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FURANS IN SYNTHESIS; STUDIES DIRECTED TOWARD THE SYNTHESIS OF GUAIANOLIDE, PSEUDOGUAIANOLIDE, AND TIGLANE DITERPENE NATURAL PRODUCTS

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MARK CHAD McMILLS

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FURANS IN SYNTHESIS; STUDIES DIRECTED TOWARD THE SYNTHESIS OF GUAIANOLIDE, PSEUDOGUAIANOLIDE, AND TIGLANE DITERPENE NATURAL PRODUCTS

By

Mark Chad McMills

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ABSTRACT

FURANS IN SYNTHESIS;
STUDIES DIRECTED TOWARD THE SYNTHESIS OF GUAIANOLIDE PSEUDOGUAIANOLIDE, AND TIGLANE DITERPENE NATURAL PRODUCTS

By

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The construction of the bicyclo[5.3.0]decane skeleton is important as the precursor to projected syntheses of the guaiane, pseudoguaiane, and tiglane classes of natural products. These compounds are of interest because of their broad spectrum of biological properties including cytotoxic, antineoplastic, and antileukemic activity. Other important biological properties include allergenic, antihelmenthic, contraceptive, molluscicidal, and antiinflammatory activity. This thesis describes entries into the bicyclo[5.3.0]decane system and approaches toward guaiane, and pseudoguaiane sesquiterpenes as well as the tiglane diterpenes. Central to the construction of these ring systems are the use of a suitably substituted furan acting as a cationic cyclization terminator in an annulative process. Use of the furyl moiety in cationic cyclizations will impart stereochemical and regiochemical control in the synthesis of guaianolide, pseudoguaianolide, and tiglane diterpene natural products. In addition, furan manipulation will then readily afford the requisite butyrolactone residue or 1,4 dicarbonyl system needed to complete this synthetic endeavor.

FOR CHAD WILLIAM AND MICHAEL MANDERSON
YOU LEFT FAR TOO SOON

ACKNOWLEDGMENTS

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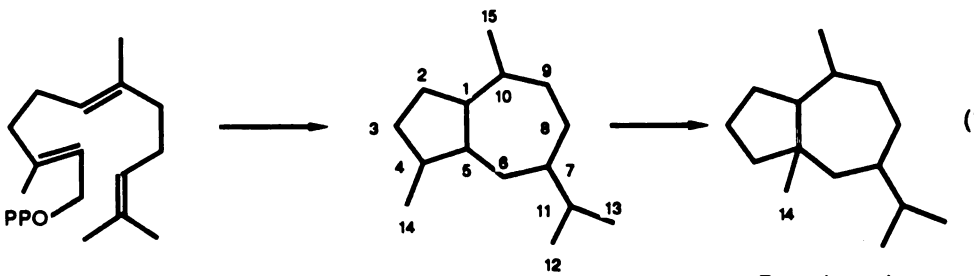
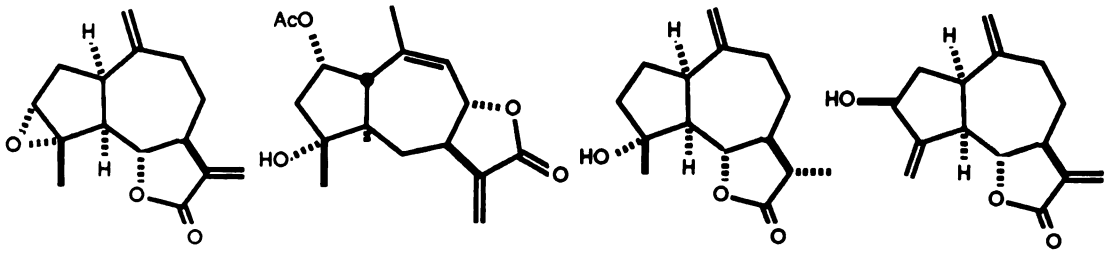
Introduction

The synthesis of the bicyclo[5.3.0]decane skeleton[1] is a crucial aspect in the construction of guaianolide[2] , pseudoguaianolide[3] , and tiglane diterpene[4] classes of natural products. The broad spectrum of biological activities exhibited by these materials and their scarcity in natural sources make facile entry into these classes important for both testing and clinical application. Potent biological properties include antitumor[5] , cytotoxic[6] , antineoplastic[7] , antileukemic[8] , as well as allergenic[9] , antihelmenthic[10], antifeedant[11] , contraceptive[12] , cocarcinogenic[13] , molluscicidal[14] and antiinflammatory activity[15]. These guaianolide and pseudoguaianolide sesquiterpene lactones are thought to be derived biosynthetically from farnesyl pyrophosphate **1** by a series of oxidations, cyclizations and rearrangements[16] (eqn. 1), a possibility which has previously been exploited for the preparation of severely underfunctionalized bicyclo[5.3.0]decanes.



1 Guaiane Pseudoguaiane (1)

The guaianolides are represented by estafiatin[17] **2**, gallardin[18]**3**, compressanolide[19] **4**, and zaluzanin C[20] **5** (figure 1).These compounds usually possess a *cis* ring fusion at C1-C5 and a butyrolactone moiety appended at C6-C7 or C7-C8. The pseudoguaianolides are a large family of sesquiterpene lactones produced by a rearrangement of the C14 methyl group from C4 to C5 as in Equation 1. These have the generalized structure of **A** and **B**(Figure2).



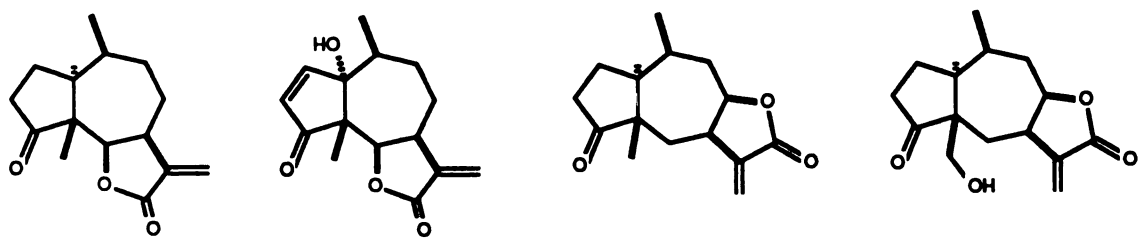
2 3 4 5

Figure 1. Guaianolides

A B

Figure 2. Generalized Pseudoguaianolides

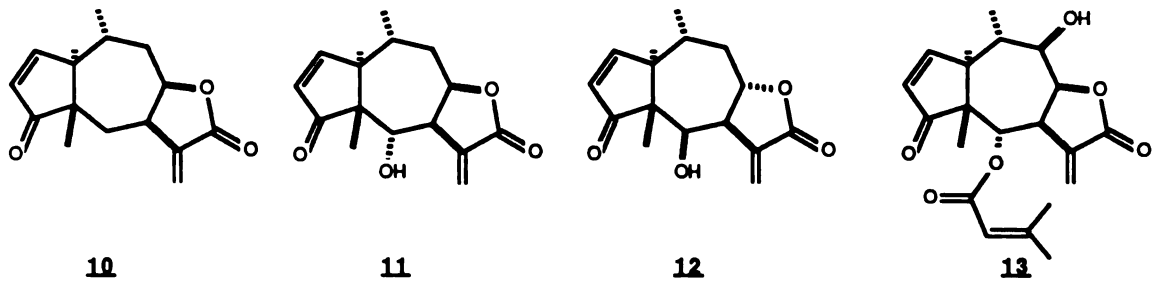
The ambrosanolides (structure **A**) exhibit the C15 methyl group in the β orientation ; less abundant are the helenanolides (as in **B**) with an α oriented C15 methyl group. The ambrosanolides are represented by damsin[21] **6**, parthenin[22] **7**, confertin[23] **8**, and rudmollin[24] **9** (Figure 3).



6 7 8 9

Figure 3. Ambrosanolides

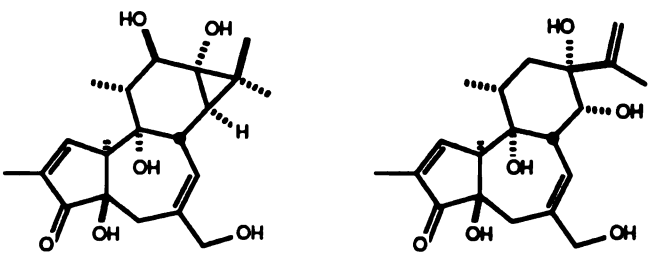
The helenanolides (Figure 4) are highly oxidized and usually possess intense biological activity. These are represented by aromatin[25] **10**, helenalin[26] **11**, mexicanin-I[27] **12** and fastigilin-C[28] **13**. Potent cytotoxic and antineoplastic



10 11 12 13

Figure 4. Helananolides

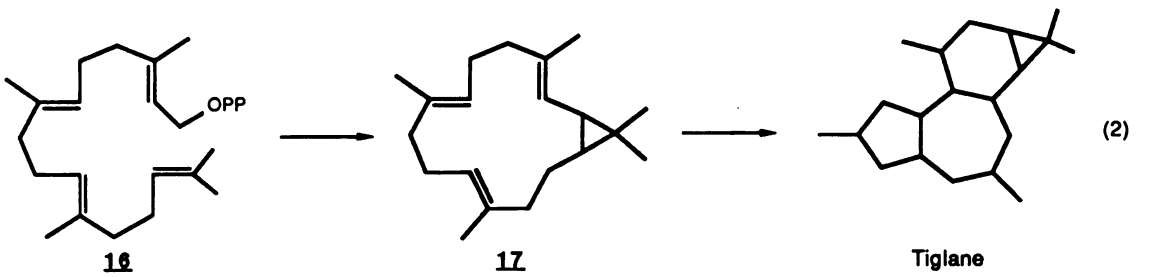
activity have been associated with fastigilin C **13**, one of the few compounds in this class with functionality at *each* carbon of the cycloheptane - B ring. Thus far, fastigilin C **13** has not yielded to total synthesis.



14 **15**

Figure 5. Tiglane Diterpenes

The tiglane diterpenes (Figure 5) represented by phorbol[29] **14**, and its derivative resiniferonol[30] **15**, are thought to arise biosynthetically from a geranyl geraniol derivative **16** to form Casbene **17** which further rearranges to the tiglane skeleton[31] (eqn. 2). Interest in this class of compounds is the result of their potent co-carcinogenic properties exhibited by a number of phorbol esters[32]. Wender[33] has published the first elegant synthesis of the [5.3.2.1] system, but a total synthesis of phorbol or its derivatives has not yet been accomplished.



16 17 Tiglane (2)

The majority of previous syntheses of guaiane and pseudoguaianes have focused on the stereocontrolled construction of the *5,7* ring system, followed by the addition of a butyrolactone moiety[34] . In the case of the tiglanes, Wender has reported the synthesis of a rigid *6,7* system, with a cyclopentyl ring being appended in the final stages. An alternative strategy utilizing the bicyclo[5.3.0]decane ring followed by a cyclohexyl annulation has not been examined. Given the common structural elements possessed by these systems, we will endeavor to develop the *5,7,6* system from a suitable bicyclo[5.3.0]decane system possessing a 1,4 dicarbonyl moiety for eventual cyclohexane annulation. A protocol which might allow the preparation of highly functionalized polycyclic systems, such as those mentioned above, with complete control of stereochemistry might result from the cationic cyclization of suitably functionalized furan derivatives. Our strategy is based on the use of furans in various capacities during a synthesis.

The furyl moiety can be thought of as a precursor to a wide variety of functional groups as is illustrated in Figure 6. Taken with the known and demonstrated ability of the furan ring system to function as a cationic cyclization terminator[35] this oxidation cascade could allow the ready construction of compounds **2-14**.

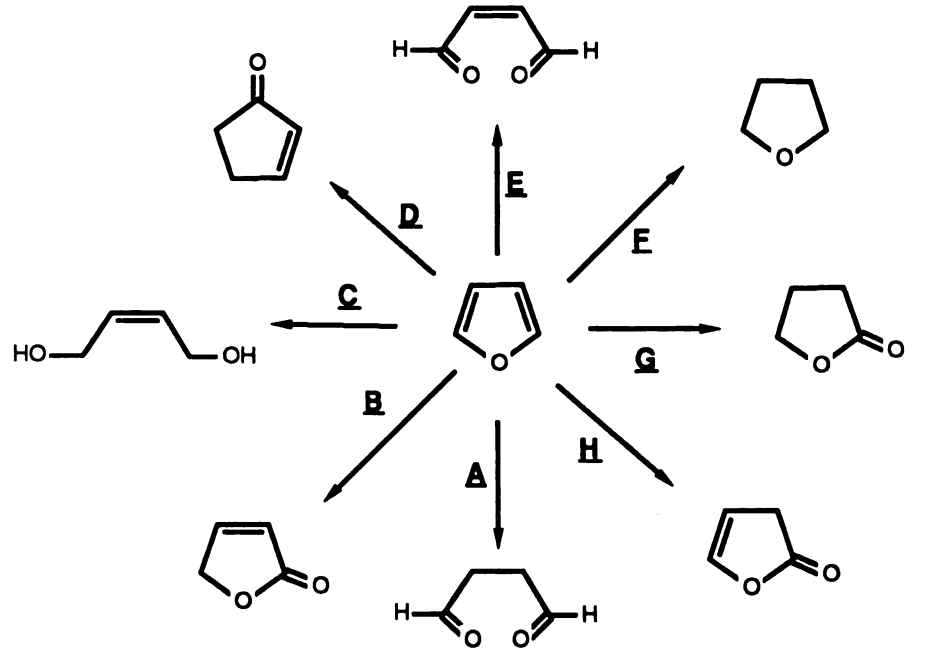
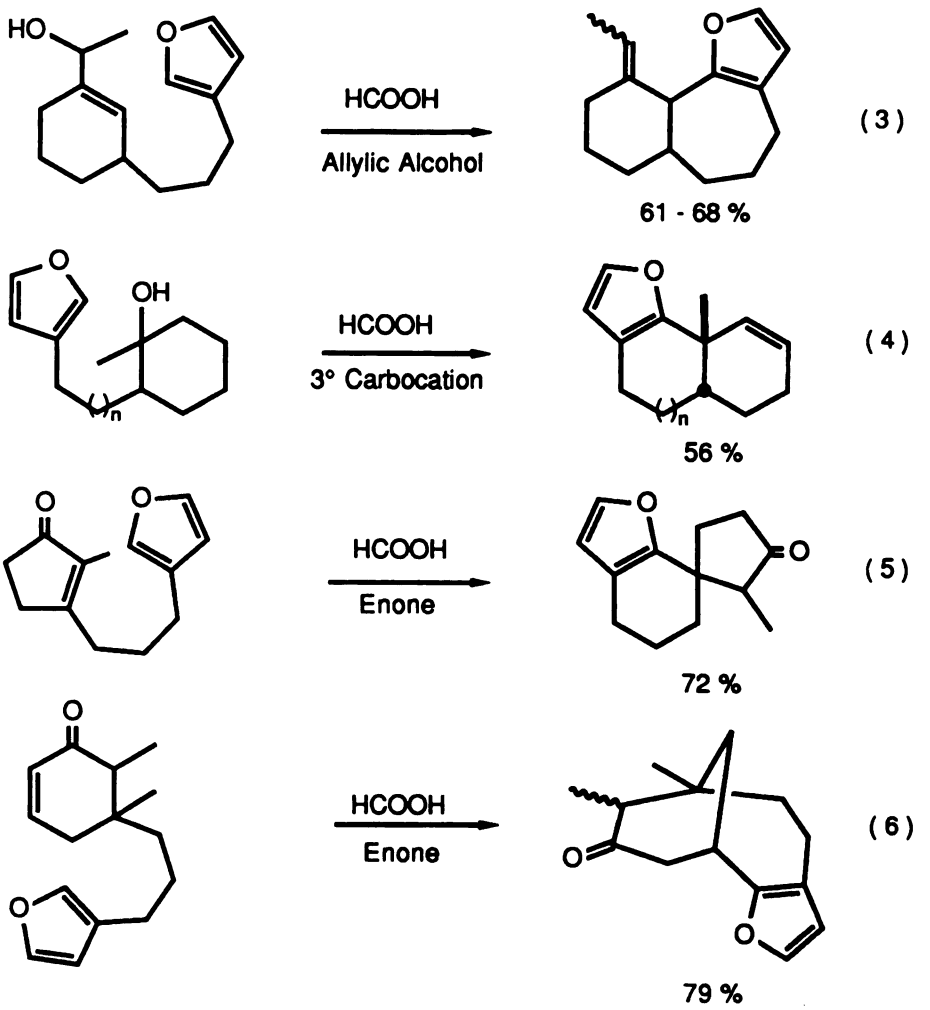


Figure 6. Furan Oxidation States

Tanis and Herrinton[36] have shown that furans can function as terminators in a variety of reaction conditions with several different functionalities used as initiators (eqn. 3,4,5,6). These cyclizations have also been studied using an epoxide initiator function. Furan terminated cationic cyclizations have now resulted in the synthesis of fused-, spirocyclic-, and bridged systems. Included among the relevant examples are the formal total synthesis of (+)- and (-)- aphidicolin[37] and (+/-)-nakafuran-9[38] .



