This is to certify that the

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Furans as Terminators
in Cationic Cyclizations

presented by

Paul Matthew Herrinton

has been accepted towards fulfillment
of the requirements for

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Major professor

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FURANS AS TERMINATORS IN CATIONIC CYCLIZATIONS

By

Paul Matthew Herrinton

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillments of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1984

To my lovely Joan.

Thank you for
making this possible.

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ABSTRACT

FURANS AS TERMINATORS
IN CATIONIC CYCLIZATION

By

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Several 3-substituted furans with latent electrophiles in the side chain were prepared as cyclization substrates. 3-Furylmethyl magnesium chloride is readily coupled with a variety of ω-haloalkenes to afford the corresponding 3-substituted furan in good to excellent yields. Epoxidation of the product furyl olefins was found to be effective in producing the desired cyclization substrates only when the olefin was trisubstituted. Less highly substituted epoxy furans were prepared via the coupling of (3-furylmethyl) lithium with ω-iodo epoxides or protected ω-iodo diols followed by closure. The cyclizations of these epoxy furans were examined with a number of Lewis acids. Treatment with $Ti(OiPr)_3Cl$ and ZnI_2 led to the isolation of cyclized products in moderate to excellent yields. Cyclization of 7,8-epoxydendrolasin with $Ti(OiPr)_3Cl$ and ZnI_2 provided 3 β-hydroxypallescensin A in 62% and 65% yields respectively.

Additionally, allylic alcohols and enones derived from the CuCN moderated SN_2' addition of Grignard reagents prepared from 2-(3-furyl)-1-bromoethane and 3-(3-furyl)-1-bromopropane to vinyl epoxides and epoxy-enolethers were employed as cyclization substrates. Treatment of substrate allylic alcohols with a two phase mixture of formic acid and cyclohexane resulted in facile cyclization when the forming ring was 6-, or 7-membered. Enone closures proceeded only when a 6-membered ring was produced or in the case of a bridged system which leads to nakafuran-9.

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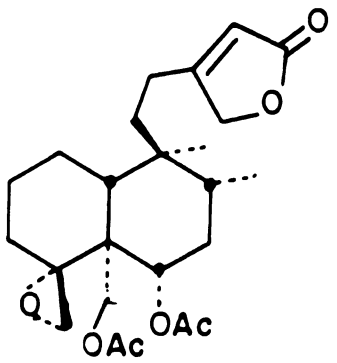
INTRODUCTION

Five-membered oxygen-containing heterocyclic rings are ubiquitous subunits that are observed in diverse classes of biologically active natural products.[1] This ring system is an integral part of molecules such as the



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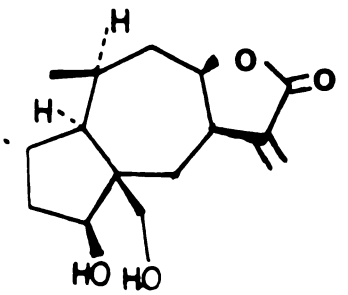

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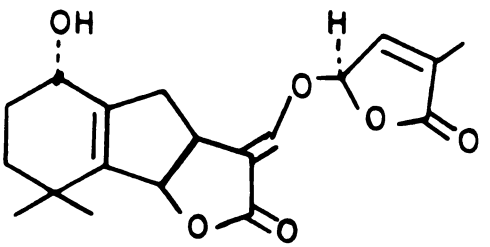

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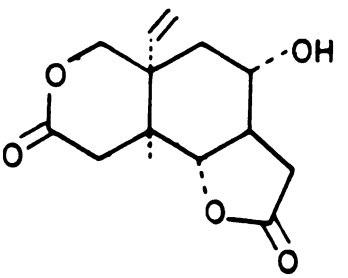

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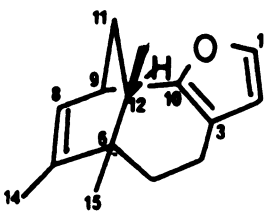

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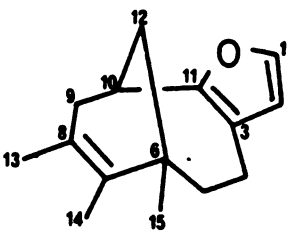
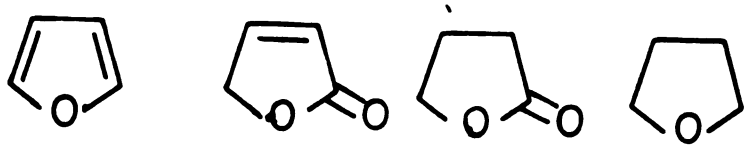


6

Figure 1 Natural Products

insect anti-feedant ent-neoclerodane ajugarin I **1**[2], the antileukemic pseudo-guaianolide rudmollin **2**[3], the witchweed germination promoter strigol **3**,[4] the cytotoxic vernolepin **4**[5,6], and the fish anti-feedants nakafuran-8 **5** and nakafuran-9 **6**.[7]

