. Finally stereochemistry must be addressed. In a case studied by Speckamp[18], cyclization of the disubstituted versus monosubstituted olefin showed a marked preference for isomer 7 when the olefin is substituted (Figure 6).

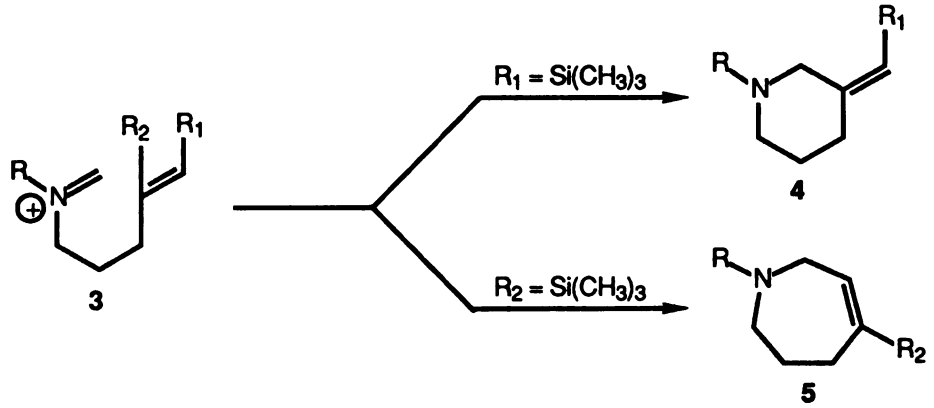
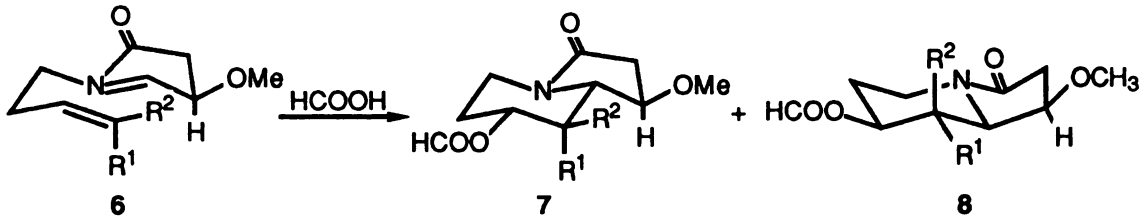


FIGURE 5: Overman Exo, Endo Cyclizations



R^1	R^2	7 / 8	% Yield
H	H	2:1	~100
Et	H	100:1	~100

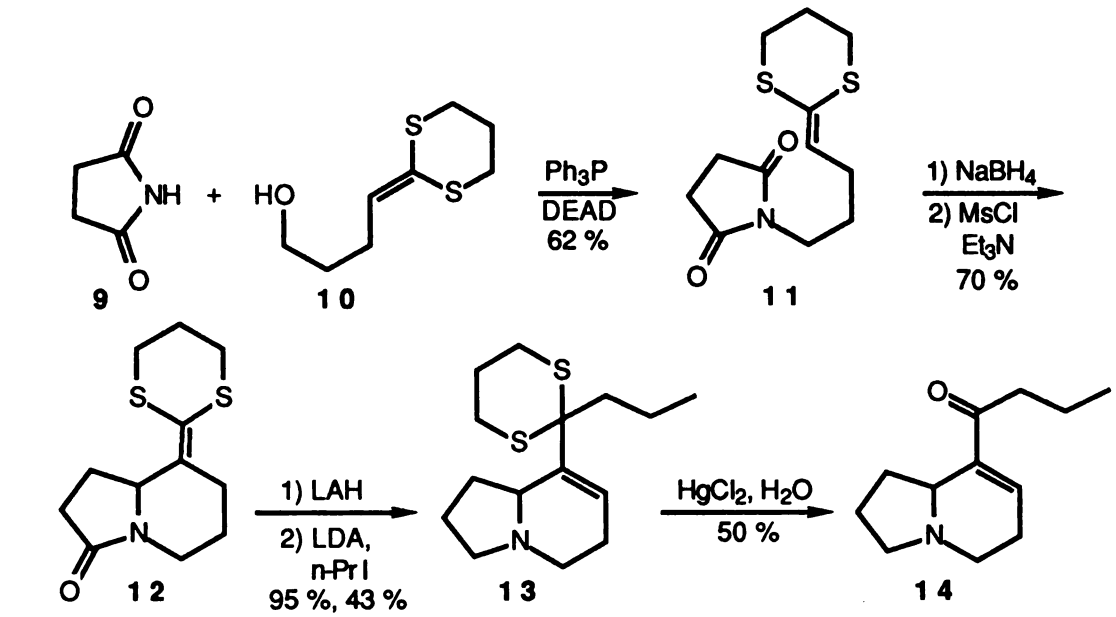
Figure 6: Stereochemical Outcome of Acyliminium Cyclization

The Eleaocarpus[19] and quinolizidine[20] alkaloids are groups of compounds that exhibit little bioactivity, but have been used as a showcase for specific methodology under study. As was the case for systems analyzed above , the relative placement of the sidechain and pendant functionality to the piperidine ring suggested employing a furan terminated cyclization for the preparation of the basic ring system bearing in mind that for each target alkaloid we must cleave a C-C bond to correctly place a C=O or C-R function.

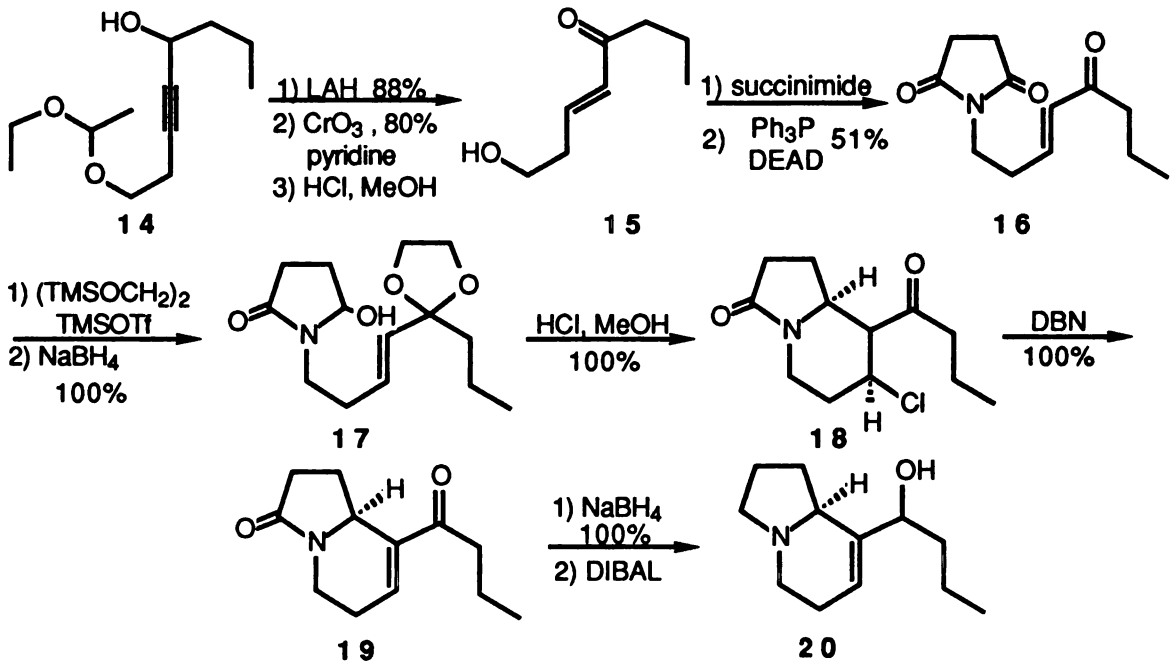
Our major concerns for the study of these molecules were: 1) are both the 3-2 and 2-3 furan closures useful in alkaloid syntheses, 2) is furan amenable to the functionality required in the eleaocarpus and quinolizidine alkaloids, 3) will it be neccessary to use acidic methodology for closure, and 4) can we complete the synthesis of one or more of the natural products?