Retrosynthetically, three different types of closures are necessary for the synthesis of guaianolides, pseudoguaianolides and tiglane diterpenes (Figure 7). We designate these as **Type A,B,** and **C.** The **Type A, B,** and **C** closures will terminate with a furyl anion equivalent; however the cyclopentane introduction might be accomplished with either sense of polarity .

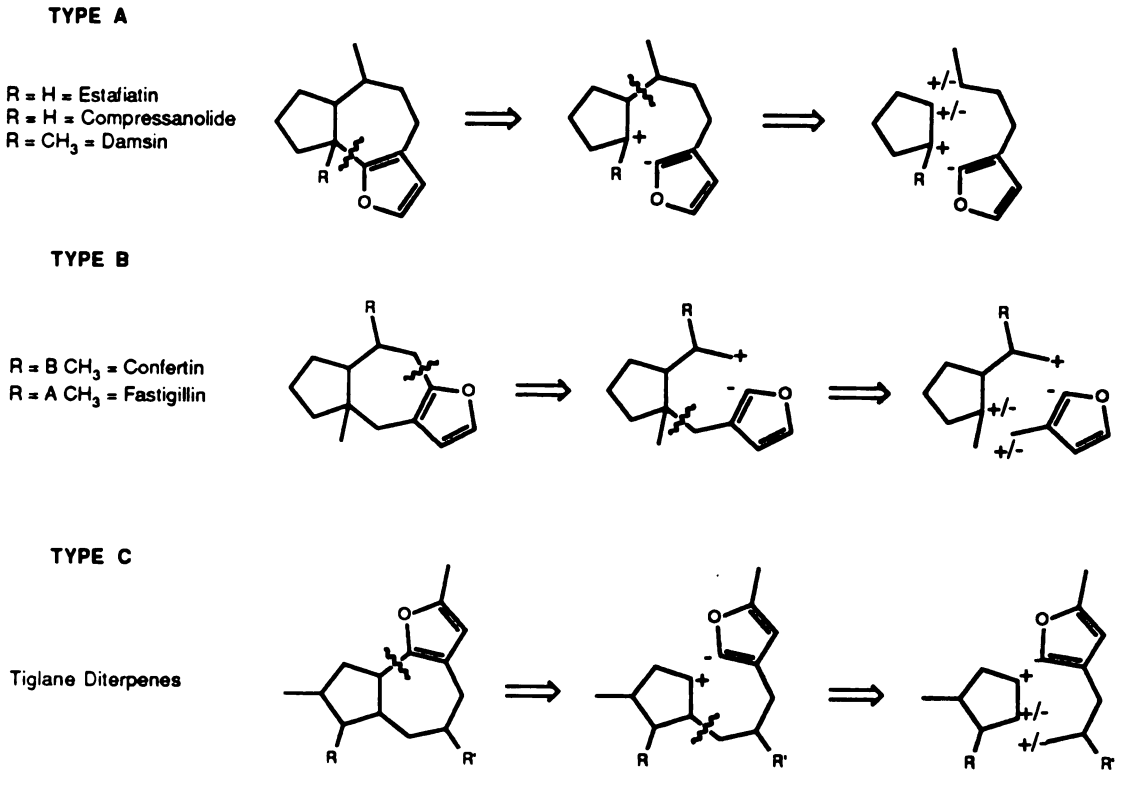
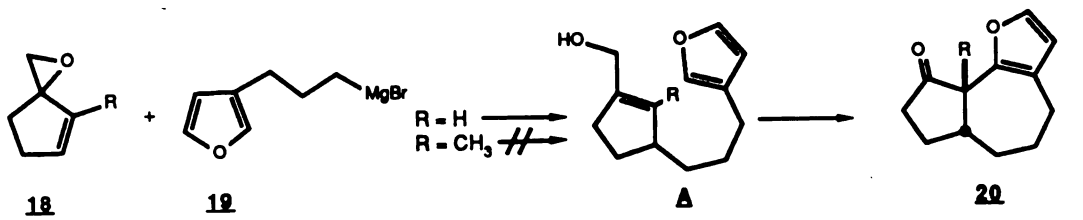


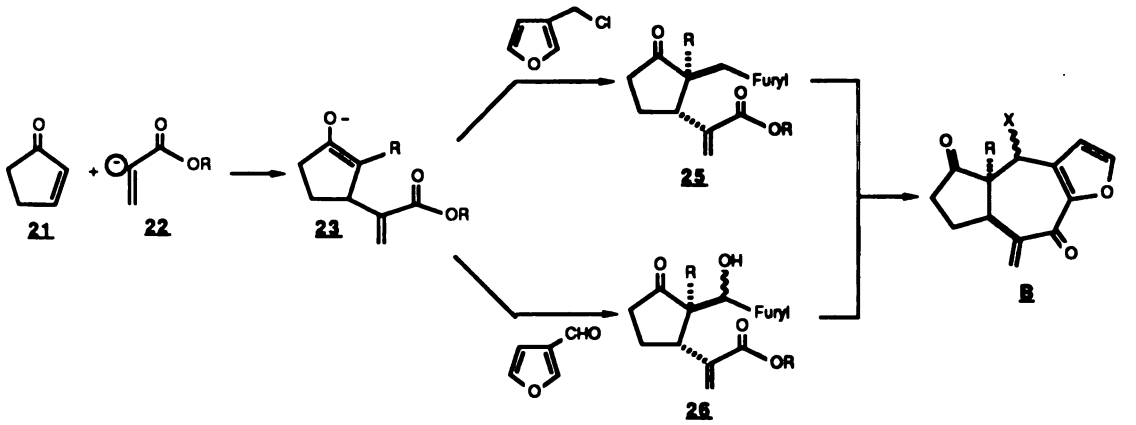
Figure 7. Generalized Cyclization Modes

The **Type A** closure could require a vicinal cyclopentane dication equivalent. We had previously investigated the use of a cyclopentenone derived vinyl spiroepoxide as such dication equivalents. The potential advantages of such an approach are regiochemical integrity and generality. That is, the first C-C bond construction *via* an S_N2' process (eqn. 7) generates the second potential electron deficient center , thus guaranteeing regiochemical integrity. The generality can be found in the use of this chemistry for either guaianolide, or pseudoguaianolide construction by simply using cyclopentenone, or 2-methylcyclopentenone for the spiro epoxide synthesis[39] .



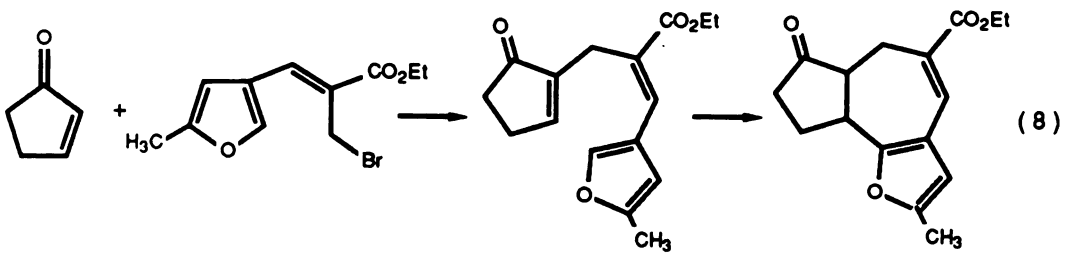
(7)

Type B closures require an addition to a cyclopentenone with either sense of polarity, then closure occurring distal to the cyclopentanone. One possible **Type B** closure is outlined in Scheme 1.



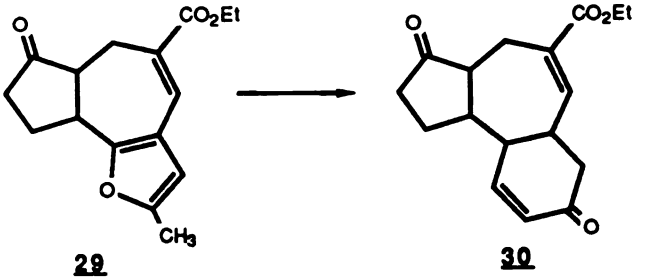
Scheme 1.

The **Type C** closure (eqn. 8) could afford a precursor to the tiglane diterpenes. In this case, we will examine an alkylative addition of an intact furyl acrylate **27** to give **28** followed by cationic closure to form the tiglane skeleton. Herein, we view the furan as a six member ring surrogate; providing the C ring after furan manipulation, one carbon homologation, and closure to the corresponding cyclohexenone (eqn. 9).



(8)

26 27 28 29

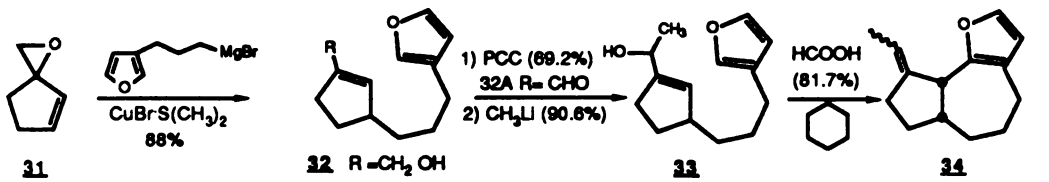


(9)

29 30

Results and Discussion

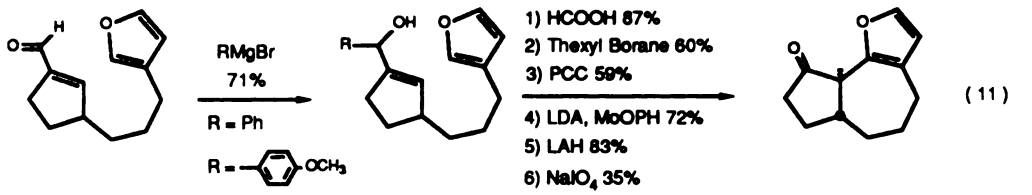
Our analysis (*vide infra*) has suggested that the guaianolides and pseudoguaianolides which fall into the **Type A** closure can be constructed *via* a furan terminated cationic cyclization in which the cyclopentane unit is introduced as a dication equivalent. Of critical importance in such a system is the regiochemical integrity of the carbon-carbon bond forming sequence. Therefore, we anticipate generating the second electron deficient center as a result of the chemistry employed in the initial carbon-carbon bond formation. As illustrated in equation 10, S_N2' addition of 3-(3-furyl)propylmagnesium bromide to **31** gave **32** (88%). Based on prior experience[40] , we oxidized **32** to aldehyde **32A** (69%) which furnished cyclization substrate **33** after addition of methyllithium(91%). The 2° alcohol smoothly cyclizes in a two phase, formic acid/cyclohexane mixture, to give the prototype bicyclo[5.3.0]decane system **34** in 50-70% yield. A slight modification[41] of the original procedure, adding catalytic p-toluene sulfonic acid to the formic acid/cyclohexane mixture increases the yields to 90%. We speculate that the initially formed formate ester is rapidly protonated and ionized in the presence of a stronger Bronsted acid, resulting in cyclization in shorter reaction times and less destruction of the product tricycle.



(10)

Unfortunately nearly all attempts to cleave the exocyclic olefin resulted in either no reaction or total destruction of starting material. We realized success only in a rather lengthy sequence (eqn. 11) involving ketone enolate hydroxylation, reduction to the corresponding vicinal diol and periodate

cleavage[42] . The low yields obtained caused considerable concern and prompted us to seek a shorter and higher yield alternative.



As an alternative, we sought a method that would not require a potentially troublesome carbon-carbon single or double bond cleavage. Given the requirement that we must carry the C-4 carbonyl into the sequence either intact (protected) or in a reduced oxidation state (OH); we considered the sequence outlined in Figure 8.

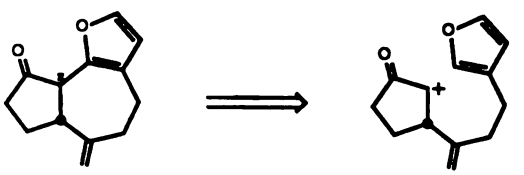
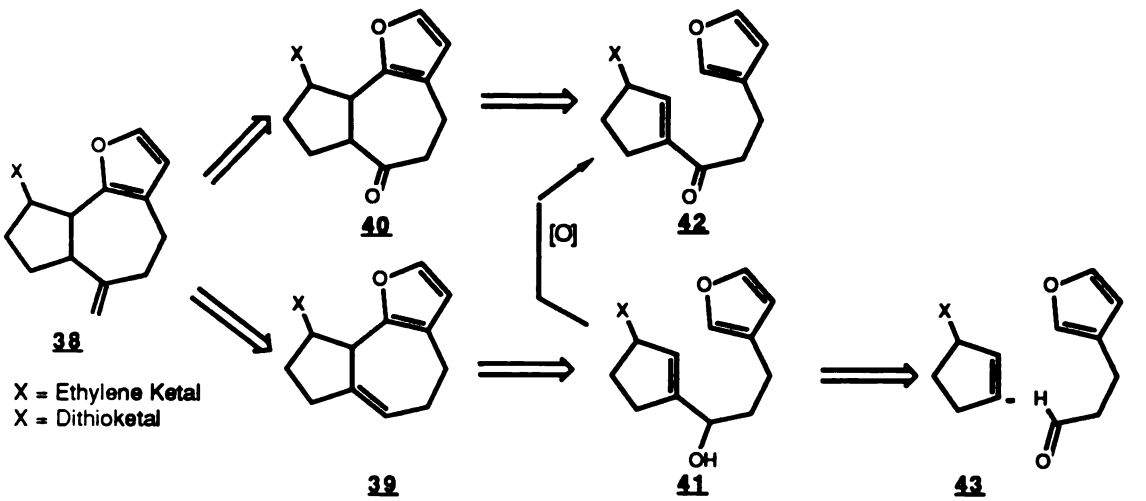


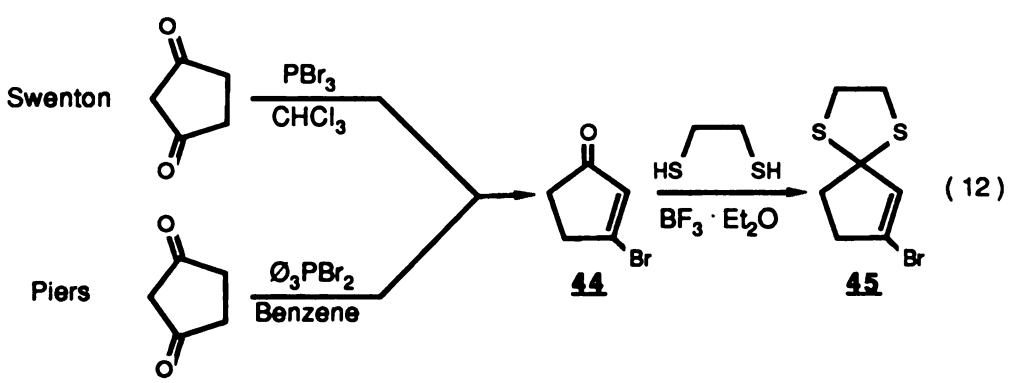
Figure 8. Retrosynthetic View

Although "enolonium" ion[43] equivalents are indeed known we did not consider this sequence further because the mildness of the furyl nucleophile is incompatible with the relatively unreactive enolonium ion equivalent of Wender and Marino. An alternative which would afford a similar molecule, without the necessity of employing a highly energetic α-keto cation is presented in Scheme 2. The crucial bond construction, then cyclization, is now to proceed *via* a cyclization initiator which is held entirely within the forming seven member ring.