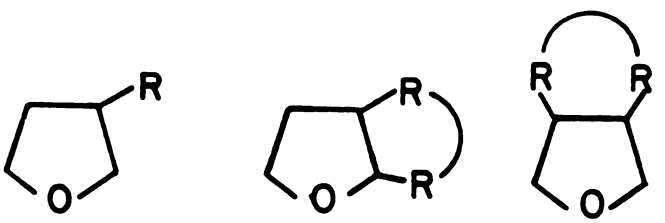
Compounds **1-6** represent two of the four common oxidation states of the five-membered oxygen-containing heterocyclic system, ranging from fully aromatic furan **7** to tetrahydrofuran **10**. Terpenoids **1-6** also exhibit two of



7 **8** **9** **10**

Figure 2 Oxidation States

the three **A-C** substitution patterns commonly observed about this ring system in natural products. Ajugarin-1 **1** illustrates the 3-substituted substructure **A** and nakafuran-8 **5** possesses a ring fused to the 2,3-positions of the five-membered heterocycle (substructure **B**).



A **B** **C**

Figure 3 Substitution Patterns

The synthesis of molecules such as **1–6** has generally been approached by a careful stereocontrolled construction of a parent carbocycle upon which the five-membered heterocycle is appended. These routes have generally not acknowledged the basic five-membered ring nucleus as an integral part of the molecule. A truly general approach to the synthesis of molecules **1–6** should provide access to the various states of oxidation **7–10** as well as the different patterns of substitution (**A–C**) about the heterocyclic nucleus. Central to such an approach is the use of common intermediates which will impart regio- and stereochemical control in bond forming reactions about the periphery of the heterocycle, as well as afford the desired oxidation state.

In principle, the oxidation states **7–10** found in representative natural products might be prepared by the reduction[8] or oxidation[9] of a furanoid precursor **7**. Tetrahydrofuran **10** might result from the reduction of **7**; butenolide **8** should be available by the oxidation of **7** and in turn butyrolactone

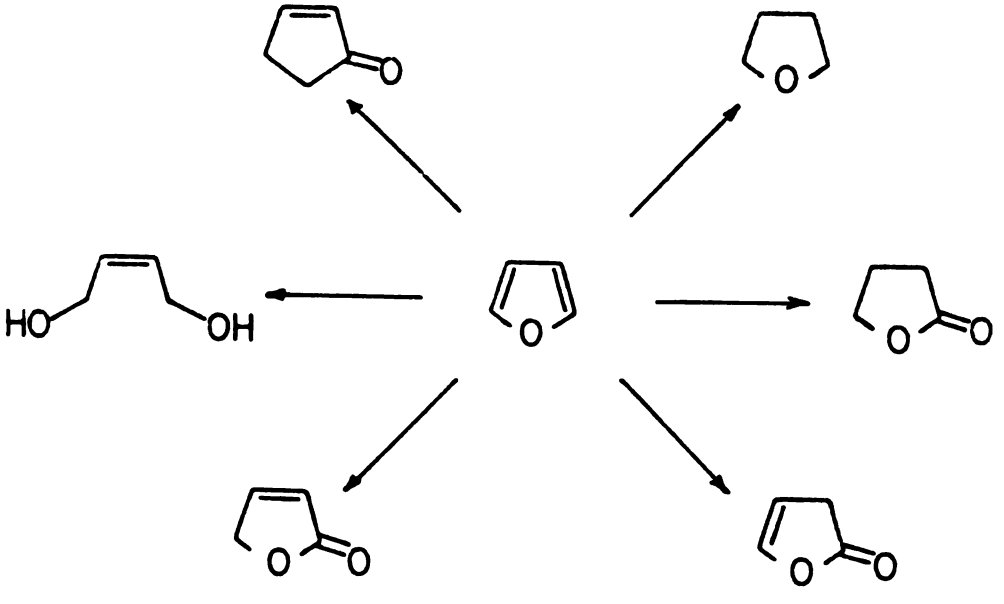
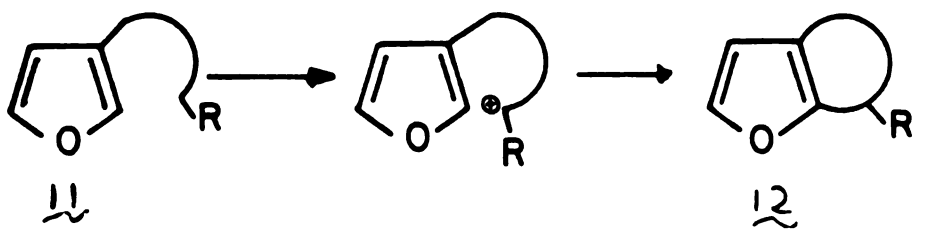


Figure 4 Furan Equivalencies

9 would result from the reduction of **8**. However, butenolides **8**, prepared from precursor furans, must be generated without regiochemical ambiguity. A more suitable solution to this problem is the unraveling of an appropriate 2- or 5-substituted-3-alkylfuran.[9] Therefore, the fully aromatic furan should serve as a precursor to the plethora of functional groupings illustrated in Figure 4. The synthesis of the type **A** substitution pattern in oxidation states **8-10** can then be simplified to the preparation of an appropriate 3-substituted furan.