Chamberlin and Speckamp have both used succinimide as the A-ring precursor in the synthesis of Eleaokanine A or B. Each has chosen a unique terminator for the cationic process. Chamberlin[21] elected (Scheme **1**) to cyclize using a ketene dithioacetal as his terminator. The ketene dithioacetal was selected because of the ability of sulfur to stabilize the carbocation that is formed from attack of the N-acyliminium ion. Also important was the ability of the ketene dithioacetal to function both as an acyl anion equivalent and as a latent carbonyl. Using a modification of Corey's procedure for protecting lactones as their cyclic dithioorthoester, Chamberlin formed the ketene dithioacetal alcohol ($Me_2AlS(CH_2)_3SAlMe_2$), heat) from valerolactone in reasonable yields. Mitsunobu condensation (Ph_3P, DEAD) of the dithioacetal alcohol with succinimide gave an overall 62% yield of **11**. Reduction ($NaBH_4$) and cyclization (MsCl, Et_3N, -20°C to RT) of the crude hydroxylactam gave compound **12** in 71% yield. Reduction of the amide (LAH) and subsequent alkylation of the thioketal anion (LDA, nPrI) resulted in the formation of advanced intermediate **13** Deprotection of the dithioketal ($HgCl_2$, H_2O) gave Eleaokanine A in 48% for the three step process.

Speckamp has used a similar system except for the cyclization terminator. In his case, Speckamp[22] (Scheme **2**) employed a protected enone to trap the N-acyliminium ion formed. Cyclization (HCl, MeOH) across the olefin occured with the regiochemistry indicated, to give the chloro-ketone **18**. Deprotection occured concurrent with cyclization, but was probably not competitive since in a separate experiment the enone was not reactive enough to form the product. Halide elimination (DBN) and reduction (LAH) gave an unstated yield of eleaokanine B.



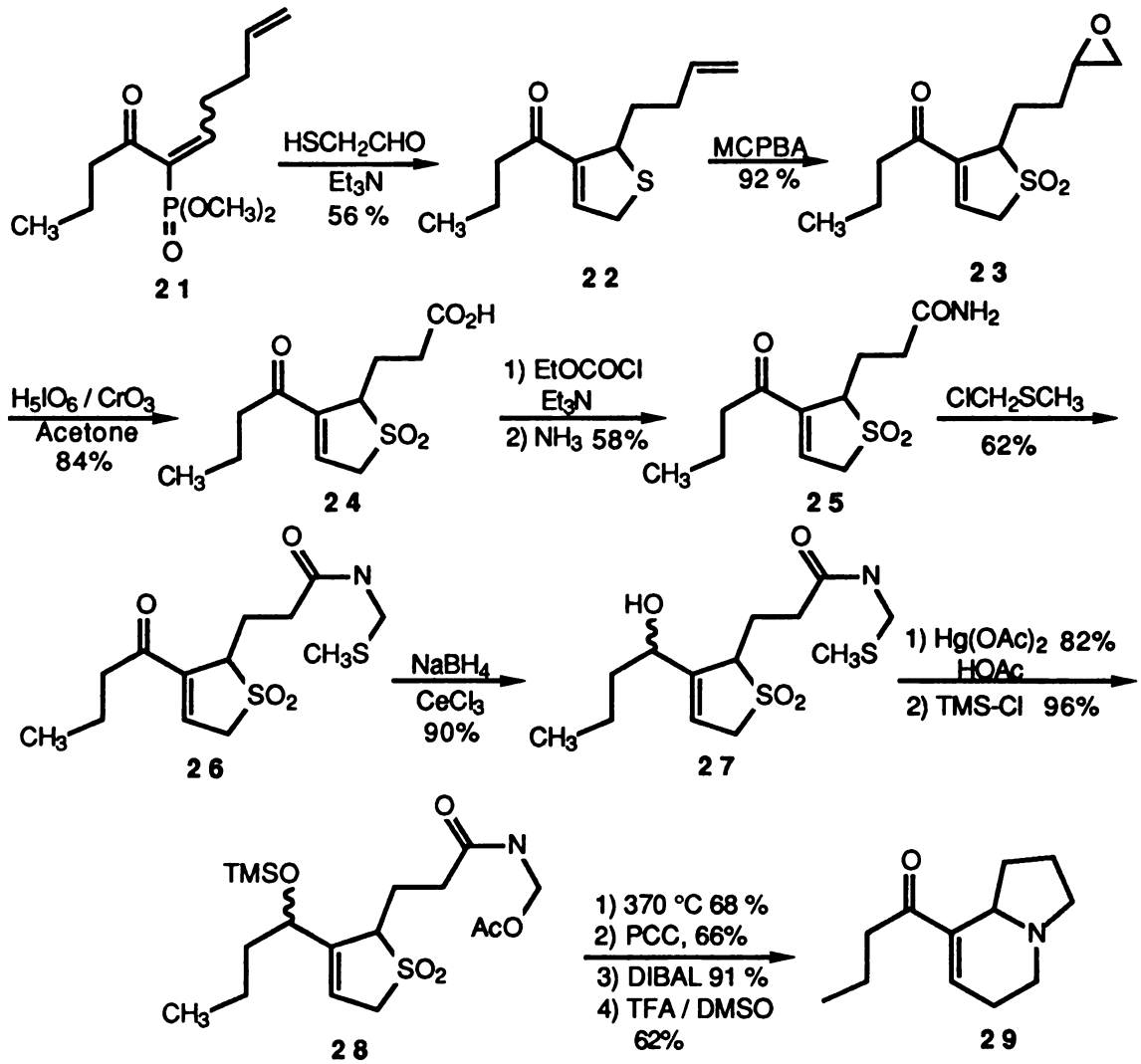
SCHEME 1: Chamberlin's Elaeokanine Synthesis



SCHEME 2: Speckamp Elaeokanine Synthesis

A final example was a non N-acyliminium ion formation of eleaokanine B. Weinreb[23] looked at eleaokanine as the product of a hetero Diels-Alder reaction of acyl imine **28** (Scheme 3). A standard Horner-Emmons reaction (piperidine, HOAc, benzene) reaction forms the disubstituted dihydrothiophene **22**, which, after oxidation (MCPBA) of both the sulfur and

olefin, gave epoxy-sulfone **23** in 92% yield. Epoxide **23** was treated with periodic acid/chromic acid to give carboxylic acid **24** (84%). The addition of ammonia to the acid chloride prepared from the corresponding carboxylic acid, gave amide **25** (58%) which led to thioamide **26** in 62% yield. The amide acetate **26** was then prepared from **27** with mercuric acetate (1 eq.) in glacial acetic acid followed by silylation. Pyrolytic cyclization of **27** (370°C) gave a 68% yield of eleaokanine B, which led to eleaokanine A (62%) after Swern oxidation.



SCHEME 3: Weinreb Non Acyliminium Cyclization to Elaeokanine

The Tanis research group[24] has been interested in the use of furans as butenolide, cyclopentenone, cyclohexane, and 1,4 dione equivalents in

cationic cyclizations. The majority of our efforts have employed standard "carbenium ion" initiator functions en route to heteroatom deficient terpenoids. More recently we have initiated a series of studies designed to construct a variety of alkaloid skeletal types *via* N-acyliminium ion initiated furan terminated cyclizations. Tanis, Dixon, and Raggon[25] have examined the use of this protocol in preparing a variety of linearly fused-, spirocyclic-, and bridged ring containing systems. The basic concepts employed are presented in Figure 7 for the electronically favored 3→2 mode of cyclization.