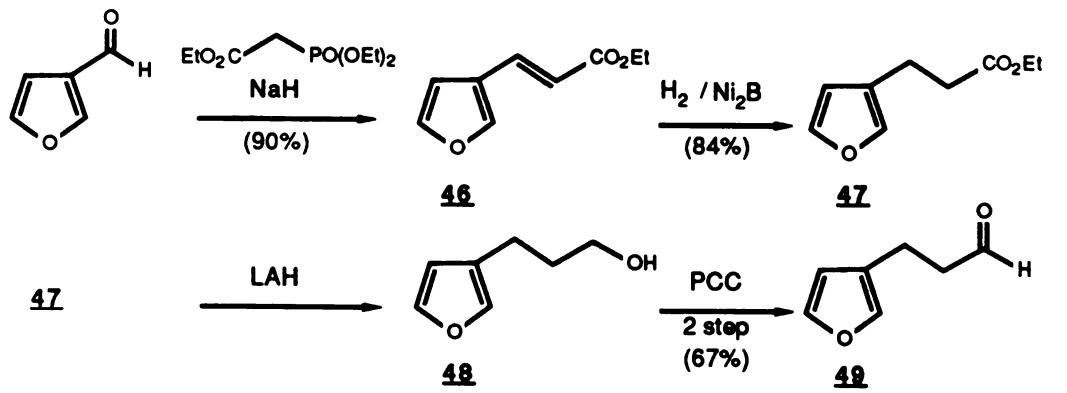
Scheme 2.

In the forward direction, this was accomplished using 1,3-cyclopentanedione as the cyclopentyl moiety and 3-(3-furyl)propanal as the remaining carbon skeleton for the cycloheptyl portion of the bicyclo[5.3.0]decane system. Bromination of 1,3 cyclopentanedione according to either Swenton[44] or Piers[44] (eqn. 11) gave 3-bromo-2-cyclopentenone **44** (56%), which was protected as the corresponding ethylene dithioketal **45** (60.3 %)[45] .



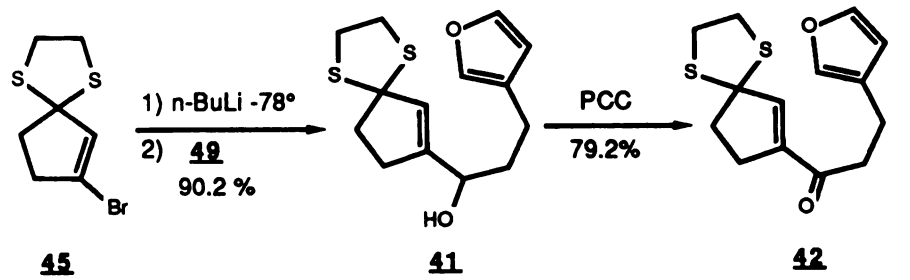
Vinyl bromide **45** will serve as the cyclopentenyl anion **43** depicted in Scheme 2. The requisite 3-(3-furyl)propanal is also readily prepared as described in equation 13. The Horner-Emmons reaction between sodio(triethyl)phosphonoacetate and 3-furaldehyde gives the ethyl-3-(3-furyl)acrylate **46** (90%) which is smoothly reduced to the corresponding

propionate ester with H_2/Ni_2B[46] to give **47** (84%). Reduction (LAH) followed by oxidation (PCC) of the 1° alcohol furnishes 3-(3-furyl)propanal **49** (67%)



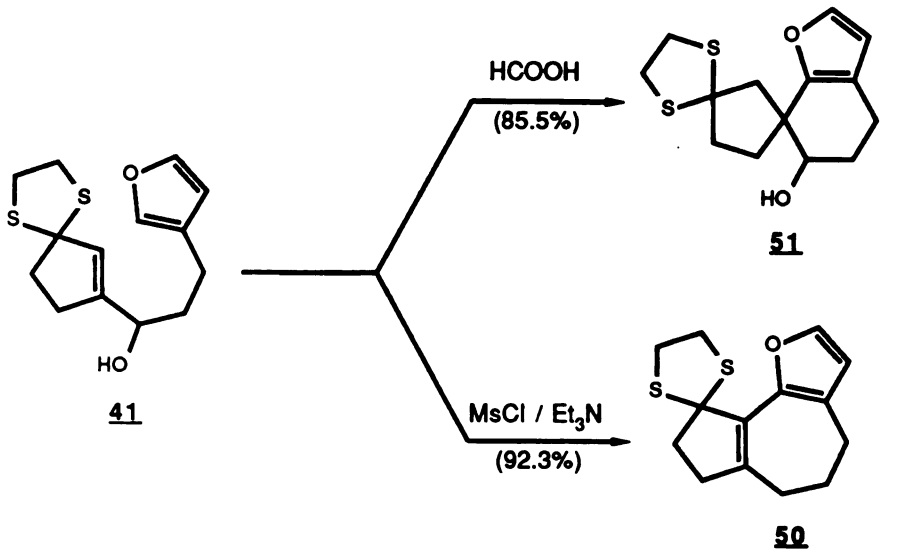
(13)

With these pieces in hand we turned our attention to the synthesis of the cyclization substrate. Metal halogen exchange (nBuLi,-78°C) and reaction with 3-(3-furyl)propanal afforded the allylic alcohol **41** in an excellent 90% purified yield (eqn. 14). We then



(14)

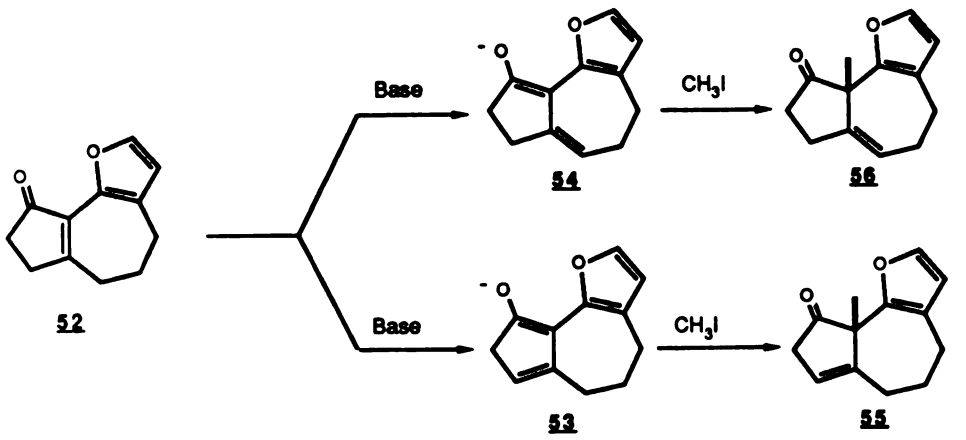
exposed **41** to "standard cyclization" conditions (HCOOH,cyclohexane, RT, 1-5 min.)[47] (eqn. 15). Using these standard conditions we obtained a less polar material in excellent yield (85.5%). The ^1H NMR spectrum of this material contains two doublets at high field (6.14 and 7.27 ppm), typical for a 2,3 disubstituted furan. We had anticipated observing the olefinic proton resonance of the trisubstituted double bond at ca. 5.00-6.00 ppm; instead we saw a doublet of doublets centered at 4.08 ppm which we assigned as a carbinol methine resonance. This led us to believe that we had not cyclized to the linearly fused [5.3.0] system **39** but instead to a spiro fused [4.5.0] system **51** (eqn.15).



(15)

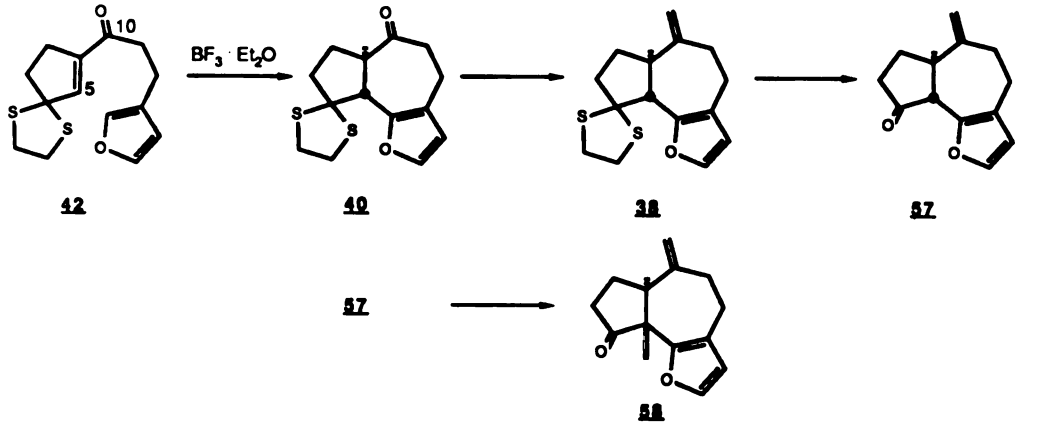
Support for this supposition was provided by the presence of an isolated AB system (α to the dithioketal) at 2.73 and 2.31 ppm. Further confirmation for the outcome was given by ^{13}C NMR with multiplicity analysis. This contained four singlets, three doublets and seven triplets, which corresponds to our proposed structure; also a hydroxyl band was found in the IR at 3650 cm^{-1}

The facility with which the spiro closure occurs suggests that the C-O bond is likely to be poorly disposed with respect to the olefin-pi system for protonation and ionization, and that instead the dithioketal is ruptured to afford a sulfur stabilized allyl cation leading ultimately to **51**. An alternative which should exclusively activate the C-O bond to cleavage was next examined. Exposure of **41** to mesyl chloride and triethylamine according to Chamberlin[48] furnished the desired bicyclo[5.3.0]decane ring system **50** (92%) with the double bond isomerized to the 1,5 position as confirmed by ^{1}H- and ^{13}C -NMR (eqn. 15). This was not the anticipated product; however, it may serve the same purpose as the desired deconjugated olefin should we be able to form the thermodynamic dienolate **54** and selectively alkylate at C-5 (Scheme 3) **56**. The alternative dienolate **55** would strand the C-C double bond in a useless C-1;C-2 position.



Scheme 3.

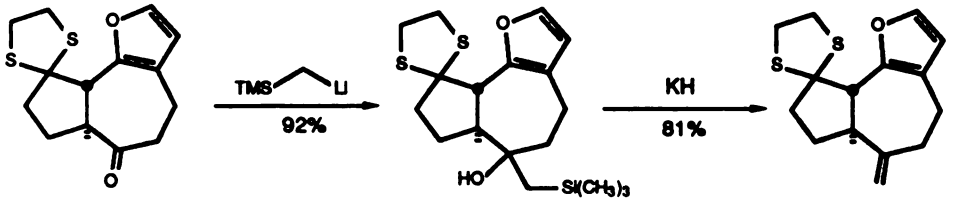
Preliminary MM2[49] calculations performed upon the dienes corresponding to the dienolates suggests that desired path to **56** is favored. Despite the "favorable" outcome of the MM2 study we were concerned that double bond placement in the actual system would be difficult to control. This caused us to question our control of C-10 stereochemistry. Given those doubts we elected to examine an enone initiated closure for the construction of the seven membered ring. In such a system we envisioned C-10 functionalization, followed by introduction of the C-5 methyl group *via* alkylation of the thermodynamic enolate (eqn. 16).



(16)

We had previously examined enone initiated furan terminated cyclizations[50] and found this route to be a productive technique for the construction of cyclic systems. Such a closure (equation 16) was believed to be more promising than those previously attempted as it held the enone initiator entirely within the forming cycle, thus reducing the degrees of freedom. In the event, oxidation of alcohol **41** with PCC gave enone **42**

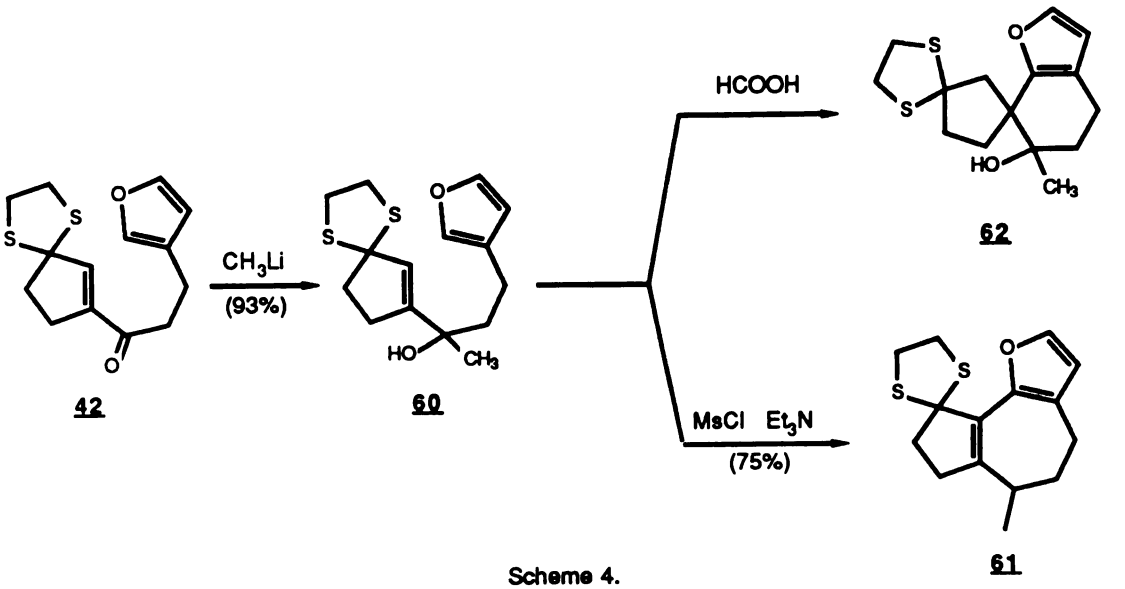
(79.2%, eqn 14) which was exposed to 10 equivalents of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to afford ketone **40** in 64% chromatographed yield. The ring fusion in equation 15, **40** is depicted as trans based upon the observation of a doublet at 3.66 ppm with a coupling constant J= 8.5 Hz, in good accord with the literature[51] range of 8.5 to 10.5 Hz for trans fused ketones related to **40**. The minor isomer shows a doublet at 3.12 ppm with a coupling constant of approximately 13 Hz. This assignment is also supported by MM2 calculations in which product **40** is found to be more stable than its *cis* congener by ca. 2 kcal/mole. Conversion of **40** to a methyl precursor **38** has been accomplished using Peterson olefination[52] technology (equation 17). Conversion of **38** to guaianolides and pseudoguaianolides is currently being pursued; the results will be reported in due course.



(17)

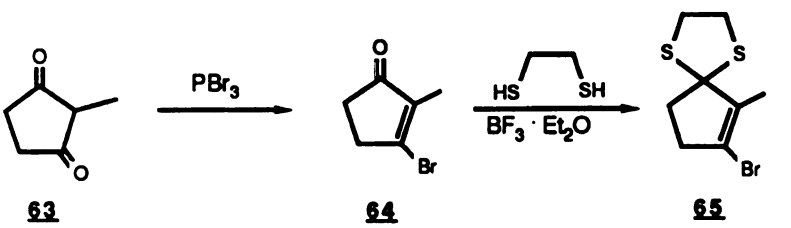
40 **59** **38**

Having successfully constructed our first generation 10-des methyl compounds, we next studied the cyclization of substrates bearing the requisite 10-methyl. Toward that end, addition of methyllithium to enone **42** gave the tertiary alcohol **60**(93%). This compound upon addition of formic acid afforded not the expected bicyclo[5.3.0]decane, but gave instead the spirocyclic 3° alcohol **62** (Scheme 4). Again we attribute the isolation of the spirocyclic material to the same factors described previously (*vide supra*). Application of direct hydroxyl activation *via* exposure of **60** to mesyl chloride-triethylamine led to the derivative bicyclo[5.3.0]decane system (Scheme 4) **61** (75 %), again with the double bond isomerized to the 1,5 position.