Although numerous syntheses of 3-substituted furans have been reported,[10] they generally require many steps, relatively inaccessible starting materials or proceed in low overall yield. However, Tanis[11] has reported a general method for the preparation of 3-substituted furans which allows for the direct introduction of a wide variety of functionality as part of the side chain (R) introduced in the coupling process.

The type **B** structure, present in compounds **2-6**, should be accessible if the propensity of furans to undergo electrophillic attack at an α-position is exploited. As illustrated in equation 1, the generation of an electron deficient center (R) in the side chain of a 3-substituted furan, should lead to **12** after an electrophilic attack and rearomitzation. Therefore, an efficient synthesis of the more complex type **B** substructure would be realized from the much simpler type **A** furan **11** possessing a latent electrophilic center in its side chain.



11 12 (1)

The exploitation of this type of cationic π-cyclization in the construction of carbocyclic ring systems has been the object of intense study since 1950.[12] These investigations have served to verify, in vitro, the Stork-Eschemoser[13] hypothesis that the stereochemical course of the biological cyclization of squalene could be rationalized on stereoelectronic grounds. Applications of this methodology have resulted in the biomimetic synthesis of a variety of naturally occurring steroids and natural products.[14,15]

For successful polyene cyclization, a suitable electrophilic initiator functionality and nucleophilic terminator functionality are necessary. A wide variety of groups have been used to "trigger" cyclization reactions. The most common initiators are simple olefins (which require strongly acidic reaction conditions), epoxides (5a,[16a] b[16f]), allylic alcohols (5c,[12a] d[17]) and their oxidation products, α - β unsaturated carbonyls (5e,[18] f[19]). Additionally, Johnson[20] has demonstrated that acetals may initiate cyclization and that chiral acetals will result in the transfer of chirality to the cyclization products (5g, h). Finally, recent attention has been directed to N-acyliminium ions, which are readily generated, very reactive, and serve as precursors to alkaloid products (5i,[21] j[22]).

The scope of nucleophilic terminators examined has been somewhat more limited than that of initiators. Only simple olefins (5e,[18] f,[19] g[20]), aromatic rings (5a[16a]), acetylenes (5d[17]), and allenes (5c[12a]) are used with regularity. Comparatively few examples of more complex terminators such as vinyl ethers (5b[16f]) or heteroaromatics, such as thiophene and pyrrole, (5j[22]) have been reported. This is particularly true of furan terminated cyclizations. The paucity of pertinent literature precedent is likely the result of the inaccessibility of suitable substrates,[10,11] the poor nucleophilic character of the furyl residue relative to standard terminator functions, [16-22], and the