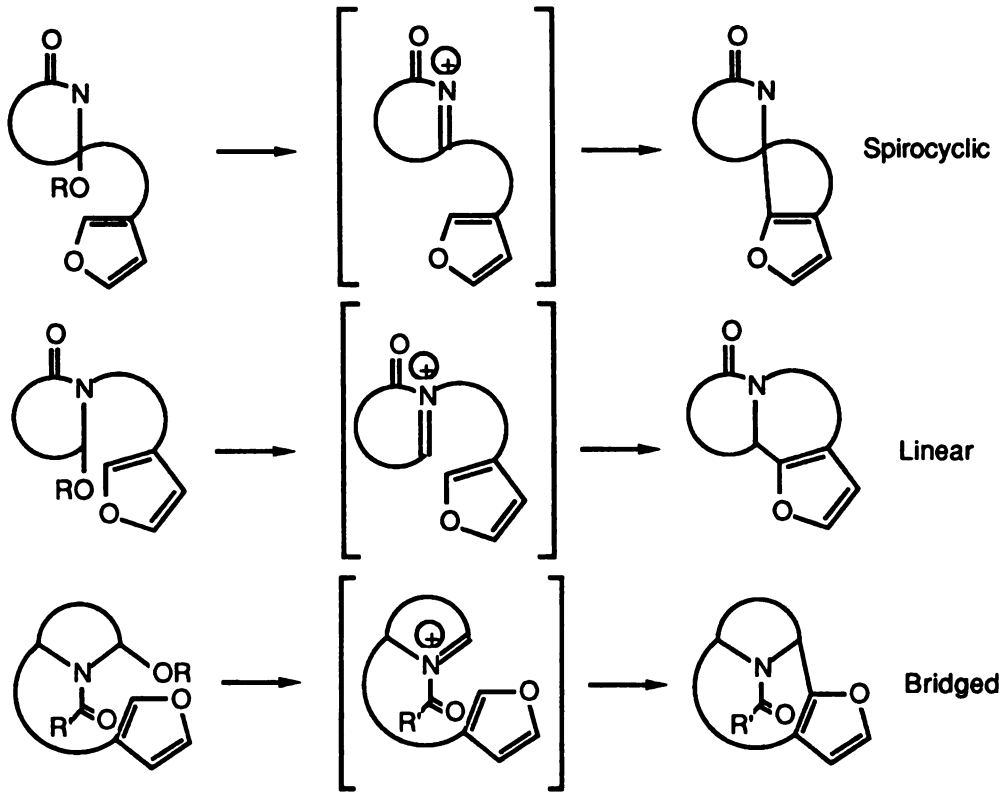
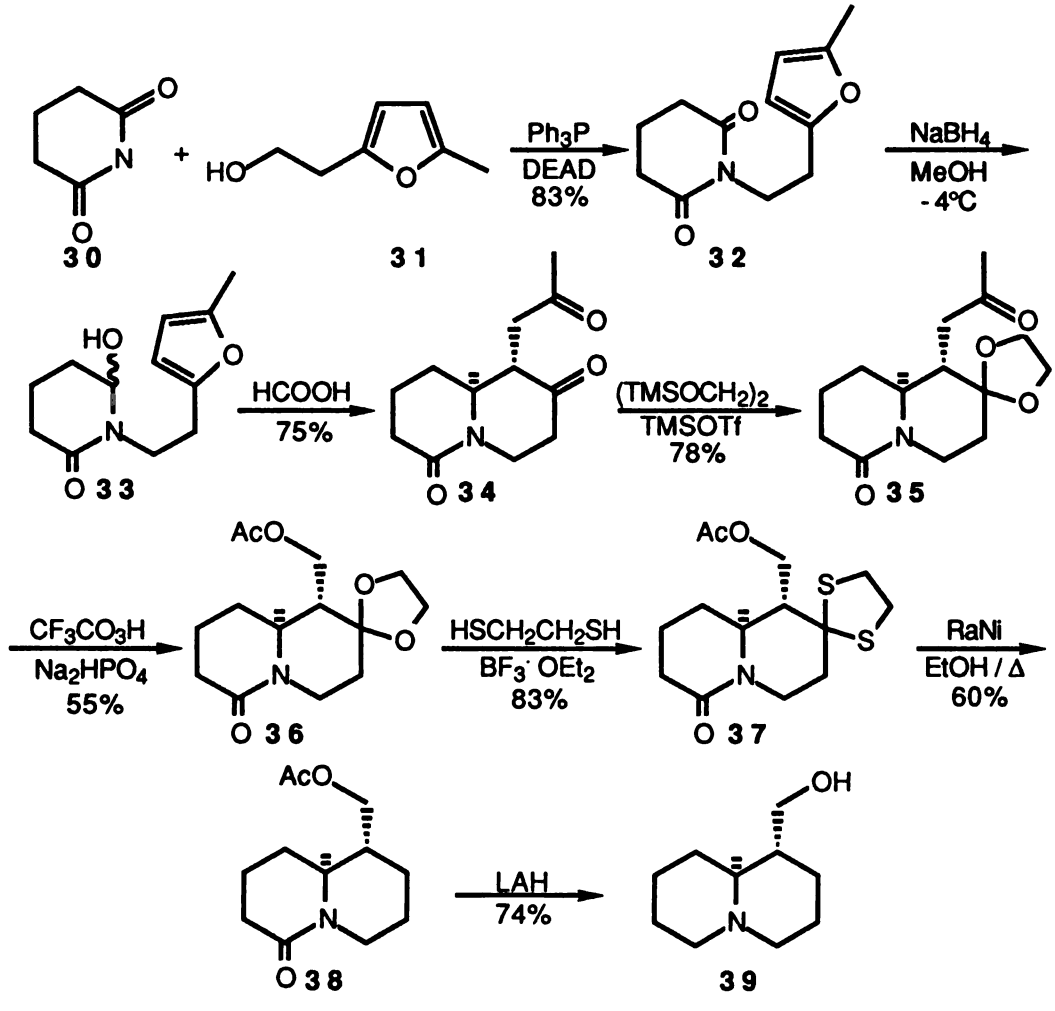


Figure7: Generalized 3→2 Cyclization Modes

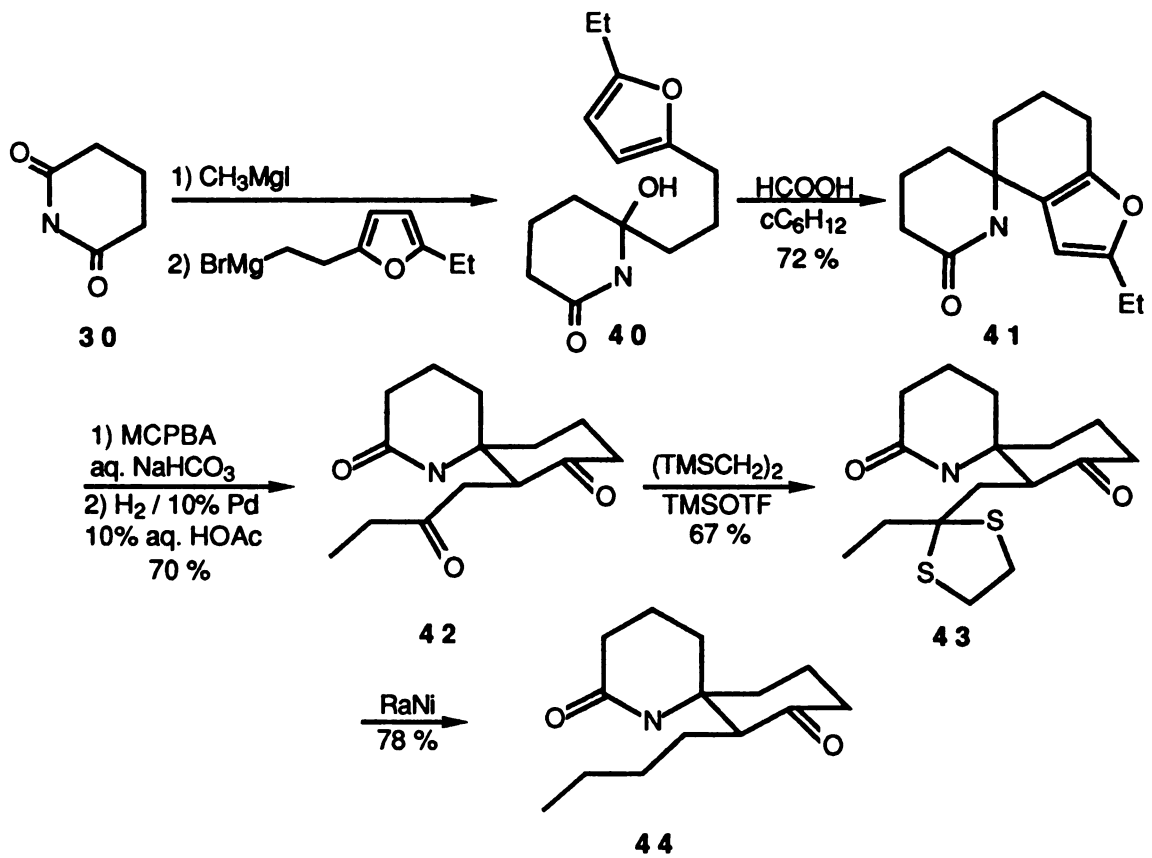
Dixon and Tanis[26] have constructed the linearly fused system **39** (Scheme 4) that represents a total synthesis of the quinolizidine alkaloid epi-lupinine. Using a system similar to Chamberlin and Speckamp, disubstituted furan **31** (2-methylfuran, nBuLi, ethylene oxide) was coupled with glutarimide utilizing Mitsunobu[27] chemistry (Ph_3P, DEAD) to give a 55% yield of **32.** Reduction ($NaBH_4$, MeOH, -4°C) gave α-hydroxyamide **33**(~100%). Cyclization (HCOOH, cC_6H_{12}) produced, directly, 1,4 dione **34** in 75% yield.