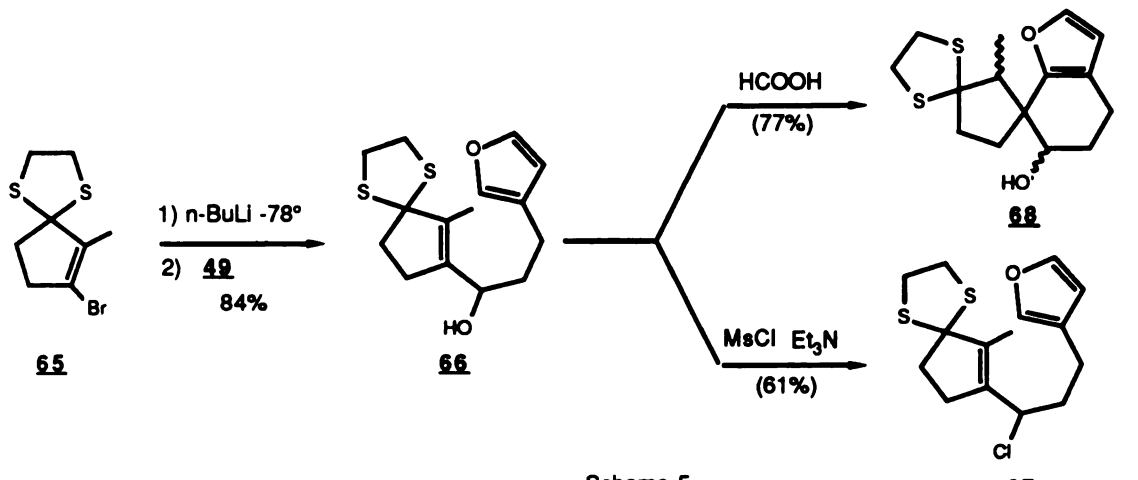
Scheme 4.

We have also examined the possibility of introduction of the pseudoguaiane C-5 methyl group prior to cyclization. In this case 2-methylcyclopentanedione serves as the source of the 5-membered ring. Careful bromination (eqn. 18) of 2-methylcyclopentanedione **63** affords the 3-bromo enone **64** (80.6%) which gives thioketal **65** after exposure to ethanedithiol and $BF_3 \cdot OEt_2$ (72%)[53] . Treatment with n-BuLi and reaction of the resulting anion with 3-(3-furyl)propanal leads to the desired allylic alcohol **66** (79.1%; Scheme 4).



(18)

Unfortunately our preliminary studies have indicated that neither acid induced cyclization or mesyl chloride-triethylamine provided a bicyclo[5.3.0]decane system (Scheme 5). These reaction conditions afforded a spirocyclic analog **68** (77.3%) and an allylic chloride equivalent **67** (60.8%) of the starting material respectively. Again allylic strain is the likely cause of the lack of desired reactivity of this allylic alcohol.



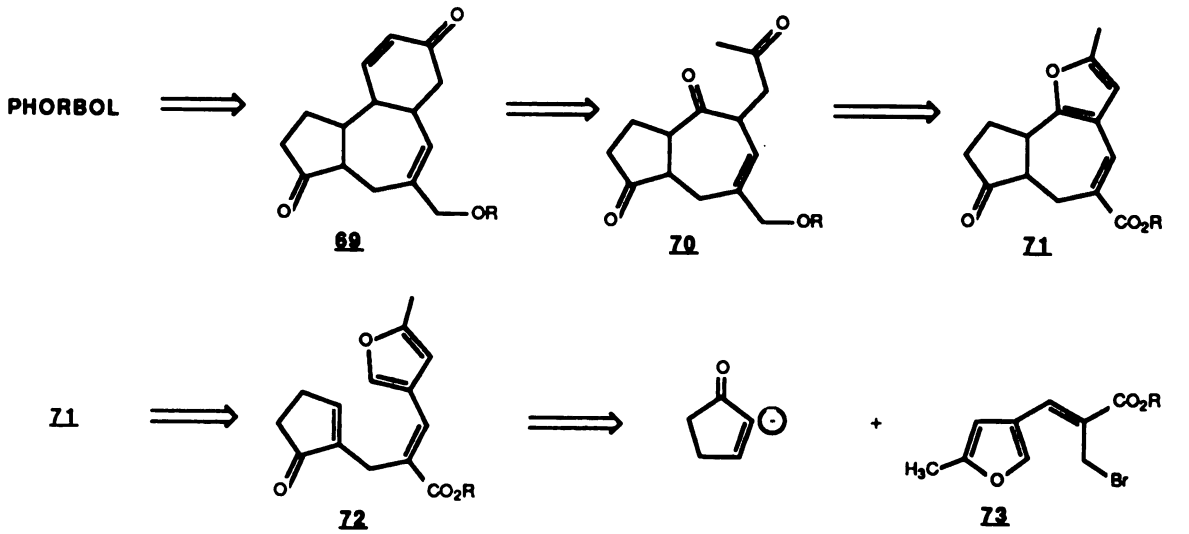
65 66 68 67

Scheme 5.

In this section we have shown the ease of forming the bicyclo[5.3.0]decane system, if a judicious choice of cyclization substrate is made. Provided the deprotection of the enone initiated cyclization product **40** can be accomplished, we can routinely synthesize gram quantities of advanced intermediates. We anticipate converting this material to a number of the simpler guaianolide and pseudoguaianolides such as damsin **6**, zaluzanin **5**, estafiatin **2**, and parthenin **8**.

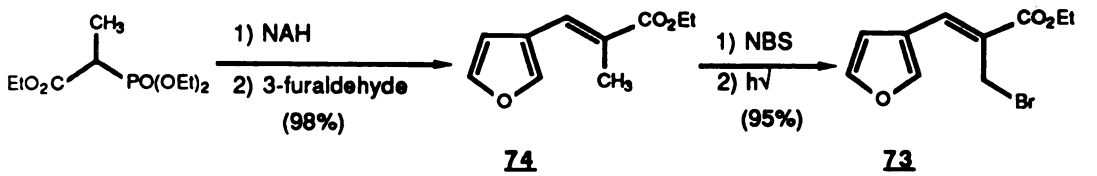
An Approach To the Synthesis of Tiglane Diterpenes

The tiglane diterpenes provide attractive targets for total chemical synthesis and thus have attracted considerable interest[54]. We have considered the possibility (Scheme 6) of constructing this basic tiglane skeleton *via* furan terminated cationic cyclization followed by elaboration of the trisubstituted furan containing product to the requisite six-membered **D** ring. This approach is presented retrosynthetically in Scheme 6.



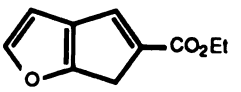
Scheme 6.

In order to prepare the desired cyclization substrate we must synthesize the operational equivalent of the depicted cyclopentenone anion and couple this with a relatively complex furan containing bromomethacrylate **73**. A model bromomethacrylate was prepared in straightforward fashion as described in equation 19.



(19)

Horner-Emmons reaction of triethylphosphonopropionate with 3-furaldehyde furnished **74** (98 %). Bromination was realized upon exposure of **74** to NBS, CCl_4, hν to give the unstable allylic bromide **73** (94.8 %). With **73** in hand, we examined its coupling with anion **76**. Many attempts to alkylate the ethylene ketal of 2-lithio-2-cyclopentenone[55] were made to no avail. After a number of attempts had failed, we examined the bromofuryl methacrylate and found that it had reacted in the dark at -20° C. Tentatively this product has been assigned as the cyclopentanoid **75** listed below. Conversion of the bromide **73** to **75** was likely accomplished via a radical like cyclization[56] .



75

The difficulties encountered in this least motion approach caused us to consider preparing **72** in two discreet steps. First, the addition of a propionate equivalent; and second, an aldol type addition-dehydration. Our initial question was the design of a propionate equivalent which could function both as an electrophile and then as a nucleophile (Figure 9).

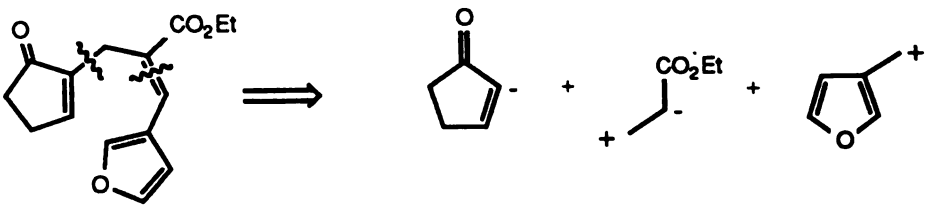
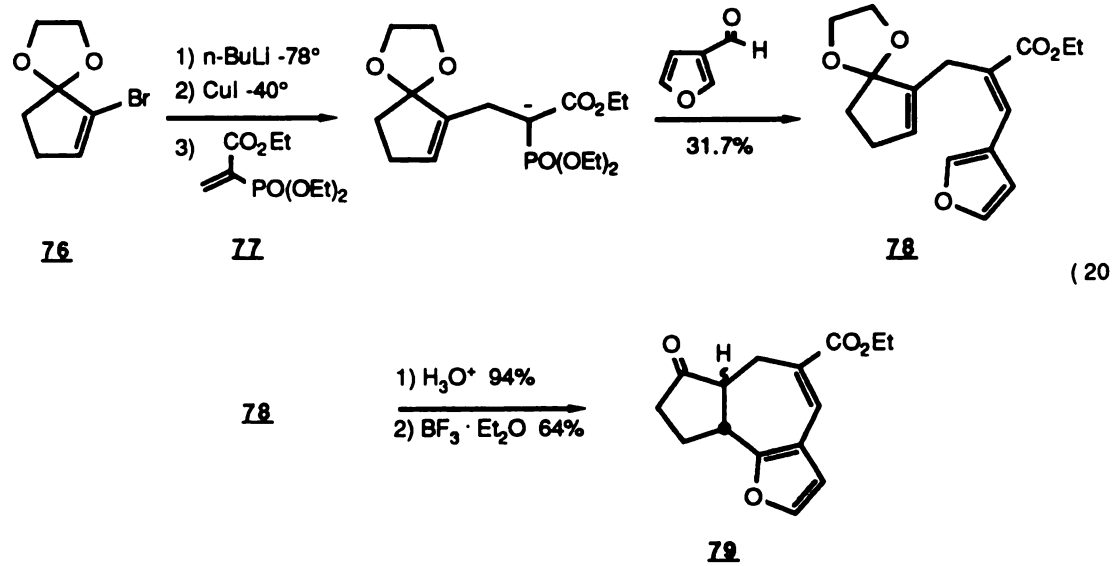
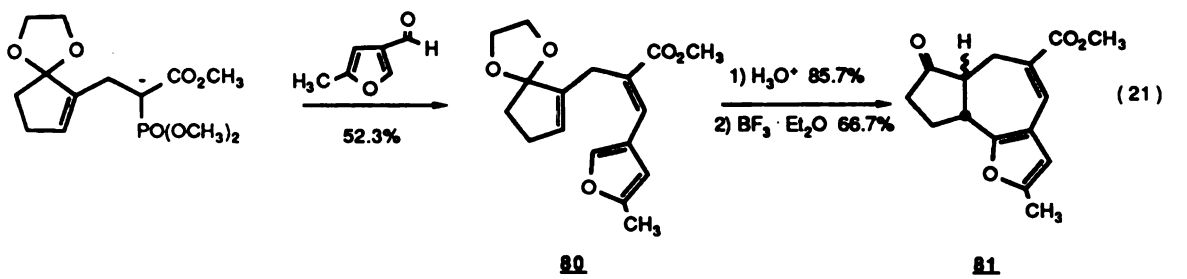


Figure 9. Tiglane Disconnection

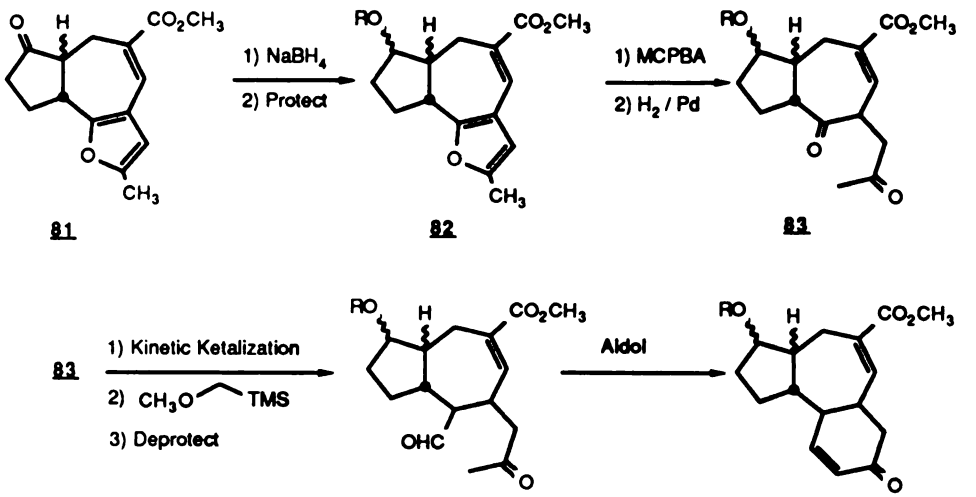
A solution was suggested by the work of Semmelhack[57] and Heathcock[58]. We considered employing triethyl-2-phosphonoacrylate **77** as the electrophile/nucleophile in a one pot conjugate addition Horner-Emmons sequence. Treatment of Smith's[59] cyclopentenyl bromide **76** with n-BuLi followed by CuI afforded the corresponding cuprate to which triethyl-2-phosphonoacrylate was added. After 2 hours at -78°C and 1 hour at 0°C, 3-furaldehyde was added to give **78** (35%). Ketal hydrolysis and cyclization with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 gave **79** in an excellent 64% yield for the two step process (eqn. 20).



Having demonstrated the utility of this protocol, we have extended the methodology to include a methyl group on the furan prior to cyclization. A similar process was followed with the exception of the exchange of 5-methyl-3-furaldehyde for 3-furaldehyde and trimethyl-2-phosphonoacrylate instead of the triethyl ester (eqn. 21).



After construction of the bicyclo[5.3.0]decane system we anticipate concluding our efforts in the synthesis of resiniferonol **15** as outlined in equation 22.



TYPE B Cyclization Toward Guaianolides

The final mode of cyclization to be investigated has been termed "**Type B**". The **Type B** closure illustrated in Figure 10 should prove useful for the synthesis of confertin and fastigilin like pseudoguaianolides.

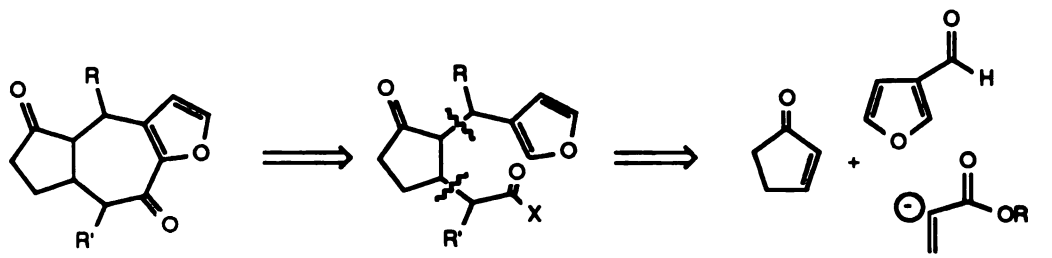
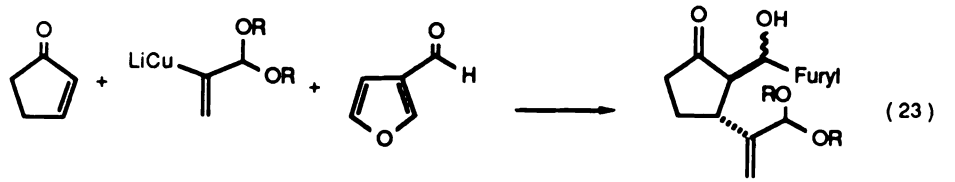


Figure 10. Retrosynthetic Disconnection

Our initial plan (eq 23) consisted of a Michael addition of the cuprate prepared from 2-bromoacrolein to cyclopentenone **86** or 2-methylcyclopentenone and subsequent aldol addition of 3-furaldehyde. Marino[60] has shown the utility of the anion of protected 2-bromoacrolein **87**, however, under no circumstance could we detect any Michael products. After many attempts, this route was abandoned.



(23)

86 87 88

We then examined possible alternatives for the introduction of a propionate or propionaldehyde equivalent. The placement of a double bond at the 5,6 position, and the reduction of the C10-15 olefin of **88** would render this the product of an Ireland ester enolate Claisen reaction[61] minus the C-6 hydoxyl moiety (Figure 11). Our first efforts were directed toward the synthesis of a simple model system without the furan present.