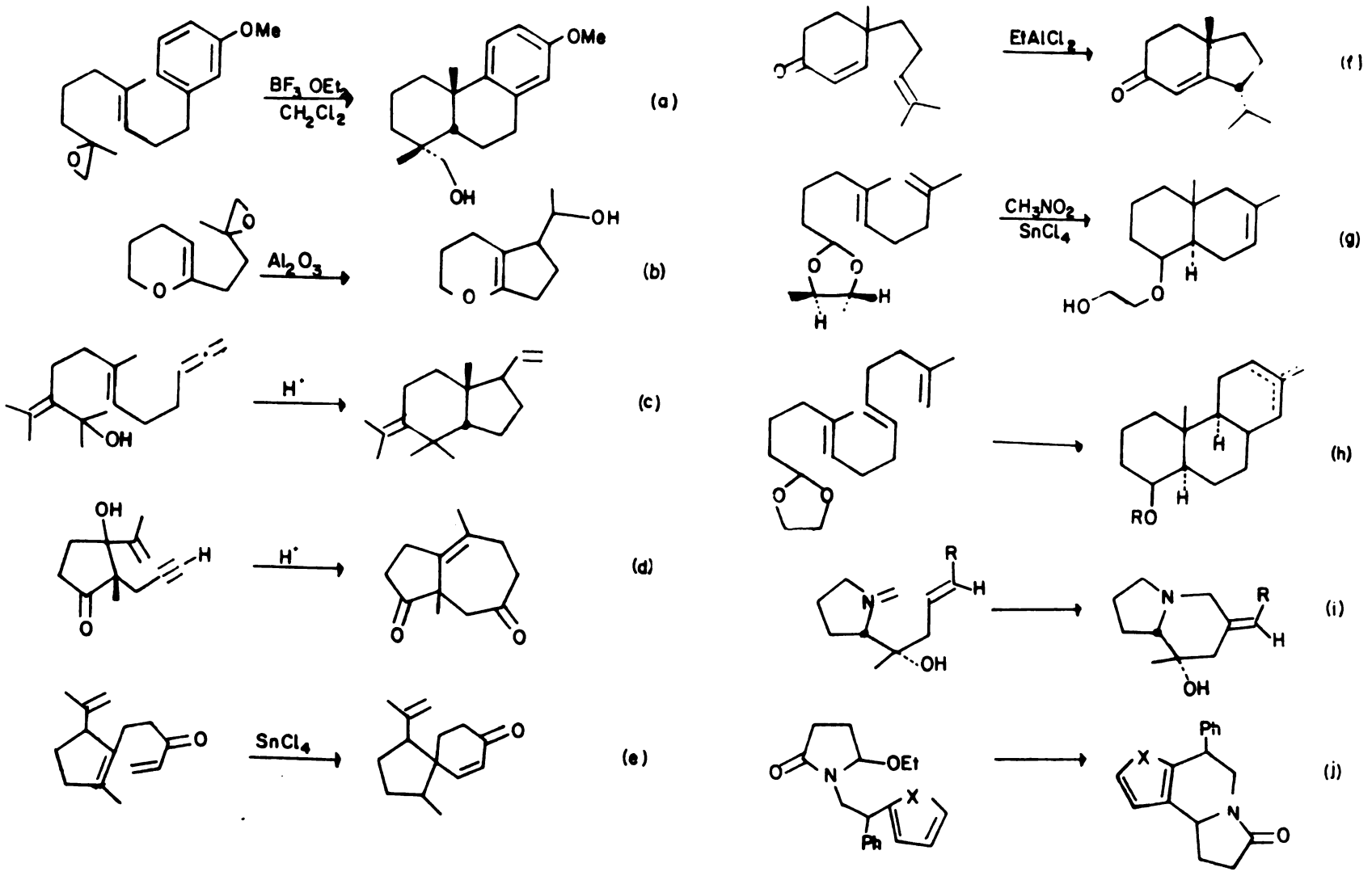


Figure 5 Cationic Cyclizations

increased acid lability of the derived disubstituted furan compared with starting material.

The use of standard terminator functions presents two major problems. The first is the apparent need for strongly acidic reaction conditions, which are not compatible with many synthetically useful functional groups. The second is the limited functionality which remains after the cyclization is completed, frequently leaving the resultant molecule without sufficient "handles" to readily complete the synthesis.

Furthermore, while methods for the preparation of fused-ring systems are well-developed and extensively utilized, relatively few general strategies for the construction of spiro-[23] and bridged-[24] ring systems exist. Therefore, methods must be developed to facilitate the preparation of spiro-, bridged-, and fused-ring systems, especially those within complex molecular environments. These methods should proceed in high chemical yield with excellent regio- and stereochemical control; and in addition, the conditions employed must be sufficiently mild to ensure the survival of synthetically useful functional groups.

It was the goal of this study to demonstrate the utility of the furyl moiety as a terminator in cationic cyclizations, and to develop a general methodology for the synthesis of bioactive natural products containing five-membered oxygen-containing heterocycles.

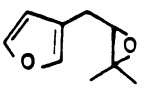
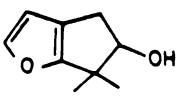
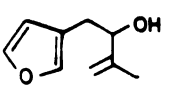
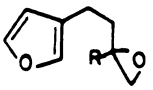
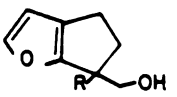
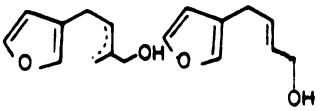
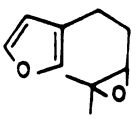
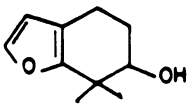
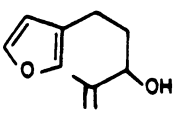
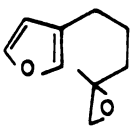
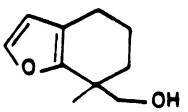
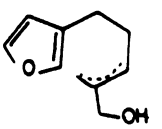
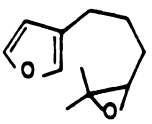
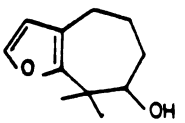
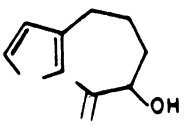
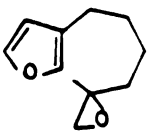
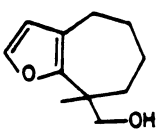
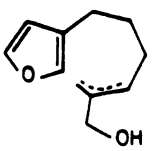
EPOXIDE INITIATED CYCLIZATIONS

The elegant studies of Goldsmith,[16a,b] vanTamelen,[16c-e] Boeckman,[16f], and Sharpless,[16g] among others, have shown that the epoxide function can be employed as the trigger for cationic cyclizations. These workers have employed a variety of Lewis acids to initiate the cyclization sequence. These relatively mild conditions coupled with the ease of epoxide introduction, either via epoxidation of a precursor olefin or direct incorporation, make the epoxide the initiator of choice.