Differentiation of the two ketones formed upon cyclization was of paramount importance. Attempted thioketalization under thermodynamic conditions ($(HSCH_2)_2$, benzene, reflux) led primarily to reclosed furan. Kinetic thioketalization[28] ($(TMSSCH_2)_2$, TMSOTf, -40°C→-20°C) gave a number of products as an inseparable mixture. Kinetic ketalization[29] ($(TMSOCH_2)_2$, TMSOTf, -78°C →RT) gave a predominance of one product (ring ketal) **35** as shown by ^1H NMR. Baeyer-Villiger oxidation (MCPBA) provided the acetate **36** in 55%. The previously reported work of Hart[30] suggested that this might be an optimized yield. Transketalization[31] (ethanedithiol, $BF_3{\cdot}OEt_2$) rapidly gave the thioketal **37**, which, after reduction (RaNi) of the thioketal, and reduction (LAH) of both the acetate and amide gave epilupinine **39** in 74%.



SCHEME 4: Dixon Synthesis of Epilupinine

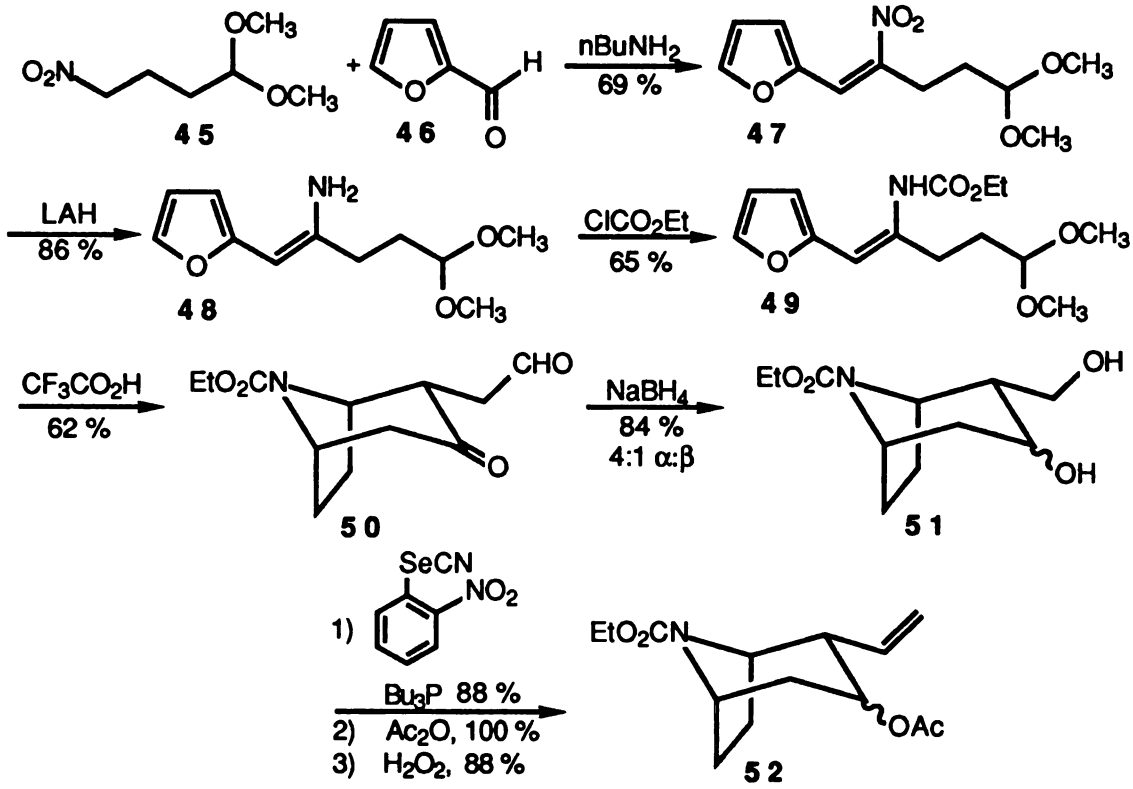
In the case of the spirocyclic alkaloids, Dixon and Tanis[32] have completed a formal total synthesis of perhydrohistrionicotoxin (Scheme 5), a compound which was reported to block postsynaptic membrane depolarization. Initially, the synthesis was attempted using a monosubstituted furan, however, after cyclization, oxidation with various reagents such as MCPBA, Br_2/MeOH, hv etc. proved useless.[33] We had previously observed, during our formal total synthesis of aphidicolin[34], that increasing substitution on furan made it more susceptible to oxidation (MCPBA) affording an ene-dione, which gave the dione **42** after hydrogenation (H_2/Pd). This was indeed the case as described in Scheme 5. Cyclization of **40** (HCOOH, cC_6H_{12}) gave **41** (72%) which was smoothly oxidized (MCPBA) and reduced (H_2, Pd) to furnish **42** in 70% yield. Differentiation of the ene-dione was accomplished using kinetic ketalization methodology developed by Noyori. In the event, kinetic thioketalization of **42** selectively (11:1) gave the product of side chain thioketalization **43** in 67% yield. Reduction (RaNi) of the thioketal gave the parent hydrocarbon, completing a formal total synthesis of perhydrohistrionicotoxin in 26% yield.