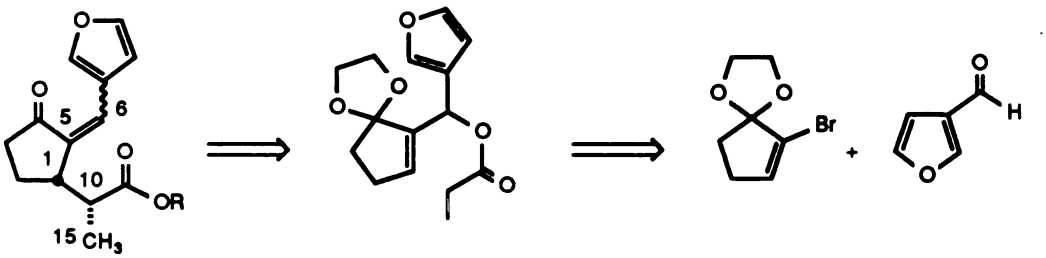
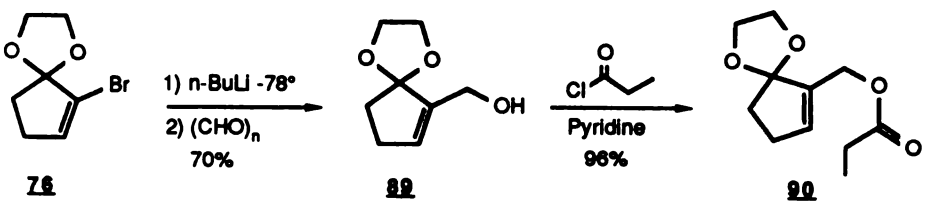


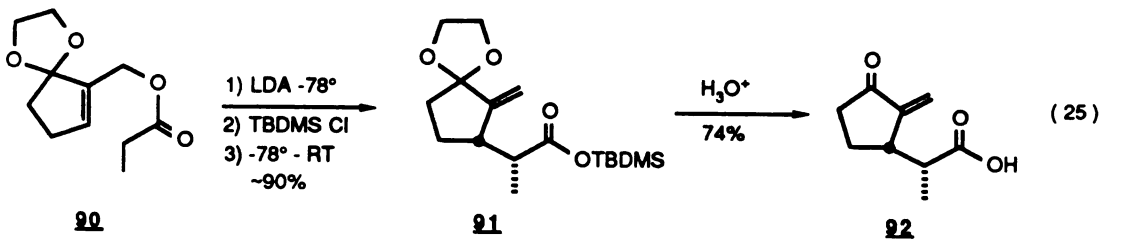
Figure 11. Enolate Claisen Disconnection

The synthesis begins with the protected 2-Bromocyclopentenone **76** as outlined in equation 24. Treatment of **76** with n-BuLi followed by formaldehyde afforded alcohol **89** (70%) which led to propionate ester **90** (96%). With the Claisen precursor **90** in hand we studied the sigmatropic rearrangement sequence leading to the α-methylene-cyclopentenone depicted in equation 25. We found that the reaction proceeded to afford a 10:1 diastereomeric ratio with the stereochemistry anticipated to be as shown.



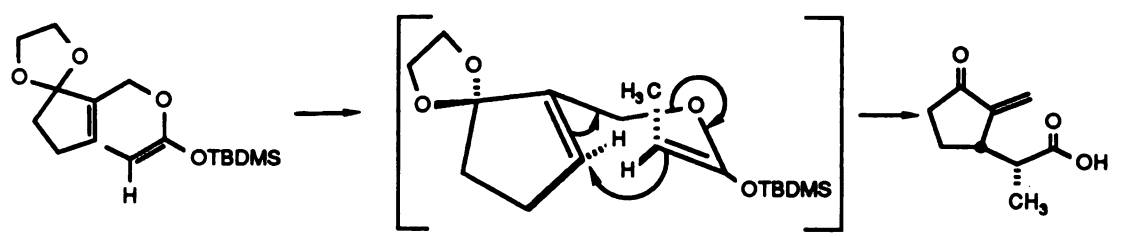
(24)

76 89 90



90 91 92

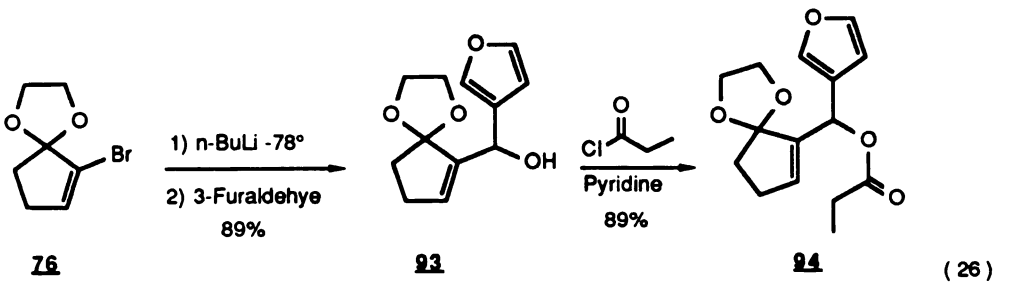
This outcome can be accounted for by assuming the formation of the E-enolate[62] (LDA no HMPA) and rearrangement of the ketene acetal via the six membered Zimmerman-Traxler[63] chair like transition state as previously described by Ireland[64] (Figure 12).



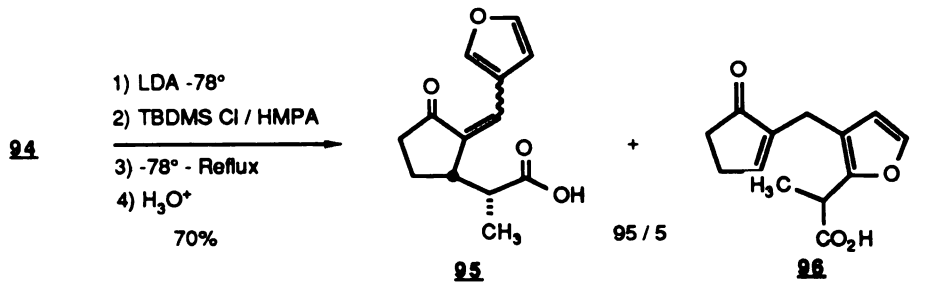
93 92

Figure 12. Enolate Claisen Stereochemistry

In a similar fashion we synthesized a compound with the furyl residue present (eqn.26). The substitution of 3-furaldehyde for formaldehyde in the initial organometallic capture gave alcohol **93** (89%) This alcohol was then converted to the corresponding propionate ester and then subjected to the Ireland conditions. This sequence provided not only the expected acid **95** (70%), but also a small amount of a second rearrangement product **96** which results from an enolate Claisen rearrangement through the furyl residue[65] (Figure 13).



(26)



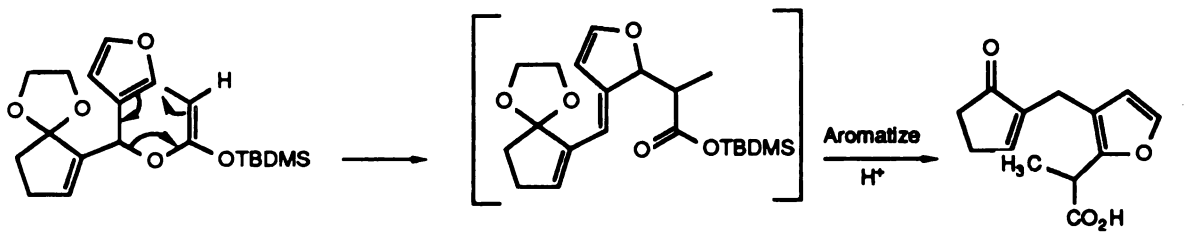
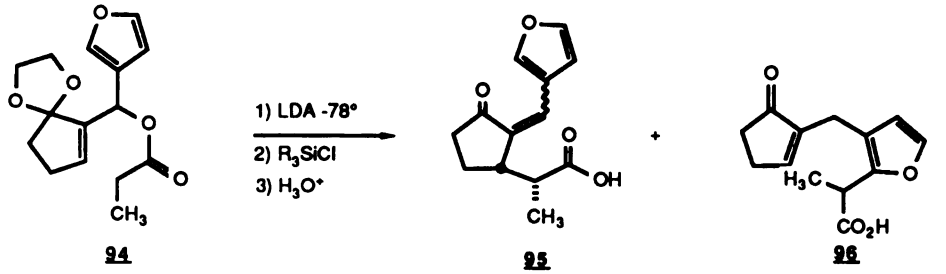


Figure 13. Furan Enolate Claisen

We then studied the effect of the silyl function in the ketene acetal upon the course of the rearrangement. Table 1 shows our results. It appears, from this limited number of examples explored, that the use of t-BuMe_2SiCl offers an optimum ratio of desired to undesired rearrangement products.

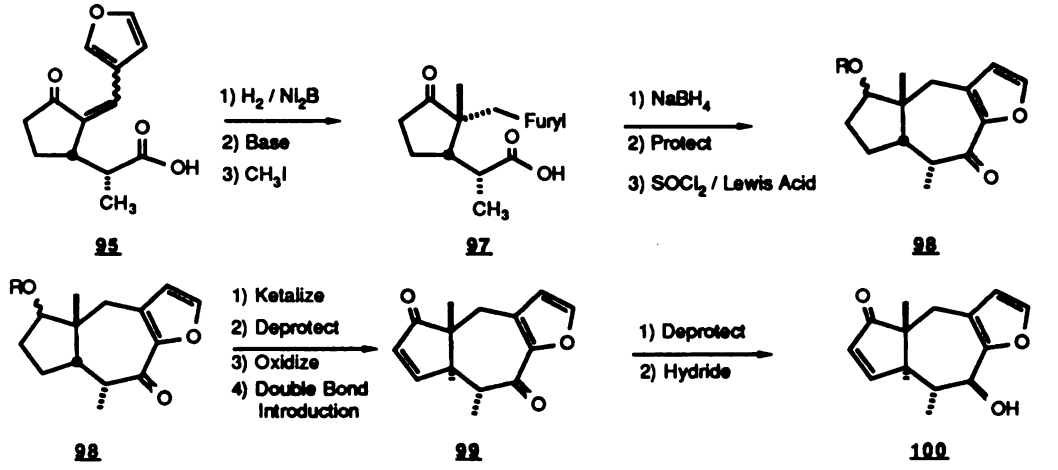
Table 1. Effect of Silyl Substituent



94 95 96

R_3SiCl	Yield	95/96
t-BuMe_2	69%	95:5
$(Me)_3$	79%	75:25
$(i\text{-}Pr)_3$	73%	20:80

Presently we are studying the synthesis of several complex compounds such as fastigilin C from **95**. A possible conversion of **95** to fastigilin is outlined in equation 27.



95 97 98 98 99 100 (27)

Conclusions

We have shown through examples in this thesis, that furan is a versatile synthon for varied reaction sequences ultimately leading to the bicyclo[5.3.0]decane ring system. Various placements of furan, and differing cyclization modes can lead ultimately to most members of the guaiane, pseudoguaiane, or tiglane classes of natural products. Work is continuing to cleave the thioketal protecting group to reveal a nearly complete pseudoguaiane like skeleton. Alkylation of the probable thermodynamic enolate and subsequent unmasking of the of the furan should give us easy access to compounds such as damsin and parthenin.

In the tiglane series we are now close to a phorbol like system. To complete the construction of the *5,7,6* system, we must open the furan, homologate one carbon, and ring close to a six member ring. With the cyclohexenone in place, we are set for addition of oxygen at C4, C9, and C14. Conjugate addition 1,4 to the enone will provide the necessary methyl group at C . Finally, addition of an isopropenyl anion to the remaining ketone of the initial enone will give the final hydroxyl group.

Type C cyclization is the least well established mode of the three. We are very close to a cyclized substrate, but have not closed to the cyclic compound as yet. Of paramount importance will be finding conditions that will cyclize , but not destroy the furan terminator. The ester enolate Claisen will be used for the synthesis of the unsubstituted compound deoxyfastigilin. Unfortunately this method may not be practical for the synthesis of fastigilin C. A new Michael variant by Mukaiyama may provide easy access to a compound using a thioester as the initiator function. This compound would also have the correct stereochemistry set at the ring fusion relative to the pendant methyl function. This will leave us with an alcohol that can be oxidized and reduced for the final stereocenter in fastigilin C. If these possibilities fail we can modify the product of the ester enolate reaction for the introduction of a hydroxyl group. These advances have made our

program in furan chemistry applicable to a great variety of synthetic targets which complement current methodology.

EXPERIMENTAL SECTION

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 (TMSCl), 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 a Perkin-Elmer Model 167 spectrometer with polystyrene as standard. Proton magnetic resonance spectra (^1H 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, or a Bruker WM-300 at 300 MHz as mentioned in deuteriochloroform 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, m = multiplet, a = apparent), coupling constant (Hz), integration. Electron impact (EI-MS, 70 ev) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. Gas chromatography was conducted on a Hewlett-Packard 5880 system using a methyl silicone 30 meter column.

Flash column chromatography was performed according to the method of Still *et. al.* [66] using Merck silica gel and eluted with solvents mentioned. The column outer diameter (OD) is listed in millimeters.

3-bromocyclopentenone 44.

To 1,3-cyclopentanedione (10.0g, 102.0 mmol) in $CHCl_3$ (150 mL) is added phosphorus tribromide (19.38 mL, 204.1 mmol, 2.0 eq) in one portion. The resulting suspension was refluxed for 19hr., cooled, cast into ice/water (500 mL), extracted with $CHCl_3$ (100 mL), the organic phases combined, dried ($MgSO_4$), and concentrated. Chromatography of the residue on a column of silica gel (150g, 230-400 mesh, 40mm OD, ether-hexane, 1:1, 25 mL fractions) using the flash technique gave **44** (10.88g, 66.3%) as a low melting solid.
^1H NMR (80 MHz, $CDCl_3$) δ= 6.42 (t, J=1.93 Hz, 1H), 3.10-2.90 (m, 2H), 2.65-2.48 (m, 2H)

1-dithianyl-3-bromo-2-cyclopentene 45.

To a round bottom flask is added bromoenone **44** (5.43g, 33.75 mmol), ethanedithiol (3.68 mL, 43.87 mmol, 1.3eq), and 4A molecular sieves (10g). To this solution was added $BF_3{\cdot}OEt_2$ (0.581 mL, 4.72 mmol) over 5 min., stirred 12 hr., quenched with sat'd. NH_4Cl (30 mL), extracted with $CHCl_3$ (50 mL), the organic phases combined, dried ($MgSO_4$), and evaporated in vacuo. The product was chromatographed on a column of silica (90g, 230-400 mesh, 30mm OD, ether-hexane, 1:1, 20 mL fractions) using the flash technique gave **45** (4.83g, 60.3%) as a fluffy white solid.
^1H NMR (80 MHz, $CDCl_3$) δ= 5.95 (t, J= 1.96 Hz, 1H), 3.40 (s, 4H), 2.78-2.65 (m, 4H)

3-(3-furyl)-2-ethylacrylate 46.