The cyclization substrates which were examined were designed to permit entry into five-, six-, or seven-membered ring systems. In order to avoid ambiguity in the ring size expected from a given oxirane, the epoxide function will be biased where necessary to favor one mode of C-O bond polarization over the alternative. This design concept is in accord with the proposed polarized nature of the intermediate.[16] We have also examined the effect of placing the initiating function within the ring being formed (endocyclic) or outside the forming cycle (exocyclic).[26] According to Baldwin,[26] the exocyclic closures which generate five-, six-, or seven-membered rings should be favorable, whereas for the endocyclic closures only the formation of a six-membered ring is favorable. The required epoxyfurans and possible reaction products are illustrated in Table I.

The most obvious, and at the outset simplest, path to the desired epoxyfurans involved preparation of 3-furyl olefins followed by oxidation with peracid. The necessary olefins could be prepared by coupling the appropriate haloalkene with a judiciously functionalized isoprenoid furyl synthon. Standard bond forming reactions to furans customarily are polarized so that the furan serves as an electrophile and the alkyl group as a nucleophile (path a, Figure 6). In this approach, we have examined the "reverse polarity" bond formation, in

Table I Cyclization Substrates and Possible Products

Designation	Epoxide	Products	
5-Endo			
	13	19	20
5-Exo			
	14a R=Me b R=H	21a R=Me b R=H	22 23
6-Endo			
	15	24	25
6-Exo			
	16	26	27
7-Endo			
	17	28	29
7-Exo			
	18	30	31

which the furyl moiety serves as a nucleophile and the alkyl group as an electrophile (path b, Figure 6).

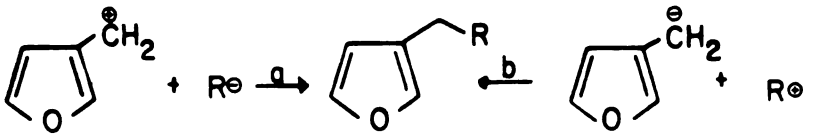
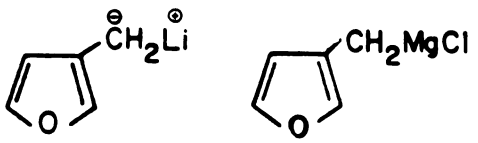


Figure 6 Bond Forming Polarities

This approach would involve the reaction of furyl organolithium **32** or Grignard reagent **33** with an appropriate electrophile. To the best of our knowledge, **32** has been reported only once in the literature.[27] Tanis[11] has demonstrated the usefulness of **33** in the preparation of 3-substituted furans by effecting its reaction with a variety of primary, secondary, and allylic halides in the presence of Kochi's catalyst Li_2CuCl_4.[11]



32 **33**

Figure 7 Furyl Anion Equivalents

A general approach to epoxyfurans is outlined in Figure 8. The coupling of Grignard reagent **33** with a haloalkene provides the corresponding (3-furyl) olefin **34**. Treatment of **34** with m-chlorobenzoic acid (MCPBA) should afford epoxide **35**. Although the furyl nucleus is known to be susceptible to oxidation

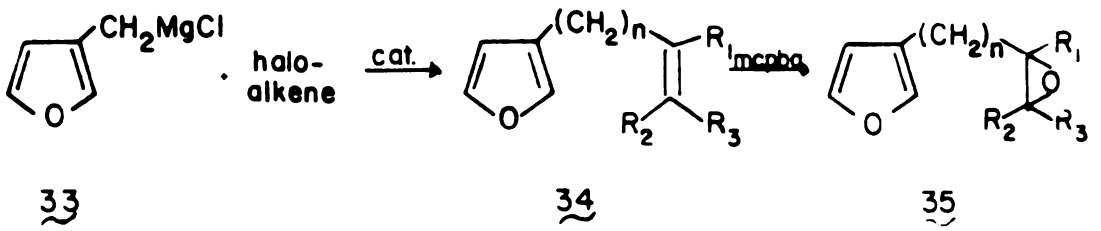


Figure 8 Furyl Epoxide Synthesis

(fig. 8[9,28,29]), relative rates of furan vs. olefin reaction with peracids as a function of the degree of substitution have not been reported.