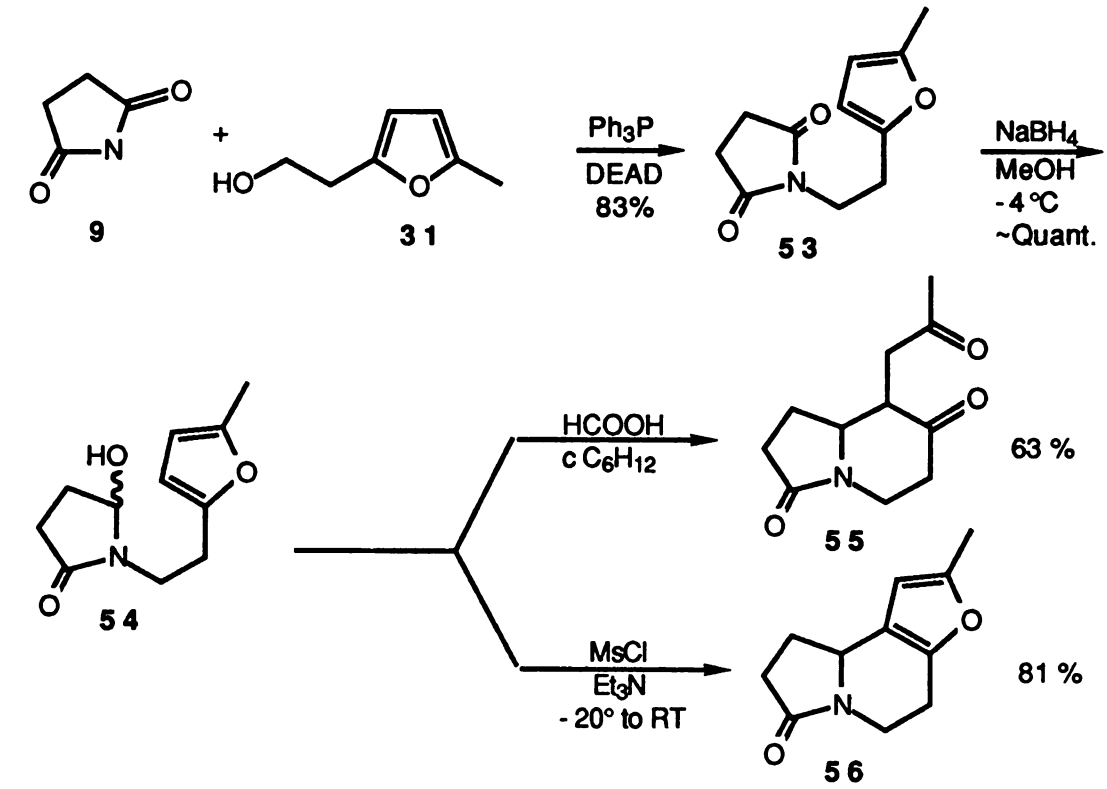
SCHEME 5: Dixon Synthesis of Perhydrhistrionicotoxin

The bridged alkaloids, represented by the aza-bicyclo[3.2.1]octane and aza-bicyclo[4.2.1]nonane ring system of cocaine[35] and anatoxin-A[36] respectively were the final systems to be investigated. To date, a formal total synthesis has not been completed, however, the results of Dixon are summarized in Scheme **6**. The synthesis of the cocaine ring system (Scheme **6**) proceeded from a mono-cyclic (furan ring) precursor which was prepared as follows: nitromethane was added to acrolein under Michael conditions and the product 4-nitro-butanal was protected as the related dimethyl acetal **45**. Nitroaldol addition to furfural ($nBuNH_2$) and dehydration gave the vinyl nitro adduct **47** (69%) which was then reduced (LAH), and acetylated (EtCOCl, 56%, **49**). Carbamate **49** was reacted with TFA in $CHCl_3$ to afford the azabicyclo[3.2.1]octane-one-al **50** in 62% yield. In this step we have observed not only a cyclization to an α-alkoxy carbamate, followed by an intramolecular furan [2→3] terminated N-acyliminium cyclization, but, in addition, the disubstituted furyl moiety has suffered hydrolysis to the related keto-aldehyde. We surmise that strain prevented rearomatization and that $CF_3CO_2^-$ capture of the intermediate oxonium ion affords a stable enol-ketol which was hydrolyzed upon workup.

This study, directed toward the synthesis of the elaeokanine alkaloids, began with the disubstituted furan, 2-methyl-5-furylethanol. This compound was prepared by the addition of ethylene oxide to the lithium salt of 2-methyl furan to give **31** in 45% yield. Mitsunobu coupling (Ph_3P, DEAD) of 2-methyl-5-furylethanol with succinimide gave imide **53** (83%), which was reduced with sodium borohydride (MeOH, -4°C) to give **54** in quantitative crude yield. Cyclization of the hydroxy lactam in a two phase mixture of formic acid in cyclohexane gave a 75% yield of dione **55**, a result which stands in contrast to that found by Dixon and Tanis[37] in the non-methylated case in which the cyclized-/unopened furan compound **56** was obtained in 71% yield. This hydroxy lactam was also cyclized according to Chamberlin's non acidic conditions (MsCl, Et_3N) to afford desired furan **56** (81%). Exposure of **56** to the same two phase cyclization conditions (HCOOH, cC_6H_{12}) containing water (2 eq.) gave, as expected, the dione **55** (62%) demonstrating the feasibility of this process in a well defined ring system.



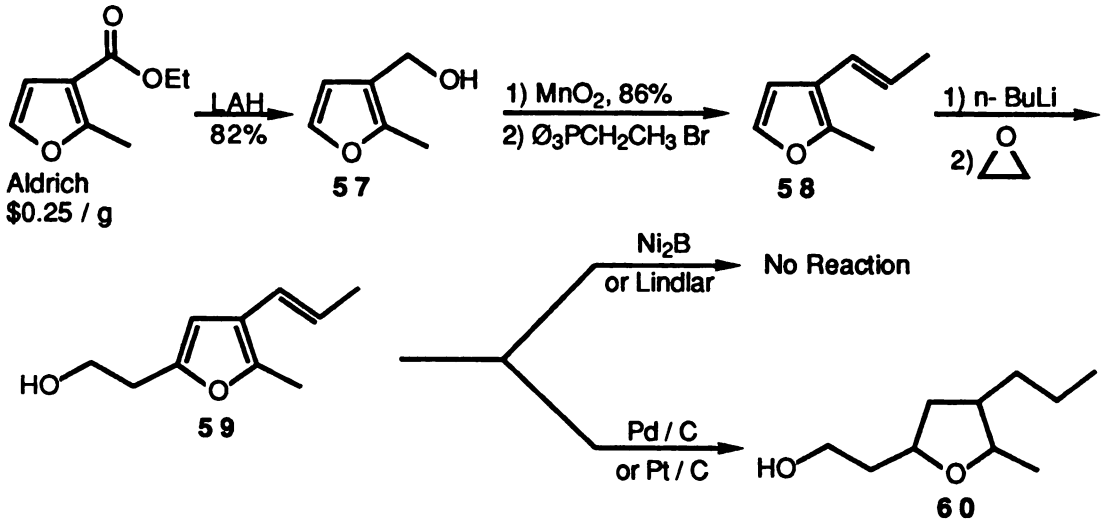
SCHEME 6: Dixon Synthetic Route Toward Cocaine