To oil free NaH (11.52g, 0.48 mole,washed 3x with hexane) covered with dry ether (1L) was added triethyl phosphonoacetate (87.4g, 0.48 mole) in 250mL ether was added dropwise over a 2 hr. period. Stirring was continued for an additional 4 hrs.; then 3-(3-furyl)propanal (34.56 mL, 0.4 mole) in 100 mL ether was added dropwise over 1 hr. The reaction was stirred overnight, quenched with brine(400 mL), the mixture was separated,the aqueous phase extracted with hexane(500 mL), the combined phases were dried (Na_2SO_4),

for an additional 4 hrs.; then 3-(3-furyl)propanal (34.56 mL, 0.4 mole) in 100 mL ether was added dropwise over 1 hr. The reaction was stirred overnight, quenched with brine(400 mL), the mixture was separated,the aqueous phase extracted with hexane(500 mL), the combined phases were dried (Na_2SO_4), and concentrated. Distillation of the residual liquid(88-90°C, 6mm) gave 70.86 (88.9%) of **46** as a water white liquid.
^1H NMR (80 MHz, $CDCl_3$) δ= 7.63 (bs, 1H), 7.58 (d, J=15.8 Hz, 1H), 7.40 (m, 1H), 6.55 (bs, 1H) ,6.13 (d, J=15.8 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 1.30 (t, J=7.2 Hz, 3H)

3-(3-furyl)-3-ethylpropionate **47.**

A Parr Hydrogenation bottle (500 mL) was charged with $Ni(OAC)_2.4H2O$ (4.98g. 0.02 mole) and 95% ethanol(100 mL). To the mixture was added $NaBH_4$ in ethanol (20mL, 1.0M 4.0g $NaBH_4$, 95 mL EtOH, 5 mL 2.0 M NaOH). Evolution of H_2 was complete within 1 hr., then 3-(3-furyl)ethylacrylate **46** (33.20g, 0.20 mole) in EtOH(50mL) was added in one portion. The mixture was hydrogenated under 30 psi of H_2, until uptake was complete (5 hr.). The catalyst was removed by filtration through a pad of celite, the filter cake washed with EtOH(100 mL), the filtrate diluted with brine(500 mL), extracted with ether/hexane(500 mL,1:4), dried (Na_2SO_4), and concentrated to give **47** as a colorless oil (31.56g, 93.9%) which was used without further purification.
^1H NMR (80 MHz, $CDCl_3$) δ= 7.30 (t, J=1.86 Hz, 1H), 7.20 (m, 1H), 6.23 (m, 1H), 4.10 (q, J=7.25 Hz, 1H), 3.00-2.15 (m, 4H), 1.,21 (t, J=7.25 Hz, 1H)
EI-MS (70eV) m/e= 169 (M^++1, 30.02) 168 (M^+, 59.84) 127 (12.17) 123 (23.69) 96 (10.38) 95 (100) 94 (32.29) 83 (17.38) 82 (12.02) 81 (55) 67 (27.84) 65 (19.31) 53 (12.71)

Thioketal allylic alcohol **41.**

To a solution of thioketal **45** (1.0g, 4.22 mmole) in dry THF(15 mL) cooled in a dry ice-acetone bath was added n-BuLi (2.81 mL, 6.75 mmol, 2.4 M) dropwise over 15 min. The solution was stirred at -78°C for 1.5 hrs., then 3-(3-furyl)propanal **49** (0.68g, 5.48 mmol) in THF(5 mL) was cooled to -78°C and added via cannula over 10 min. After 2 hrs. at -78°C the reaction was quenched with sat'd. $NaHCO_3$ (20 mL) , extracted with ether (3x15 mL), the combined organics were dried ($MgSO_4$), and evaporated *in vacuo* to yield a

yellow oil. The oil was purified by chromatography on a column of silica gel (50g, 230-400 mesh, 30mm OD, 1:1, ether-hexane, 20 mL fractions) using the flash technique to yield 1.07g (90.8%) **41** of a slightly yellow oil.
^{1}H NMR (250 MHz, C_6D_6) δ= 7.12 (t, J=1.66 Hz, 1H), 7.05 (m, 1H), 6.05 (m, 1H), 5.76 (d, J=1.77 Hz, 1H), 5.75 (d, J=1.77 Hz, 1H), 3.89 (bt, J=6.5 Hz, 1H), 2.85 (m, 2H), 2.55 (t, J=6.6 Hz, 2H), 2.45-2.10 (m, 6H), 1.6-1.4 (m, 2H), 1.35 (bs, 1H)
^{13}C NMR (62.95 MHz, C_6D_6) δ= 147.95, 142.96, 139.32, 130.61, 124.76, 111.26, 69.66, 45.48, 40.58, 35.72, 30.72 30.98, 29.90
EI-MS (70 eV) m/e= 283 (M^++1,0.46),282 (M^+, 7.81) 254 (1.01), 238 (19.62), 188 (13.31), 131 (44.73), 99 (32.39), 98 (14.93), 97 (12.85), 95 (21.49), 82 (21.16), 81 (100), 65 (16.76), 53 (33.46)
IR (neat) 3410, 2930, 2860, 1710, 1485, 1420, 1250, 1135, 1035, 995, 899, 720, 600 cm^{-1}

Thioketal enone **42**.

To a solution of PCC (0.57g, 2.66 mmol) and celite (10g) covered with CH_2Cl_2(70 mL) was added **41** (0.50g, 1.77 mmol) in CH_2Cl_2(10 mL) over 5 min. After 2 hrs. an additional 1.5 eq. PCC (0.57g) was added in one portion. The reaction was stirred for an additional 2 hrs.; then was filtered through a fritted filter covered with a plug of celite and silica gel. The resulting water white solution was concentrated and the residue chromatographed on a column of silica gel(30g 230-400 mesh, 1:1 ether-hexane) using the flash technique to yield 0.39g (79.2%) of the thioketal **42**.
^{1}H NMR (250 MHz, C_6D_6) δ= 7.09 (t, J=1.7 Hz, 1H), 7.01 (m, 1H), 6.35 (at, J=1.87 Hz, 1H), 6.02 (m, 1H), 2.78 (s, 4H), 2.7-2.3 (m, 8H)
^{13}C NMR (62.9MHz, C_6D_6) δ= 196.46, 144.39, 143.08, 142.90, 141.96, 139.40, 124.38, 111.32, 73.71, 43.13, 40.75, 39.66, 30.48, 19.22
EI-MS (70eV) m/e= 281 (M^++1), 1.79) 280 (M+, 21.87) 252(5.25) 221 (2.37) 220 (2.32) 219 (10.23) 187 (13.53) 186 (10.40) 185(20.59) 157 (11.25) 130 (11.63) 125 (12.76) 97 (21.12) 95 (50.89) 81 (100, base) 67 (10.65) 65 (17.49) 61 (15.64) 53 (45.83)
IR (neat) 2920, 2850, 1720, 1665, 1600, 1500, 1370, 1275, 1185, 1022, 872, 785 cm^{-1}

Cyclized allylic alcohol **50**.

To allylic alcohol **41** (0.64g, 2.27 mmol) in CH_2Cl_2(40 mL) was added Et_3N (1.39 mL, 9.98 mmol, 3 eq); followed by mesyl chloride (0.527 mL. 6.81 mmol, 4 eq) over 10 min. After 0.5 hr. the reaction was quenched with saturated NH_4Cl (10 ml). extracted with CH_2Cl_2 (4x20 mL), the organic phases were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated to yield an oil. The crude product was purified by chromatography on a column of silica gel (15g , 230-400 mesh,20 mm OD 1:1 ether-hexane, 5 mL fractions) using the flash technique gave 0.553g (92.2%) of **50** as a water white oil.

^1H NMR (250 MHz, C_6D_6) δ= 7.09 (d, J=1.89 Hz, 1H), 5.99 (d, J=1.89 Hz, 1H), 2.65-1.98 (m, 10H), 1.73-1.35 (m, 4H)

^{13}C NMR (62.9 MHz, C_6D_6) δ= 153.13, 141.30, 123.15, 119.02, 110.38, 53.63, 35.56, 35.49, 35.01, 27.20, 26.57, 22.63, 22.01

EI-MS (70 eV) m/e= 266 (M^++2, 15.44) 264 (M^+,100) 236 (19.05) 235 (13.30) 208 (61.08) 207 (69.95)

IR (neat) 2940, 2870, 1600, 1505, 1440, 1429, 1315, 1295, 1230, 1200, 1160, 1120, 1045, 920, 890, 860, 750 cm^{-1}

Spirocyclized allylic alcohol **51**.

To allylic alcohol **41** (0.114g, 0.404 mmol) in cyclohexane (5 mL) was added formic acid (0.018g, 0.404 mmol, 98%) over 2 min. After 5 min. the reaction was quenched with sat'd. $NaHCO_3$, extracted with CH_2Cl_2 (10 mL), the organic phases combined, dried ($MgSO_4$), and concentrated. Chromatography of the product on a column of silica gel (5g, 230-400 mesh, 10mm OD, ether-hexane, 1:1, 2 mL fractions) gave **51** (0.098g, 85.5%) as an oil.

^1H NMR (300 MHz, $CDCl_3$) δ=7.27 (d, J=1.87 Hz, 1H), 6.14 (d, J=1.87 Hz, 1H), 3.94 (dd, J=6.60, 3.28 Hz, 1H), 3.36 (m, 4H), 2.63 (d, J=14.68 Hz, 1H) 2.31 (d, J=14.68 Hz, 1H), 2.61-2.18 (m, 6H) 2.08 (m, 4H)

^{13}C NMR (75.47 MHz, $CDCl_3$) δ=154.36 (s), 141.47 (d), 114.31 (s), 109.97 (d), 74.33 (d), 70.48 (s), 53.91 (t), 48.37 (s), 45.12 (t), 39.60 (t), 39.51 (t), 33.50 (t), 28.07 (t), 18.08 (t)

EI-MS (70 ev) m/e= 282 (M^+,68.89) 238 (21.41) 189 (34.60) 178 (15.63) 150 (54.17) 145 (18.66) 135 (14.11) 132 (54.02) 131 (100) 118 (49.17) 115 (31.56) 107 (25.34)

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

Cyclized enone **40**

To solution of enone **42** (0.212g, 0.714 mmol) in CH_2Cl_2(20 mL) was added $BF_3{\cdot}OEt_2$ (0.0439 mL, 0.357 mmol) over 2 min. After 2 hrs. the reaction was complete by thin layer chromatography. The reaction was quenched with sat'd. NH_4Cl(10 mL), extracted with CH_2Cl_2 (3x10 mL), the organic phases were combined, washed with brine(30 mL), dried ($MgSO_4$) and concentrated. Chromatography on a column of silica gel(12g, 230-400 mesh, 1:1 ether - hexane 20mm OD, 2 mL fractions) using the flash technique gave 0.132g (62.2%) of **40** as a clear oil.

^1H NMR (250 MHz, C_6D_6) δ= 7.02 (d, J=1.8 Hz, 1H), 5.93 (d, J=1.8 Hz, 1H), 3.66 (bd, J=8.5 Hz, 1H), 2.96-1.9 (m, 10H), 1.45-1.19 (m, 3H)

40 *Cis* isomer ^1H NMR (250 MHz, C_6D_6) δ= 7.00 (d, J=1.94 Hz, 1H), 5.81 (d, J=1.94 Hz, 1H), 3.12 (d, J=13.1 Hz, 1H)

^{13}C NMR (62.9 MHz, C_6D_6) δ= 209.10, 140.03, 123.19, 113.15, 110.02, 75.36, 56.22, 54.31, 42.57, 42.40, 40.57, 39.25, 24.37, 23.06

EI-MS (70 eV) m/e= 282 (M^++2, 3.89(281 (M^++1, 6.17) 280(M^+, 41.21) 252 (2.68) 219 (3.22) 187 (10.47) 186 (9.93) 149 (49.26) 134 (12.48) 133 (16.91) 132 (26.04) 131 (100) 119 (48.72) 118 (33.29) 104 (35.97) 91 (51.28) 77 (36.91)

IR (neat) 2920, 2849, 1695, 1498, 1430, 1330, 1260, 1190, 1150, 1055, 720, 600 cm^{-1}

GC **42** retention time= 28.76 min.

40 *trans* retention time= 27.26 min.

40 *cis* retention time= 27.65 min.

Tertiary allylic alcohol **60.**

To thioketal enone **42** (0.070g, 0.25 mmol) in THF (5 mL) cooled to -78°C with a dry ice acetone bath, was added methyllithium (0.25 mL, 0.35 mmol, 1.4M, 1.4 eq) over 2 min., the solution stirred for 45 min., warmed to 0°C, quenched with sat'd. $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (20 mL), the organic phases combined, dried($MgSO_4$), and concentrated. The resulting oil was chromatographed on a column of silica gel (7g, 230-400 mesh, 10mm OD, ether-hexane, 1:1, 5 mL fractions) using the flash technique to give **60** (0.069g, 93.2%) as an oil.

^{1}H NMR (80 MHz, $CDCl_3$) δ=7.35 (t, J= 1.91 Hz, 1H), 7.25 (m, 1H), 6.30 (bs,1H), 5.72 (t, J=1.36 Hz, 1H), 3.35 (s, 4H), 2.95-2.25 (m, 6H), 1.95-1.60 (m, 2H), 1.40 (s, 3H)

Cyclized tertiary alcohol **61**.

To tertiary alcohol **60** (0.069g, 0.233 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.13 mL, 0.0932 mmol, 4 eq) and mesyl chloride (0.054 mL, 0.699 mmol, 3 eq). The reaction was stirred 2 hr., quenched with sat'd. $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (20 mL), the organic phases combined, dried ($MgSO_4$), and concentrated. The residue was chromatographed on a column of silica gel (6g, 230-400 mesh, 10mm OD, ether-hexane, 1:1, 2 mL fractions) using the flash technique gave **61** (0.064g, 75%) as a water white oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ= 7.30 (d, J=1.91 Hz, 1H), 6.18 (d, J=1.91 Hz, 1H), 3.29-3.03 (m, 4H), 2.66-2.35 (m, 4H), 2.24-1.87 (m, 2H), 1.83-1.68 (m, 2H), 0.96 (d, J=7.63 Hz, 3H)

Petersen intermediate **59**.

To a flame dried round bottom flask was added ketone **40** (0.064g, 0.230 mmol) and THF(15 mL). Trimethylsilylmethyllithium (0.299 mL, 1.0 M, 1.3 eq.) was added over 10 min. at RT, the reaction was stirred for 2 hrs; then quenched with sat. NH_4Cl. The aqueous portion was extracted with CH_2Cl_2 (10 mL) and ether (10 mL), the organic phases were combined, washed with brine(15 mL) and dried ($MgSO_4$). Concentration *in vacuo* furnished the crude product as an oil, which was purified by chromatography on a column of silica gel (5g, 230-400 mesh, 10 mm OD, ether-hexane, 1:1, 2 mL fractions) using the flash technique to provide 0.085g (91.7%) of **59** as a colorless oil.

^{1}H NMR (250 MHz, C_6D_6) δ= 7.00 (d, J=1.83 Hz, 1H), 5.93 (d, J=1.83 Hz, 1H), 3.75 (d, J=10.23 Hz, 1H), 2.90-2.56 (m, 7H), 2.49-1.92 (m, 4H), 1.82-1.67 (m, 1H), 1.58-1.42 (m, 1H), 0.13 (m, 9H)

50 *cis* compound ^{1}H NMR (250MHz, C_6D_6) δ= 6.96 (d, J=1.94 Hz, 1H), 5.76 (d, J=1.94 Hz, 1H), 3.16 (d, J=14.5 Hz, 1H)

IR (neat) 3460, 2958, 2930, 2885, 1508, 1443, 1425, 1250, 1160, 1060, 950, 900, 865, 845, 743, 695 cm^{-1}

Olefination of cyclized enone **38**.

To a flame dried round bottom flask was added oil free KH (0.0236g, 0.206 mmol, washed 3x with hexane) covered with THF(5 mL) and a solution of **59** (0.0379g, 0.103 mmol) in THF(2 mL) was added over 5 min. The reaction was stirred at RT for 3hr, then carefully quenched with sat'd. NH_4Cl(5 mL). The mixture was cast into CH_2Cl_2(10 mL), the organic phase was washed with brine(5 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel (3g, 230-400 mesh, 5mm OD, ether-hexane, 1:1, 1 mL fractions) using the flash technique to provide **38** (19.4 mg., 67.8%) as a colorless oil.

^1H NMR (250 MHz, C_6D_6) δ = 7.06 (d, J=1.82 Hz, 1H), 7.00 (d, J=1.82 Hz, 1H), 4.75 (m, 1H), 4.72 (m, 1H), 3.91 (d, J=10.45 Hz ,1H), 3.05-2.0 (m, 9H), 1.89-1.68 (m, 4H)

38 *cis* compound ^1H NMR (250 MHz, C_6D_6) 7.00 (d, J=1.88 Hz, 1H), 5.90 (d, J=1.88 Hz, 1H), 3.12 (d, J=15.04 Hz, 1H)

^{13}C NMR (62.9 MHz, C_6D_6) δ = 150.34, 140.16, 121.52, 113.19, 112.61, 110.32, 77.23, 56.10, 49.07, 44.69, 39.99, 39.16, 32.07, 31.87, 27.75

EI-MS (70 eV) m/e= 280 (M^++2, 2.26) 279 (M^++1, 3.77) 278 (M^+, 20.59) 252 (1.98) 251 (3.04) 250 (19.27) 185 (11.70) 160 (15.31) 133 (10.81) 132 (12.88) 131 (100) 118 (15.40) 115 (10.78) 104 (11.79) 91(16.16)

38 *cis* compound EI-MS(70 eV) m/e= 280 (M^++2, 0.95) 279 (M^++1, 1.49) 278 (M^+, 8.42) 186 (7.66) 185 (53.67) 147 (12.68) 146 (100) 145 (10.75) 128 (4.21) 129 (2.88) 117 (11.6) 116 (3.06) 115 (9.77) 103 (4.78) 91 (9.09)

IR (neat) 2918, 2840, 1635, 1495, 1430, 1330, 1210, 1180, 1143, 1050, 720, 680 cm^{-1}

GC **38** *trans* retention time = 17.90 min.

GC **38** *cis* retention time = 18.63 min.