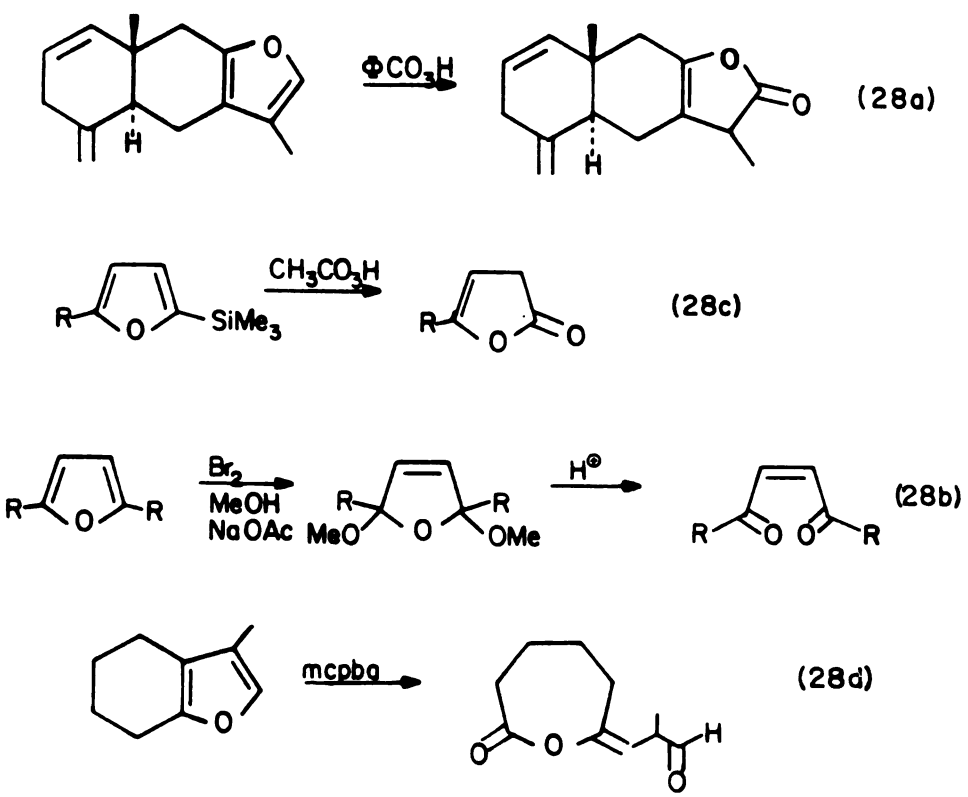
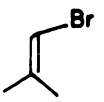
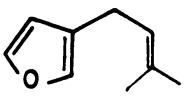
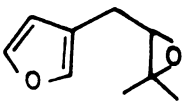
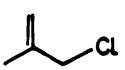
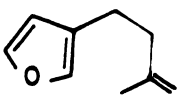
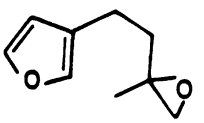
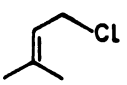
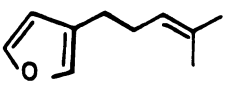
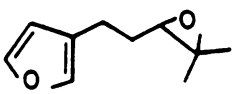
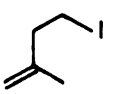
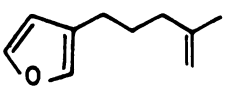
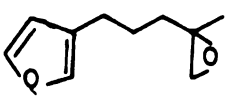
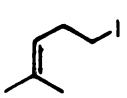
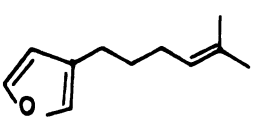
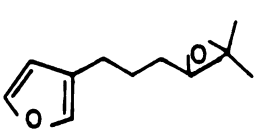


Figure 9 Furan Oxidations

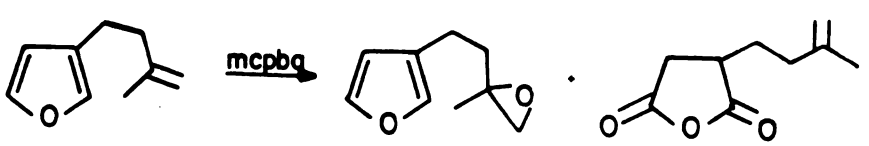
As shown in Table II the coupling reactions proceeded smoothly and in high yield when **33** was reacted with alkyl and allylic haides (runs **2-5**, Li_2CuCl_4

Table 2 Synthesis and Oxidation of (3-furyl)-olefins

Run	Olefin	Catalyst	Product (yield)	Oxidation Product (yield)
1		$FeCl_3$		
			36 (82%)	13 (88%)
2		Li_2CuCl_4		
			37 (82%)	14a (25%)
3		Li_2CuCl_4		
			38 (85%)	15 (85%)
4		Li_2CuCl_4		
			39 (83%)	16 (0%)
5		Li_2CuCl_4		
			40 (73%)	17 (81%)

as catalyst).[11] However the synthesis of **36** (n = 1, Figure 8) required a vinyl halide as a coupling partner. In this case anhydrous $FeCl_3$[30] (run 1, Table II) was employed as the catalyst providing an excellent yield of **36** (88%). Furyl olefins **36-40** were then each submitted to standard epoxidation conditions, 1.05 equiv of MCPBA in CH_2Cl_2 at 0°C. As can be seen in Table II the yield of the derived epoxide was dependent upon the olefin substitution. Trisubstituted furyl alkenes **36, 38** and **40** gave oxiranes **13, 15,** and **17** in 81-88% yields. Furyl alkene **37** afforded epoxide **14a** in a greatly reduced yield (25%), and **39** failed to give even trace quantities of **16**.

A closer examination of the oxidation of **37** (Figure 10) showed that epoxide **14a** was accompanied by anhydride **41** (37%), with 23% of alkene **37** recovered. However, olefin **39**, a homologue of **37**, afforded only the corresponding anhydride and unreacted **39**. Replacing MCPBA with other oxidants[31] did not lead to increased selectivity. Clearly, the degree of olefin substitution has a profound effect on the product distribution. In general, the protocol outlined in Figure 8 is not viable if the olefin is mono- or disubstituted.