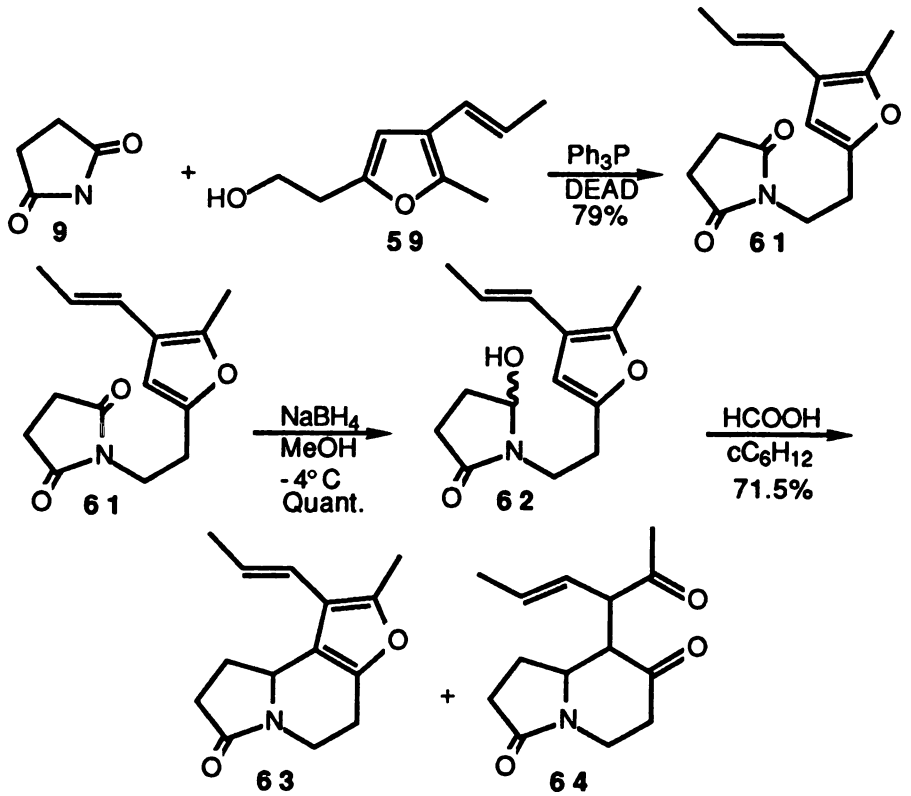
SCHEME 7: First Elaeokanine Generation

After demonstrating the viability of the cyclization process, our task was to manipulate the resulting dione so as to eliminate the excess carbon chain. We considered two possible strategies, first we thought that the addition of a propyl sidechain onto the existing 1,4 dione, and second that we could incorporate this three carbon residue from the outset. The former approach would require either a selective alkylation of the sidechain C=O or a protection protocol similar to those described earlier. After careful consideration, we decided that a more efficient synthesis might be realized if the addition of a sidechain came initially from a trisubstituted furan. We hoped that closure of the this furan would proceed as expected resulting in a dione with a propyl sidechain placed in the correct position. This strategy required us to develop the synthesis of a rather complex trisubstituted furylethanol (Scheme **8** or **10**). We were pleased to find an inexpensive, commercially available starting material 2-methyl-3-methylfurancarboxylate (Aldrich). Our first route toward the trisubstituted furan **59** is outlined in Scheme **8**. A two carbon Wittig homologation ($Ph_3P{=}CHCH_3$) to 2-methyl-3-furfural gave furan (**58**) with a propenyl side chain. Previous work in our laboratories[39], had suggested that reduction of the propenyl side chain, without concurrent reduction of the furan to a disubstituted tetrahydrofuran was possible. Reduction catalysts such as Lindlar's ($Pd/Pb/CaCO_3$) and Ni_2B gave either no reduction or a poor mixture of products; platinum or palladium generally afforded products of overreduction (**60**). At this point, we considered conducting the reaction sequence with the olefin intact. Toward that end, we reacted the propenyl-methyl furan with 2-3 equivalents of butyllithium, then quenched with either gaseous ethylene oxide or a 1.0M solution of ethylene oxide in ether to give **59** in 40-70% yields.

With **59** in hand, we proceeded as described in Scheme **9**. Furan **59** was coupled with succinimide to furnish **61** (79%), which was reduced ($NaBH_4$, MeOH, -4°C) to yield carbinol-amide **62** Cyclization (HCOOH, cC_6H_{12}) led to **64** in 71% yield. All attempts at further functionalization have been thwarted.

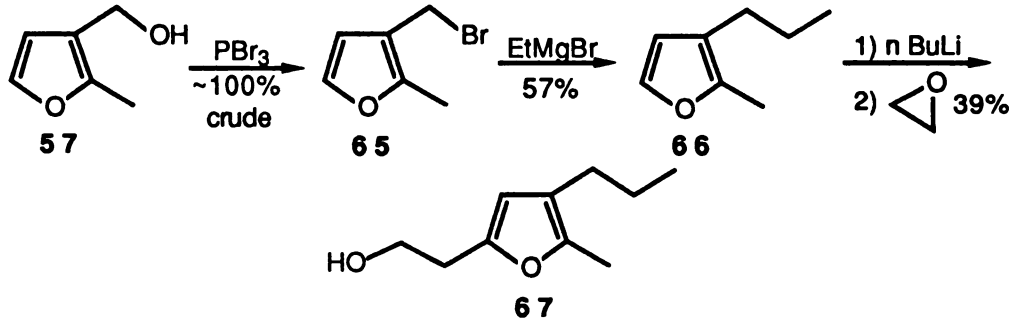


SCHEME 8: Synthesis of Trisubstituted Furan



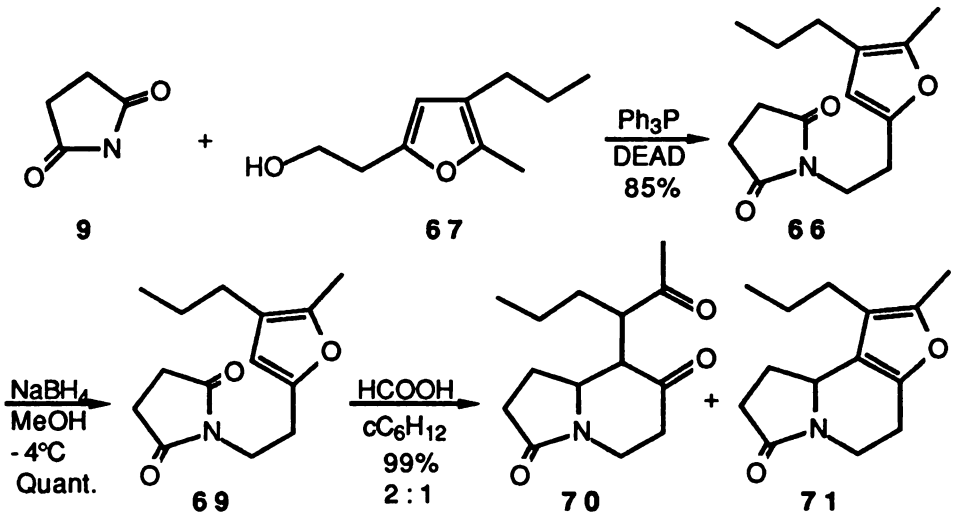
SCHEME 9: Second Generation Elaeokanine Synthesis

In the hope of circumventing these problems we chose modify the furan and incorporate the desired propyl sidechain instead of the propenyl compound. Methyl-2-methyl-5-furancarboxylate was reduced (LAH) to give 2-methyl-3-furanmethanol in 89% yield, which was brominated, according to Padwa[40] (Scheme **10**) to give unstable methyl bromomethylfuran **65** as a crude product. After numerous attempts, we were unable to purify **65**, therefore, **65** was stored as a solution shielded from light at - 20°C. Alkylation of **65** with a large excess of ethyl magnesium bromide gave a reasonable 57% overall yield of 3-propyl-2-methylfuran. Furan **66** was then lithiated (nBuLi) and ethylene oxide was added to the resulting anion to give **67** (39%) contaminated with n-hexanol.