Methyl cyclopentenyl allylic alcohol **66**.

n-BuLi (0.324 mL, 2.4 M, 0.876 mmol, 1.1 eq) was added to bromoeneone **65** (0.200g, 0.797 mmol) in dry THF (10 mL) cooled to -78°C using a dry ice acetone bath. After 1 hr. 3-(3-furyl)propanal (0.118g, 0.956 mmol) in THF (5 mL) cooled to -78°C was added over 5 min., stirred 2 hr., quenched with sat'd. $NaHCO_3$, extracted with ether (10 mL), the organic phases combined, dried

($MgSO_4$), and concentrated. Chromatography of the resultant oil on a column of silica gel (15g, 230-400 mesh, 20mm OD, ether-hexane, 1:1, 5 mL fractions) using the flash technique gave **66** (0.186g, 79.1%) as a water white oil.

^1H NMR (250 MHz, $CDCl_3$) δ= 7.38 (t, J=1.78 Hz, 1H), 7.25 (m, 1H), 6.29 (m, 1H), 4.46 (t, J=5.3 Hz, 1H), 3.32 (m, 4H), 2.84-2.68 (m, 3H), 2.58-2.26 (m, 3H), 2.04-1.47 (m, 2H), 1.79 (t, J=0.87 Hz, 3H)

Chloride displacement of allylic alcohol **67**.

To a round bottom flask was added methyl cyclopentene **66** (0.0195g, 0.0658 mmol) in CH_2Cl_2 (2.5 mL), triethylamine (0.036 mL.0.263 mmol, 4 eq), and mesyl chloride (0.0153 mL, 0.197 mmol, 3 eq) over 10 min. The reaction was stirred for 36 hr., quenched with sat'd. $NaHCO_3$, extracted with CH_2Cl_2 (10 mL), the organic phases combined, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on a column of silica gel (2.5g, 230-400 mesh, 5mm OD, ether-hexane, 1:1, 1mL fractions) using the flash technique to give **67** (0.0126g, 60.8%) as an oil.

^1H NMR (250 MHz, $CDCl_3$) δ= 7.39 (t, J=1.8 Hz, 1H), 7.26 (bs, 1H), 6.29 (bs, 1H), 4.70 (t, 5.8 Hz, 1H), 3.32 (m, 4H), 2.48 (dt, J=8.3, 1.05 Hz, 2H), 2.65-1.86 (m, 6H), 1.78 (t, J=0.96 Hz, 3H)

Methyl 2-dimethylphosphonoacrylate **77**.

To a round bottom flask is added trimethylphosphonoacetate (34.67g, 0.19 mol), paraformaldehyde (12.0g, 0.40 mol), pyrrolidine (20 drops, catalytic) with methanol (600 mL). The solution was refluxed for 20 hr., cooled, evaporated *in vacuo*, taken up in benzene (500 mL), p-toluenesulfonic acid added (0.10g, catalytic), and refluxed with a Dean-Stark condenser. After 16 hr., the solution was cooled, evaporated in vacuo, and the residue distilled (94-100°C, 1mm) to give **77** (25.52g, 67.8%)as a slightly yellow liquid

^1H NMR (250 MHz, C_6D_6) δ= 6.61 (dd, J=26.5, 1.23 Hz, 1H), 6.56 (m, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.29 (s, 3H)

EI-MS (70 ev) m/e= 195 (M^+,30.05) 163 (82.21) 162 (35.10) 136 (13.90) 135 (22.08) 134 (17.87) 133 (34.05) 109 (100) 105 (16.03) 93 (32.77) 79 (23.28) 54 (21.83) 47 (29.65)

IR (neat) 3005, 2958, 2855, 1727, 1442, 1399, 1303, 1260, 1190, 1167, 1140, 1038, 840 cm^{-1}

1-cyclopentenyl-2-3-(3-furyl) ethylacrylate **78**

To cyclopentenylbromide **76** (0.20g, 0.976 mmol) covered with THF(15 mL) cooled to -78°C with a dry ice acetone bath was added n-BuLi (0.468mL, 2.5M, 1.3eq.) over a 5 min. period. After stirring 45 min. , CuI (0.009g, 5 mol %) was added in one portion stirred for an additional 30 min., warmed to -40°C for 15 min., then recooled to -78°C with a dry ice acetone bath. Phosphonoacrylate **77** (0.23g, 0.976 mmol) in THF(5 mL) was added, stirred 30 min. at -78°C, warmed to 0°C and 3-(3-furyl)propanal (0.093g, 0.976 mmol) in THF(1 mL) was added over 10 min. After stirring for 1 hr. the reaction was quenched with sat'd. NH_4Cl (50 mL), extracted with ether (30 mL) the organic phases combined, washed with brine(10 mL), dried ($MgSO_4$), and concentrated. Chromatography of the residue through a column of silica gel (15g, 230-400 mesh, 10mm OD, ether-hexane, 1:1, 2 mL fractions) using the flash technique gave **78** (0.094g, 31.7%) as a clear oil.

^1H NMR (250 MHz, $CDCl_3$) δ= 7.73 (bs, 1H), 7.61 (s, 1H), 7.41 (m,1H), 6.64 (m, 1H), 5.51 (at, J=2.20 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.04-3.82 (m,4H), 3.26 (aq, J=1.4 HZ, 2H), 2.65-1.95 (m, 4H), 1.31 (t, J=7.2 Hz, 3H)

EI-MS (20 eV) m/e= 304(M+, 100) 275 (31.94) 260 (20.83) 259 (23.61) 231 (95.83) 223 (28.47) 215 (22.92) 214 (40.97) 213 (45.83) 203 (27.08) 186 (72.22) 185 (48.61) 149 (37.50) 125 (61.81) 115 (65.28) 91 (45.83) 81 (66.67) 55 (70.14)

IR (neat) 3120, 2950, 1715, 1650, 1600, 1520, 1430, 1335, 1298, 1200, 1150, 1043, 1020, 935, 918, 803, 758 cm^{-1}

2-cyclopentenone-2-3-(3-furyl)ethylacrylate **78A**

To furylacrylate **78** (0.085g, 0.279 mmol) in THF(5 mL) was added 5% HCl (10 drops), stirred 0.5 hr., quenched with sat'd. $NaHCO_3$(5 drops), extracted with CH_2CL_2(20 mL), the organic phases combined, dried ($MgSO_4$), and evaporated *in vacuo* . The oil recovered was chromatographed on a column of silica gel (5g, 230-400 mesh, 10mm OD, ether-hexane, 1:1, 2 mL fractions) using the flash technique to give **78A** (0.065g, 90.2%) as a light yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ= 7.64 (s,1H), 7.63 (s,1H), 7.41 (t, J=1.66 Hz, 1H), 7.20 (m,1H), 6.49 (m,1H), 4.24 (q, J=7.1 Hz, 2H), 3.42 (d, J=2.40 Hz, 1H), 3.40 (d, J=2.40 Hz, 1H), 2.68-2.36 (m,4H), 1.31 (t, J=7.1 Hz, 3H)
EI-MS (70 eV) m/e= 261 (M^++1, 7.84) 260 (M^+, 53.59) 215 (26.26) 214 (80.12) 187 (18.12) 186 (100) 185 (76.76) 155 (33.03) 148 (22.25) 127 (28.36) 115 (24.01) 109 (20.45) 99 (43.12) 91 (30.24) 81 (37.39) 77 (27.10) 57 (31.08) 55 (37.96)
IR (neat) 3055, 2959, 2920, 1765, 1690, 1630, 1420, 1265, 1248, 1205, 1122, 1020, 910, 735, 708, 616 cm^{-1}

Cyclized enone acrylate **79**.

To a flame dried round bottom flask was added cyclopentenone **78A** (0.0168g, 0.0646 mmol), covered with CH_2Cl_2(5 mL), and $BF_3{\cdot}OEt_2$ (0.079 mL, 0.0646 mmol., 10 eq.) was added over 2 min. from a microliter syringe. The reaction was stirred for 4 hr. , quenched with sat'd. NH_4Cl, extracted with CH_2Cl_2(10 mL), the organic phases combined, washed with brine(20 mL), dried ($MgSO_4$), and concentrated. Chromatography of the residue on a column of silica gel (2g, 230-400 mesh, 5mm OD, ether-hexane, 1:1, 1mL fractions) using the flash technique gave **79** (0.0108g, 64.3%) as a clear oil.
^{1}H NMR (250 MHz, $CDCl_3$) δ= 7.44 (s, 1H), 7.38 (d, J=1.92 Hz, 1H), 6.34 (d, J=1.92 Hz, 1H), 4.28 (q, J=7.15 Hz, 1H), 3.57 (t, J=10.3 Hz, 1H), 2.95-2.45 (m,4H), 2.28-2.03 (m, 1H), 1.34 (t, J=7.15 Hz, 1H)
EI-MS (70 eV) m/e= 261 (M^++1,5.69) 260 (M^+, 42.00) 231 (11.60) 215 (30.40) 214 (75.83) 203 (20.41) 187 (22.13) 186 (17.85) 185 (9.94) 175 (100) 159 (16.65) 158 (45.33) 131 (69.92) 130 (64.34) 115 (23.63) 102 (17.51) 91 (28.36) 81 (3.76) 77 (47.91) 55 (37.70)
IR (neat) 2930, 2920, 1740, 1703, 1635, 1610, 1570, 1422, 1258, 1203, 1178, 1125, 960, 803, 750 cm^{-1}

1-cyclopentenyl-2-3-(5-methyl-3-furyl)-2-ethylacrylate **80**.

To a flame dried round bottom flask was added bromocyclopentene **76** (0.500g, 2.44 mmol), covered with THF(30 mL), cooled to -78°C with a dry ice acetone bath, and n-BuLi (1.62 mL, 3.90 mmol, 2.4M) added over 10 min. After 45 min. at -78°C, CuI (0.557g, 2.92 mmol, 1.2eq) was added in one portion, stirred at -78°C for 30 min, warmed to -40°C for 15 min., and recooled

to -78°C. Phosphonoacrylate **77** (0.568g, 2.92 mmol, 1.2eq) in 5 mL THF was cooled in a dry ice acetone bath, added via cannula, stirred for an additional 2 hr., and warmed to 0°C. 5-Methyl-3-furfural (0.322g, 2.92 mmol, 1.2eq) in THF(5 mL) was cooled to -78°C added via cannula, stirred for 2 hr., quenched with sat'd. $NaHCO_3$, extracted with ether(30 mL), the organic phases combined, washed with brine, and concentrated. Chromatography of the residue on a column of silica gel (60g, 230-400 mesh, 30mm OD, ether-hexane, 1:1, 10 mL fractions) using the flash technique gave **80** (0.388g, 52.3%) as a light yellow oil.

^1H NMR (250 MHz, C_6D_6) δ= 7.86 (bs, 1H), 7.50 (bs, 1H), 6.28 (at, J=1.03, 1H), 5.56 (m, 1H), 3.48 (s, 3H), 3.66-3.43 (m, 6H), 1.89 (d, J=1.03 Hz, 3H), 2.19-1.92 (m, 4H)

80 *cis* compound ^1H NMR (250 MHz, C_6D_6) δ= 7.57 (bs, 1H), 6.39 (at, J=1.05 Hz, 1H), 6.37 (bs, 1H), 5.75 (m, 1H), 3.40 (s, 3H), 1.92 (t, J=1.05 Hz, 3H)

^{13}C NMR (62.95 MHZ, C_6D_6) δ= 157.57, 153.49, 144.02, 131.63, 131.47, 122.99, 107.26, 106.36, 65.30, 63.97, 51.67, 36.08, 34.39, 27.95, 26.39, 25.22, 24.14, 13.07

EI-MS (70 eV) m/e= 304 (M^+,0.58) 260 (5.35) 200(12.12) 199 (8.95) 129 (9.75) 128 (8.67) 115 (12.35) 91 (14.59) 77 (15.91) 65 (15.94) 59 (12.19) 57 (11.31) 55 (23.71) 43 (100)

IR (neat) 3128, 2950, 2880, 1710, 1648, 1605, 1530, 1438, 1340, 1298, 1250, 1205, 1140, 1088, 1043, 1014, 950, 912, 810, 763 cm^{-1}

80 GC retention time = 15.51 min.

Deprotection of oxoketal **80A**.

To a solution of furyl cyclopentene **80** (0.066g, 0.217 mmol) in THF(10 mL) was added 5% HCl (10 drops). After 15 min. the reaction was quenched with sat'd. $NaHCO_3$ (2 mL), extracted with ether(10 mL), the organic phases combined, dried ($MgSO_4$), and concentrated. Chromatography of the residue on a column of silica gel (5g, 230-400 mesh, 5mm OD, ether-hexane, 1:1, 1 mL fractions) using the flash technique gave **80A** (0.048g, 85.7%) as a mobile oil.

^1H NMR (250 MHz, C_6D_6) δ= 7.70 (bs, 1H), 7.23 (bs, 1H), 6.81 (m, 1H), 6.08 (bs, 1H), 3.63 (d, J=2.44 Hz, 1H), 3.61 (d, J=2.44 Hz, 1H), 3.47 (s, 3H), 1.84 (d, J=1.00 Hz, 3H), 2.05-1.68 (m, 4H)

80A *cis* compound ^1H NMR (250 MHz, C_6D_6) δ= 7.59 (bs, 1H), 6.82 (m, 1H), 6.42 (bs, 1H), 6.35 (bs, 1H), 3.37 (s, 3H), 1.89 (d, J=1.66, 3H)

^{13}C NMR (62.9 MHz, C_6D_6) δ= 207.62, 157.29, 154.08, 144.02, 131.46, 129.67, 127.32, 122.85, 107.76, 106.38, 51.63, 34.33, 26.32, 24.19, 13.05

EI-MS (70 eV) m/e= 261 (M^++1, 2.11) 260 (M^+, 15.41) 228 (7.42) 201 (5.75) 200 (25.72) 199 (19.44) 158 (9.23) 157 (10.46) 149 (23.51) 129 (13.49) 128 (12.95) 115 (18.67) 91 (25.45) 77 (22.93) 65 (26.08) 55(23.15) 43 (100)

IR (neat) 3058, 2955, 2922, 1765, 1695, 1632, 1438, 1265, 1248, 1205, 1140, 1090, 918, 735, 700 cm^{-1}

GC **80A** *cis* retention time = 13.57 min.

GC **80A** *trans* retention time = 13.75 min.

Cyclization of enone **81**.

To a round bottom flask with furyl cyclopentenone **80A** (0.048g, 0.1846 mmol) covered with CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (0.090 mL, 0.732 mmol, 3.96 eq.) via a microliter syringe. The reaction was stirred for 4 hrs., quenched with sat'd. NH_4Cl, extracted with CH_2Cl_2 (20 mL), the organic phases combined, washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residual oil was chromatographed on a column of silica gel (4g, 230-400 mesh, 5mm OD, ether-hexane, 1:1, 1 mL fractions) using the flash technique to give **81** (0.032g, 66.7%) as a yellow oil.