37 14a(25%) 41(37%)

Figure 10 Oxidation of 37

We then examined alternate routes to epoxides **14b, 16,** and **18**. Our observation[11] that the reaction of **33** with an allylic halide possessing a potentially reactive distal epoxide function afforded only 7,8-epoxydendrolasin

42 (79%, eq 2) suggested this sequence be applied to the preparation of **14b, 16** and **18.** Epoxy iodides **43, 44a,** and **45a** and tosylates **44b** and **45b** were each separately treated with **33** (Figure 11) to provide only the products of attack at the epoxide residue. Although Boeckman has demonstrated that organolithium reagents may be coupled with epoxy iodides in good yields,[16f] we initially avoided employing of 3-furylmethyllithium (**32**) in this context. Our major concern was the possibility that the precedented allylic-type rearrangement of anion **32** would intervene, resulting in electrophile capture at the adjacent α-position.[32]

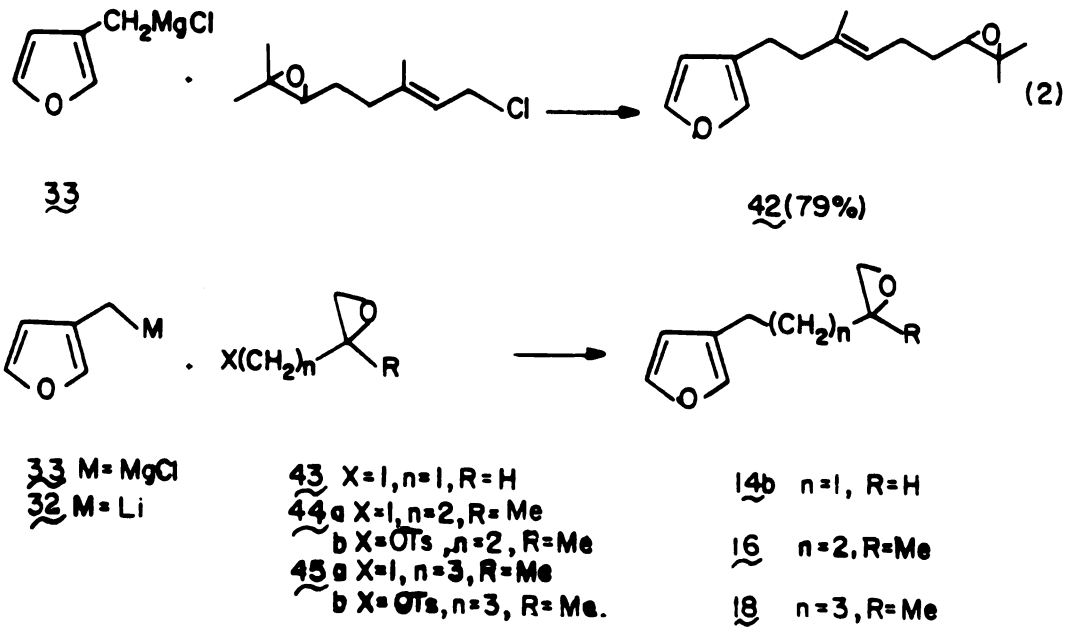
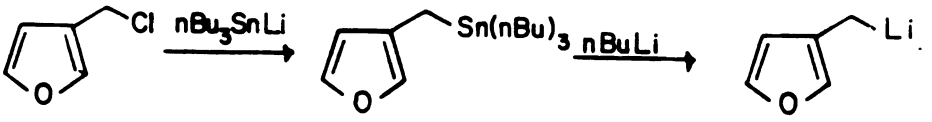


Figure 11 Coupling of Iodoepoxides

Organolithium **32** was readily prepared as described in (Figure 12). Treatment of 3-(chloromethyl)furan[11] **46**, with n-Bu_3SnLi[33] provided stannylfuran **47** in 89% distilled yield. Tin-lithium exchange proceeded smoothly, affording a virtually quantitative yield of **32** as determined by