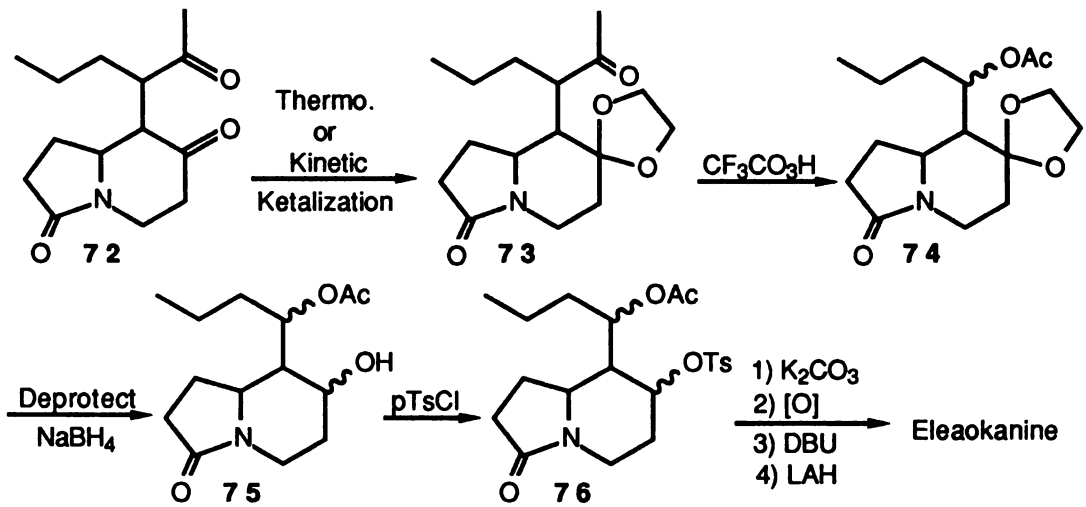


Scheme 10: Synthesis of Reduced Trisubstituted Furan

Purification of **65** followed by Mitsunobu coupling (Ph_3P, DEAD) of **67** with succinimide gave **68** (85%), which was reduced ($NABH_4$, MeOH, - 4°C), then exposed to HCOOH, cC_6H_{12} to yield a mixture (49:52, 99%) of furan **71** and dione **70**. As of this writing, we are examining the cyclization conditions in an effort to obtain a single product. We are also attempting to open the furan obtained with acid catalyzed hydrolysis. We have found that the dione is very susceptible to closure, and as a result we are attempting to find conditions that will trap the dione in the open form. Should we succeed in this endeavor we anticipate completion of eleaokanine **2** as outlined in scheme **12**. The results will be reported in due course.



Scheme 11: Synthesis of Elaeokanine Precursor



Scheme 12: Future Synthetic Scheme

Starting with the hypothesis that furan terminated cationic cyclizations are useful for the synthesis of various carbocyclic and azacyclic systems, we have shown that indeed, furan cyclizations (2→3 and 3→2) are useful for the preparation of alkaloid, pseudoguaianolide, and tigliane/daphnane systems. These processes have provided both *5,5* and *5,6* membered fused rings required for the alkaloid systems under study, and also the *5,7,5* membered ring systems required for the pseudoguaianolides, and as a template for the tetracyclic daphnane products. We have also shown that furan terminated

cationic cyclizations meet the criteria we require to be useful: 1)they cyclize under mild conditions (both acidic and neutral), and 2) they proceed with regiochemical predictability. During the course of these studies, we have found that furan oxidation and hydrolysis are the limiting factors in the effectiveness of the cationic process. These factors tend to be substrate dependent therefore making conclusions about the generality of furans use difficult. We hope that through the many examples we have shown that furan oxidation and hydrolysis can become predictable. Currently, we are in the process of completing formal total syntheses of several molecules including phorbol/resiniferonol, fastigilin-C, aromatin, and elaeokanine A. We should also be able to control the stereochemistry of various functional groups about the periphery of all three rings contained in the bicyclo[5.3.0]-decane skeleton.

EXPERIMENTAL

EXPERIMENTAL

Cyclization to Indolizidine Furan **56**

To a stirring solution of hydroxy amide **54** (0.130g, 0.622 mmol) in CH_2Cl_2 (-20°C) was added triethylamine (0.203ml, 1.86 mmol) and mesyl chloride (0.089g, 0.933 mmol) sequentially. The reaction was warmed to RT over a 3 hr. period, stirred overnight, and quenched with sat. aq. $NaHCO_3$ (20 ml). The aqueous phase was extracted (3 x 20 ml CH_2Cl_2), the organic phases combined, dried over $MgSO_4$, concentrated *in vacuo* to give clear oil **56**. Chromatography (230-400 mesh, 10g, 20 mm O.D., EtOAc/Hexane, 2:1) on silica gel using the flash technique gave 0.103g (86.6%) of **56**, the closed furan product

^{1}H NMR (250 MHz, $CDCl_3$) δ = 5.84 (s, 1H), 4.59 (m, 1H), 4.43 (dd, J=9.36, 6.21 Hz, 1H), 3.55 (m, 1H), 3.05-2.33 (m, 4H), 2.26 (s, 3H), 1.73 (m, 2H).
IR (neat): 2950, 2922, 2880, 1702, 1565, 1431, 1384, 1240, 1210, 1180, 992, 825, 685 cm^{-1}.
EI-MS (70eV) m/e = 192 (M^++1, 13.78), 191 (M^+, 100), 190 (80.41), 176 (18.29), 148 (24.86), 135 (27.61), 134 (44.59), 133 (13.54), 431 (17.98), 91 (17.71), 77 (16.58), 55 (12.10), 43 (16.02).

Mitsunobu Product **61**.

To a solution of **59** (1.66g, 10 mmol) in THF (25 ml) was added succinimide (0.990g, 10 mmol), triphenylphosphine (3.01g, 11.5 mmol), and DEAD (diethylazo-dicarboxylate) (1.81 ml, 2.00g, 11.5 mmol). The resulting solution was stirred overnight, then concentrated *in vacuo*. Ether (60 ml) was added to the residue and, after filtration, the solution was concentrated to give fluffy white solid **61**. Solid **61** was chromatographed (230-400 mesh, 200g, 50 mm O.D., EtOAc/Hexane, 70:30 on silica) using the flash technique to give purified **61** (1.96g, 79.3%).

^{1}H NMR (250 MHz, C_6D_6) δ = 6.24 (s, 1H), 6.11 (m, 1H), 6.51 (dq, J=9.25, 7.07 Hz, 1H), 3.65 (t, J=7.18 Hz, 2H), 2.84 (t, J=7.22 Hz, 2H), 2.00 (s, 3H), 1.75 (dd, J=7.07, 1.73 Hz, 3H), 1.60 (s, 4H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 175.88, 149.90, 131.9, 124.05, 120.91, 118.6, 108.20, 56.5, 37.22, 27.81, 26.34, 14.66, 11.75, -0.71.
IR (neat) 2955, 2918, 2856, 1701, 1592, 1422, 1399, 1233, 1218, 1175, 952, 830 cm^{-1}.
EI-MS (70eV) m/e= 249 (M^++2, 0.48), 248 (M^++1, 4.68), 247 (M+, 29.56), 149 (12.92), 148 (100), 147 (33.60), 135 (36.15), 133 (23.83), 105 (6.91), 91 (9.13), 55 (10.62), 43 (28.47).

Reduction to α-Hydroxy Amide **62**.

To a solution of **61** (1.30g, 5.28 mmol) in MeOH (15 ml, -4°C) was added in one portion. After stirring for 2 hr. at -4°C, the solution was warmed to RT, cast into aq. $NaHCO_3$, extracted with CH_2Cl_2 (3 x 41 ml) the organic phases combined, dried over $MgSO_4$, and concentrated *in vacuo* to give **62** (~100%). The product was used without further purification.

^{1}H NMR (250 MHz, C_6D_6) δ = 6.25 (s, 1H), 6.10 (m, 1H), 5.51 (dq, J=9.36, 6.55 Hz, 1H), 4.82 (m, 1H), 4,53 (m, 1H), 3.94-3.29 (m, 3H), 2.87 (dt, J=7.64, 3.40 Hz, 1H), 2.30 (m, 1H), 2.00 (s, 3H), 2.00-1.54 (m, 3H), 1.77 (dd, J=7.10, 1.66 Hz, 3H).

Formation of Indolizidine Dione **64** and Furan **63**.

To a vigorously stirring solution of **62** (1.30g, 5.22 mmol) in cyclohexane (70 ml) was added 90% formic acid (0.25 ml) dropwise. After 5 min. the reaction mixture was cast into a mixture (1:1) of CH_2Cl_2 and aq. $NaHCO_3$ (100 ml). the phases were separated, the aqueous was washed with CH_2Cl_2 (4 x 20 ml), the organic fractions combined, dried over $MgSO_4$, and concentrated *in vacuo* to give a faint yellow oil. Chromatography (230-400 mesh, 100g 30 mm O.D., EtOAc/MeOH/TEA, 20:1:0.5) using the flash technique gave 0.93g (71.5%) of **64** and a second fraction of 0.26g of **63**.