^1H NMR (250 MHz, C_6D_6) δ= 7.55 (bs, 1H) 5.55 (m, 1H), 3.91-3.62 (m, 1H), 3.49 (s, 3H), 3.48-3.20 (m, 1H), 3.10-2.68 (m, 2H), 2.24-1.53 (m, 4H), 1.90 (s, 3H)

81 *cis* compound ^1H NMR (250 MHz, C_6D_6) δ= 7.58 (d, J=2.98 Hz, 1H), 5.59 (m, 1H), 3.48 (s, 3H)

^{13}C NMR (62.9 MHz, C_6D_6) δ= 215.86, 167.43, 155.67, 151.43, 131.14, 129.31, 119.09, 108.18, 51.63, 49.45, 40.81, 34.63, 28.01, 25.75, 12.96

EI-MS (70 eV) m/e= 261 (M^++1, 4.41) 260 (M^+, 33.59), 229 (16.92) 228 (33.59) 217 (10.30) 203 (32.82) 201 (25.58) 200 (14.32) 190 (12.77) 189 (100) 175 (12.77) 173 (22.01) 172 (24.42) 159 (22.59) 158 (14.09) 157 (13.48) 145 (78.38) 144 (56.31) 143 (13.48) 131 (14.25) 129 (21.01) 128 (18.89) 127 (10.39) 115 (63.06) 102 (13.48) 91 (34.94) 77(21.36) 59 (21.20) 55 (22.94) 43 (95.75)

81 *cis* compound EI-MS (70 eV) m/e= 261 (M^++1, 6.13) 260 (M^+,47.37) 229 (17.74) 228 (26.77) 217 (11.99) 203 (36.94) 201 (36.13) 200 (15.00) 190 (12.85) 189 (100) 175 (11.88) 173 (23.87) 172 (23.55) 159 (27.85) 158 (15.59) 157 (13.33) 145 (76.45) 144 (52.10) 143 (13.28) 131 (16.02) 129 (23.17) 128 (20.43) 127 (9.89) 116 (15.16) 91 (37.85) 77 (27.10) 63 (20.59) 59 (23.44) 55 (20.57) 51 (51.72) 43 (99.89)

IR (neat) 2950, 2920, 1742, 1707, 1635, 1612, 1575, 1438, 1260, 1200, 1178, 1129, 953, 800, 758 cm^{-1}

Esterification of cyclopentene methanol **90.**

To a solution of cyclopentene methanol **89** (0.200g, 1.28 mmol) in CH_2Cl_2 (10 mL) was added pyridine (0.155 mL, 1.92 mmol, 1.5 eq.), cooled to 0°C, and propionyl chloride (1.33 mL, 1.53 mmol, 1.2 eq.) added over 5 min. The reaction was stirred 0.5 hr. at 0°C, quenched with sat'd. $NaHCO_3$, extracted with ether (25 mL), the organic phases combined, washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Chromatography of the resulting oil on a column of silica gel (25g, 230-400 mesh, 30mm OD, ether-petroleum ether, 1:1, 20 mL fractions) using the flash technique gave **90** (0.261g,95.9%) as an oil.
^1H NMR (80 MHz, $CDCl_3$) δ= 6.07 (m, 1H), 4.70 (d, J=1.8 Hz, 1H), 4.67 (d, J=1.8 Hz, 1H), 3.95 (s, 4H), 2.35 (q, J=7.2 Hz, 2H), 2.55-1.95 (m, 4H), 1.17 (t, J=7.2 Hz, 3H)
EI-MS (70 eV) m/e= 212 (M+, 3.37) 169 (1.02) 156 (9.08) 155 (50.06) 139 (77.12) 138 (30.66) 125 (14.69) 11 (12.22) 95 (21.72) 94 (10.19) 86 (9.15) 79 (11.73) 67 (45.44) 66 (22.00) 65 (10.75) 57 (100)
IR (neat) 2930, 2900, 1735, 1615, 1250, 1190, 1030, 960, 840 cm-1

Ester enolate Claisen **91.**

To a solution of LDA (n-BuLi, 2.5mL, 2.45 M, 1.3 eq., diisopropylamine, 0.859 mL, 6.13 mmol, 1.3 eq.) in THF (40 mL) cooled to -78°C with a dry ice acetone bath was added cyclopentenyl ester **90** (1.0g, 4.72mmol) in THF (10 mL) over 5 min. After 1 hr., TBDMS chloride (0.924g, 6.13 mmol) and HMPA (1.067 mL, 6.13 mmol) in THF (10 mL) were added over 10 min. stirred at -78°C for 1 hr., warmed to RT for 2 hrs., refluxed for 15 min., quenched with sat'd. NH_4Cl, extracted with CH_2Cl_2 (60 mL), the organic phases combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The oil was purified on a silica gel column (75g, 230-400 mesh, 30mm OD, ethyl acetate, 15 mL fractions) using the flash technique to give **91** (0.586g, 73.9%) as a water white oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 5.28 (d, J=2.2 Hz, 1H), 4.99 (d, J=2.2 Hz, 1H), 3.94 (m, 4H), 2.52 (m, 1H), 1.98-1.44 (m, 5H), 1.16 (d, J=6.8 Hz, 3H), 0.91 (s, 9H), 0.26 (s, 6H)

EI-MS (70 eV) m/e= 326 (M^+, 0.55) 301 (0.63) 269 (1.98) 233 (4.90) 225 (7.87) 179 (9.58) 170 (7.93) 169 (57.22) 147 (25.47) 139 (59.20) 135 (26.72) 111 (11.36) 99 (13.43) 95 (12.54) 92 (10.48) 77 (11.74) 75 (94.53) 74 (10.01) 73 (10.01) 73 (100) 67 (23.84) 66 (10.86) 57 (43.36)

IR (neat) 2965, 2920, 1655, 1415, 1308, 1257, 1221, 1142, 1030, 920, 880, 656 cm-1

Hydrolysis of Claisen product **92.**

To the aqueous phase retained from above was added 5% NaOH until basic. The solution was extracted with CH_2Cl_2 (50 mL) and ethyl acetate (30 mL), the organic phases combined, and 5% HCl was added until acidic. The combined organic solution was stirred for 3.5 hr., extracted with CH_2Cl_2 (20 mL), ethyl acetate (20 mL), the organic phase washed with brine (20 mL), dried ($MgSO_4$), and concentrated.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.17 (d, J=1.95 Hz, 1H), 5.39 (d, J=1.95 Hz, 1H), 3.10 (m, 1H), 2.76 (m, 1H), 2.55-1.71 (m, 4H), 1.26 (d, J=6.5 Hz, 3H)

EI-MS (70 eV) m/e= 169 (M^++1, 14.75) 168 (M^+, 2.40) 140 (5.54) 119 (8.33) 111 (22.70) 96 (16.11) 95 (20.32) 83 (8.83) 77 (10.94) 75 (100) 73 (19.43) 67 (31.38) 57 (44.98)

IR (neat) 3012, 2945, 1710, 1655, 1520, 1420, 1300, 1218, 1034, 961, 882,645 cm^{-1}

GC **92** *syn* retention time = 7.03 min.

GC **92** *anti* retention time = 7.57 min.

3-(3-furyl)cyclopentene methanol **93.**

To a flame dried round bottom flask with bromocyclopentene **70** (1.00g, 4.88 mmol) in dry THF (50 mL) cooled to -78°C with a dry ice acetone bath, was added n-BuLi (2.78 mL, 6.83 mmol, 2.45 M, 1.4 eq.) over 10 min, stirred for 2 hrs., TMEDA (1.03mL, 6.83 mmol, 1.4 eq.) added, stirred for 2 hrs., and 3-furaldehyde (0.655g, 6.83 mmol) in THF (5 mL) was added over 10 min. The solution was stirred 2 hrs., warmed to 0°C, quenched with sat'd. NH_4Cl, extracted with ether (50 mL), the organic phases combined, washed with brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* . Chromatography of the

resulting oil on a column of silica gel (75g, 230-400 mesh, 30mm OD, ether-hexane, 1:1, 20 mL fractions) using the flash technique gave **93** (0.963g, 88.9%) as an oil.

^{1}H NMR (80 MHz, $CDCl_3$) δ= 7.45 (m, 1H), 7.40 (t, J=1.36 Hz, 1H), 6.40 (m, 1H), 5.40 (m, 1H), 4.62 (d, J=8.6 Hz, 1H), 4.05 (m, 4H), 2.50-1.95 (m, 4H)

EI-MS (70 eV) m/e= 222 (M^+, 19.12) 194 (11.87) 193 (68.78) 1769 (17.74) 178 (76.38) 177 (26.73) 163 (21.08) 161 (31.34) 149 (25.35) 121 (28.92) 111 (41.82) 109 (47.23) 107 (31.80) 105 (24.88) 97 (29.15) 95 (95.16) 91 (39.40) 87 (22.12) 83 (80.88) 82 (32.83) 81 (100) 79 (38.36) 77 (39.17) 69 (43.89) 55 (76.73)

IR (neat) 3630, 2993, 2903, 1622, 1501, 1422, 1382, 1304, 1120, 1030, 940, 880,723, 660 cm-1

Esterification of cyclopentene methanol **94.**

Pyridine (3.43 mL, 34.0 mmol) and DMAP (10 mg., catalytic) were added to furylcyclopentenyl methanol **93** (6.29g, 28.33 mmol) in CH_2Cl_2 (100 mL), cooled to 0°C, and propionyl chloride (2.95 mL, 34.00 mmol) was added over 5 min. The solution was stirred for 0.5 hr., cooling removed, stirred an additional 0.5 hr., quenched with sat'd. $NaHCO_3$, extracted with CH_2Cl_2 (35 mL), washed with water (20 ml), brine (20 mL), dried ($MgSO_4$), and concentrated. Chromatography of the resulting oil on a column of silica gel (200g, 230-400 mesh, 60mm OD, ether-petroleum ether, 1:1, 50 mL fractions) using the flash technique gave **94** (7.03g, 89.2%) as a water white liquid.

^{1}H NMR (80 MHz, $CDCl_3$) δ= 7.43 (m, 1H), 7.37 (t, J=1.20 Hz, 1H), 6.49 (bs, 1H), 6.42 (m,, 1H), 6.12 (m, 1H), 3.90 (bs, 4H), 2.65-1.95 (m, 6H), 1.15 (t, J=6.5 Hz, 3H),

EI-MS (70 eV) m/e= 278 (M^+, 3.59) 205 (16.16) 177 (10.00) 161 (9.16) 136 (27.21) 109 (31.55) 105 (14.43) 103 (10.51) 101 (37.29) 99 (13.16) 95 (14.65) 91 (15.95) 87 (11.71) 86 (14.75) 81 (13.96) 79 (14.33) 77 (22.5) 66 (12.29) 65 (19.67) 57 (100)

IR (neat) 2952, 1730, 1612, 1510, 1426, 1250, 1190, 1030, 933, 880, 773, 621 cm-1

Ester enolate Claisen **95.**

To LDA (n-BuLi, 1.92 mL, 2.43 M, 4.67mmol, 1.3 eq., diisopropylamine, 0.655 mL, 4.67 mmol, 1.3 eq.) in THF (50 mL) cooled to -78°C in a dry ice acetone bath was added furylcyclopentenyl ester **94** (1.00g, 3.597 mmol) over 5 min. After stirring 45 min. at -78°C TBDMS Cl (0.704g, 4.67 mol, 1.3 eq.) and

HMPA (0.813mL, 4.67 mmol) in THF (5 mL) were added over 10 min., stirred for 2 hrs., warmed to RT, then refluxed 4 hrs. The reaction was quenched with sat'd. NH_4Cl, 5% NaOH (until basic) was added to the aqueous phase, extracted with CH_2Cl_2 (65 mL), the organic phases combined, stirred with 5% HCl (until acidic) for 3 hrs., extracted with CH_2Cl_2 (50 mL), ethyl acetate (30 mL), dried (Mg SO_4), and concentrated. Chromatography of the residue on a column of silica gel (65g, 230-400 mesh, 20mm OD, ethyl acetate, 15 mL fractions) using the flash technique gave **95** (0.588g, 69.8%) as a mobile oil.
^1H NMR (250 MHz, $CDCl_3$) δ = 8.43 (bs, 1H), 7.41 (t, J=1.2 Hz, 1H), 6.92 (m, 1H), 6.52 (m, 1H), 3.16 (m, 1H), 2.87-1.65 (m, 5H), 1.27 (d, J=6.8 Hz, 3H)
EI-MS (70 eV) m/e= 235 (M^++1, 2.43) 234 (M^+, 20.11) 205 (6.01) 189 (4.08) 162 (6.93) 161 (73.56) 160 (7.14) 150 (7.74) 149 (100) 119 (9.07) 115 (6.58) 112 (6.68) 111 (14.94) 105 (23.77) 104 (8.72) 103 (10.41) 97 (8.79) 91 (13.54) 83 (16.39) 81 (32.24) 79 (11.71) 77 (18.53)
IR (neat) 3008, 2967, 1735, 1670, 1618, 1500, 1422, 1304, 1248, 1130, 1041, 920, 880, 730, 661 cm-1

Compound **96.**
^1H NMR (250 MHz, $CDCl_3$) 7.33 (d, J=1.6 Hz, 1H) 7.29 (m, 1H) 6.22 (d, J=1.6 Hz, 1H) 3.96 (d, J=2.34, 1H) 3.94 (d, J=2.34, 1H) 3.26 (m, 2H) 2.8-2.29 (m, 4H), 1.53 (d, J=7.06, 3H)
MS (EI, 70 eV) m/e 234 (M^+, 25.10) 233 (25.03) 188 (6.46) 162 (9.68) 161 (100) 159 (7.46) 149 (12.05) 147 (11.90) 145 (11.93) 133 (10.35) 131 (15.56) 119 (12.84) 115 (15.17) 105 (30.27) 103 (15.60) 95 (20.01) 91 (27.34) 79 (20.87) 78 (10.12) 77 (31.75) 75 (27.79) 73 (41.39) 55 (36.71)

2-3-(3-furyl)-1-methyl ethylacrylate **74.**

NaH (5.00g, 50%, 104.2 mmol, washed 3X with hexane) was coated with 150 mL of dry benzene. Ethyl methyl phosphonoacetate (24.79g, 104.2 mmol) was added over a 20 min. period. Copious foaming occurred with H_2 evolution. After stirring 1 hr., 3-furylaldehyde (10.0g, 104.17 mmol) was added, the solution was warmed gently with a heat gun, and stirred 1.5 hr. more. The reaction was carefully quenched with sat'd. NH_4Cl, extracted with ether (150 mL), the organic phases combined, washed with brine (50 mL), dried ($MgSO_4$), and evaporated *in vacuo*. Purification of the product on a column of silica gel

(120g, 230-400 mesh, 40mm OD, petroleum ether-ether, 5:1, 50 mL fractions) using the flash technique gave **74** (18.00g, 96%) as a water white liquid.
^{1}H NMR (250MHz, $CDCl_3$) δ= 7.58 (bs, 1H), 7.18 (bs, 1H), 7.00 (t, J=1.86 Hz, 1H), 6.20 (m, 1H), 4.07 (q, J=6.86 Hz, 2H), 1.97 (d, J=1.3 Hz, 3H), 1.03 (t, J=6.86 Hz, 3H)
EI-MS (70 ev) m/e= 182(M^++2, 44.69) 181 (M^++1, 100) 180 (M^+, 56.72) 149 (13.19) 135 (52.62) 124 (10.65) 95 (12.70) 84 (17.64) 79 (12.84) 76 (35.62) 75 (94.09) 74 (17.64) 73 (85.48) 59 (76.08)

2-3-(3-furyl)-1-bromomethyl ethylacrylate **73.**

To a round bottom flask was added furyl ethyl acrylate **74** (18.00g, 100.0 mmol), NBS (17.99g, 100.0 mmol), benzoyl peroxide (0.09g, catalytic), and carbon tetrachloride (400 mL). The solution was heated to reflux under argon, and a GE lamp (250 watt) was shown on the reaction flask. The reaction was stirred 4 hr., cooled, filtered through florisil, and concentrated. Chromatography of the product on a column of silica gel (250g, 230-400 mesh, 60mm OD, petroleum ether-ether, 5:1, 30 mL fractions) using the flash technique gave **73** (24.54g, 94.8%) as a light brown oil.
^{1}H NMR (250MHz, $CDCl_3$) δ= 7.52 (bs, 1H), 7.28 (bs, 1H), 6.94 (bs, 1H), 6.39 (bs, 1H), 4.22 (s, 2H), 4.03 (q, J=6.90 Hz, 2H), 0.96 (t, J=6.90 Hz, 3H)
EI-MS (70 ev) m/e= 261 (M^++2, 2.24) 260 (M^++1, 7.27) 259 (M^+, 6.68) 258 (7.18) 180 (12.72) 179 (100) 151 (10.65) 107 (10.93) 106 (13.15) 105 (17.78) 79 (39.01) 78 (30.83) 77 (35.70)

Cyclization of bromofuryl acrylate **75.**

Bromofuryl acrylate **73** (2.0g, 7.92 mmol) was placed in a -20°C freezer, after two weeks the product was chromatographed on a column of silica gel (40g, 230-400 mesh, 20mm OD, petroleum ether-ether, 5:1, 25 mL fractions) to give **75** (1.1g, 80%) as a mobile oil.
^{1}H NMR (80 MHz, $CDCl_3$) δ= 7.55 (d, J=2.5 Hz, 1H), 7.50 (bs, 1H), 6.95 (d, J= 2.5 Hz, 1H), 4.40 (s, 2H), 4.30 (q, J= 6.1 Hz, 2H), 1.39 (t, J=6.1 Hz, 3H)
EI-MS (70 ev) m/e= 131 (2.05) 120 (2.86) 119 (4.77) 117 (9.70) 116 (5.50) 107 (4.89) 105 (3.55) 99 (3.23) 92 (12.71) 91 (45.72) 89 (8.83) 85 (41.78) 84 (34.76) 83 (13.08) 74

(95.03) 73 (61.99) 61 (55.22) 60 (13.96) 56 20.33) 55 (70.29) 53 (22.47) 45 (28.08) 44 (57.45) 43 (100)

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