64: ^{1}H NMR (250 MHz, C_6D_6) δ = 5.92 (m, 0.5H), 5.86 (m, 0.5H), 5.54 (dq, J=9.41, 6.62 Hz, 1H), 4.42 (m, 1H), 4.01 (m, 1H), 2.42 (m, 1H), 2.11 (m, 4H), 1.98 (s, 3H), 1.88-1.64 (m, 2H), 1.44 (dd, J = 7.22, 1.51 Hz, 3H), 1.26 (m, 2H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 173.2, 147.4, 132.6, 128.9, 120.4, 115.5, 53.8, 37.7, 32.1, 26.3, 24.8, 16.2, 13.6.
IR (neat) 2920, 2848, 1730, 1690, 1589, 1440, 1420, 1271, 1180, 1121, 947, 922, 723, 696 cm^{-1}.
EI-MS (70eV) m/e = 232 (M^++1, 19.26), 231 (M^+, 100), 230 (67.51), 216 (42.80), 188 (44.94), 174 (42.02), 160 (16.46), 145 (16.49), 131 (10.24), 121 (15.54), 91 (17.90), 77 (17.97), 55 (21.16), 43 (78.31).

63: ^{1}H NMR (250 MHz, C_6D_6) δ = 5.51 (m, 2H), 4.11 (ddd, J=12.58, 6.41, 3.39 Hz, 1H), 3.04 (m, 1H), 2.76 (m, 1H), 2.34 (m, 2H), 2.15-1.63 (M, 6H), 2.04 (s, 3H), 1.22 (dd, J=7.31, 1.39 Hz, 3H).
IR (neat) 2930, 2910, 2851, 1718, 1705, 1445, 1430, 1280, 1230, 1180, 1130, 951, 843, 696 cm^{-1}.
EI-MS (70eV) m/e = 249 (M^+, 1.61), 149 (12.23), 148 (100), 135 (23.98), 133 (11.59), 98 (7.11), 91 (11.22), 68 (23.31), 55 (8.84), 43 (58.23).

Mitsunobu Adduct **68**.

To a solution of **67** (0.650g, 4.77 mmol) in THF (22 ml) was added succinimide (0.568g, 5.73 mmol), triphenylphosphine (1.75g, 6.69 mmol) and DEAD (diethylazo-dicarboxylate) (1.18g, 6.69 mmol). The resulting solution was stirred overnight, then concentrated *in vacuo*. Ether (40 ml) was added to the residue, and after filtration, the solution was concentrated to give a clear oil. The oil was chromatographed (230-400 mesh, 100g, 40 mm O.D., EtOAc/Hexane, 70:30) using the flash technique to give **68** (0.818g, 84.9%)

^{1}H NMR (250 MHz, C_6D_6) δ = 5.78 (s, 1H), 3.64 (t, J=7.3 Hz, 2H), 2.81 (t, J=7.4 Hz, 2H), 2.12 (t, J=7.3 Hz, 2H), 1.99 (s, 3H), 1.78 (s, 4H), 1.42 (s, J=7.4 Hz, 2H), 0.82 (t, J=7.3 Hz, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 176.14, 149.41, 146.26, 119.66, 188.67, 37.46, 27.89, 27.06, 26.42, 23.81, 13.80, 11.30.
IR (neat) 2959, 2932 2872, 1776, 1705, 1441, 1435, 1402, 1242, 1159, 1145, 821, 663 cm^{-1}.

Reduction to α-Hydroxy Amide **69**.

To a solution of **68** (0.284g, 1.14 mmol) in MeOH (5 ml) cooled to 0°C, was added $NaBH_4$ (0.064g, 1.71 mmol) in one portion. After stirring at RT for 2 hrs., the excess $NaBH_4$ was quenched with H_2O (2 ml), concentrated, the residue taken up in CH_2Cl_2 (10 ml), dried over Na_2SO_4, and concentratged *in vacuo* to provide 0.278g (97%) of **69** as a yellow oil. The product was used without further purification.

^{1}H NMR (250 MHz, C_6D_6) δ = 5.85 (s, 1H), 3.80 (m, 1H), 3.62 (m, 1H), 2.89 (dt, J=7.33, 3.51 Hz, 1H), 2.44 (m, 1H), 2.15 (m, 4H), 2.01 (s, 3H), 2.00-1.69 (m, 5H), 1.44 (d, J=7.43 Hz, 2H), 0.84 (t, J=7.29 Hz, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 175.14, 150.46, 145.87, 119.76, 108.44, 83.56, 39.28, 29.16, 26.40, 27.13, 26.98, 23.83, 13.84, 11.31.
IR (neat) 3317, 2957, 2930, 2872, 1695, 1670, 1576, 1464, 1458, 1421, 1284, 1211, 1068, 989, 800.

Cyclization to Indolizidine Furan **71** and Dione **70**.

To a vigorously stirred solution of **69** (0.140g, 0.557 mmol) in cyclohexane (15 ml) was added HCOOH (0.084 ml) rapidly. After stirring 5 min., the two-phase mixture was immeidately cast into H_2O (10 ml) and CH_2Cl_2 (10 ml). The aqueous layer was separated, extracted with CH_2Cl_2 (3 x 15 ml), the combined organic layers were washed with sat. $NaHCO_3$ (50 ml), brine (50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The clear oil was purified on a column of silica gel (230-400 mesh, 14g, 20 mm O.D., EtOAc, CH_2Cl_2, MeOH, 8:1:1) to provide 0.064 g (49.3%) of **70** and 0.073g (52.1%) of **71** using the flash technique.

71: ^{1}H NMR (250 MHz, C_6D_6) δ= 4.41 (dd, J=12.61, 5.04 Hz, 1H), 3.95 (m, 1H), 2.36 (m, 2H), 2.18-2.00 (m, 4H), 1.97 (s, 3H), 1.70 (m, 1H), 1.4-1.1 (m, 4H), 0.81 (t, J=7.3 Hz, 3H).
^{13}C NMR (62.95 MHz, C_6D_6) δ = 172.33, 1465.61, 145.11, 119.79, 116.48, 53.89, 36.41, 31.62, 26.46, 26.14, 23.51, 23.45, 13.96, 11.36.
IR (neat) 2959, 2932, 2870, 1695, 1419, 1269, 1149, 945, 884, 705 cm^{-1}

EI-MS (70eV) m/e = 233 (M^++2, 12.55), 232 (M^++1, 10.08), 204 (11.59), 176 (4.62), 150 (4.26), 137 (3.02), 121 (5.40), 96 (7.87), 91 (6.43), 77 (9.02), 68 (14.23), 55 (28.56), 43 (100).

70: ^{1}H NMR (250 MHz, C_6D_6) δ = 4.07 (ddd, J=13.08, 6.54, 3.89 Hz, 1H), 3.42 (bq, J=7.01 Hz, 1H), 3.25 (m, 1H), 2.43 (m, 1H), 2.13-1.73 (m, 5H), 1.94 (s, 3H), 1.64-1.00 (m, 6H), 0.85 (t, J=7.27, 3H).
^{13}C NMR (62.95 MHz, C6D6) δ = 208.83, 206.21, 173.20, 62.07, 58.42, 57.19, 50.06, 39.52, 38.54, 33.68, 29.91, 29.93, 21.49, 14.21.
IR (neat) 2996, 2910, 1720, 1692, 1495, 1435, 1376, 1320, 1287, 1175, 1003, 865, 690 cm^{-1}.
EI-MS (70eV) 252 (M^++1, 0.30), 208 (2.90), 153 (5.47), 152 (65.65), 125 (6.15), 115 (6.99), 114 (7.15), 110 (3.97), 96 (24.91), 84 (22.74), 71 (29.09), 68 (34.61), 55 (48.26), 43 (100).

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