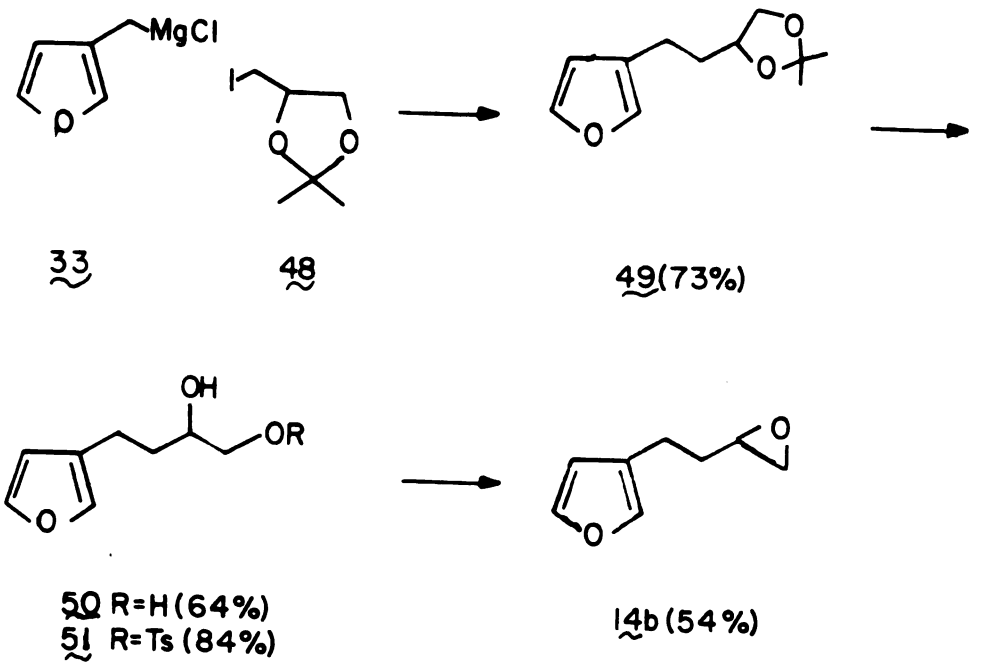
titration. To our delight, **32** reacted with iodo epoxides **44a** and **45a** in the presence of HMPA (-25°C)[16f] to give epoxy-furans **16** and **18** in 73% and 68%



46 47 32

Figure 12 Preparation of 32

yields, respectively. Products resulting from the rearranged anion or from attack at the epoxide could not be detected. However, oxirane **14b** could not be prepared by this technique. As a result, we were forced to take the rather circuitous route to **14b** described in (Figure 13). Coupling of **33** with the protected iodo diol **48** afforded furan **49** in 73% yield. This, after hydrolysis, conversion of **50** to the monotosylate **51**, and closure of the epoxide ring with NaH gave **14b** (94%).



33 48 49(73%)

50 R=H(64%)
51 R=Ts(84%)

14b(54%)

Figure 13 Preparation of 14b

Cyclization Studies. With the desired cyclization substrates in hand, the ring closing sequence was then examined. Of the many Lewis acids which are available, powerfully acidic substances such as boron trifluoride etherate are often selected to catalyze epoxy olefin cyclizations. Given the relatively poor nucleophilic character of the furyl residue and the acid lability of the starting materials and desired products, the choice of Lewis acid should have a profound effect in the partitioning of this reaction between a fruitful cyclization pathway and undesired products.

Six Lewis acids were selected to determine their ability to promote epoxy furan cyclization (Table III). Other than the standard $BF_3 \cdot OEt_2$[16a-f] the choice of these Lewis acids was dictated by two factors: (i) the ability to modify the potency of a group of Lewis acids with a common metal center and (ii) the possibility of moderating the Bronsted acidity of the medium through the choice of Lewis acid. Thus, adventitious protic acid might be scavenged by Lewis acids possessing a carbon-metal bond. Alternatively, with proper choice of metal, the product metal-alcohol complex should be a much weaker protic acid compared to a BF_3-alcohol complex.

Snider has reported the successful application of alkyl aluminum halides as Lewis acids in acid-sensitive cyclizations. The alkyl aluminum halides cover a wide range of Lewis acidity[35] from $EtAlCl_2$, which is only slightly less potent than $AlCl_3$, to the very mild Me_3Al. Both the range of Lewis acidity presented by the alkyl aluminum halides and their ability to scavange protic acids make them likely candidates for initiating epoxy furan cyclizations. Further modification of aluminum centered Lewis acids is possible, as demonstrated by Boeckman.[16f] Basic alumina in hexane (24 h, room temperature) was also found to cyclize various epoxy vinyl ethers (Figure 5b) in good yields.[16f]

TABLE 3

Cyclization Results

Epoxy-furan	Lewis acid (eq)	BF_3OEt_2 (0.3eq)	$EtAlCl_2$ (2eq)	Et_2AlCl (2eq)	Al_2O_3	$Ti(OiPr)_3$ (3eq)	$ClZnI_2$ (3eq)
13		**20**(62%)	—	**20**(85%)	**20**(83%)	**20**(80%)	**20**(76%)
14a		**22**(53%)	—	**22**(81%)	—	**22**(72%)	**22**(70%)
14b		**23**(49%)	—	**23**(78%)	—	No Rxn.	**21b**(25%), **23**(44%)
15		**24**(47%)	**24**(16%), **25**(57%)	**24**(22%), **25**(49%)	**24**(32%), **25**(51%)	**24**(78%)	**24**(71%)
16		**26**(30%) **27**(10%)	**26**(0%), **27**(73%)	**26**(10%), **27**(70%)	**26**(0%), **27**(81%)	**26**(89%)	**26**(70%)
17		**28**(0%), **29**(41%)	**28**(0%), **29**(76%)	**28**(10%), **29**(69%)	**28**(0%), **29**(83%)	**28**(87%), **29**(8%)	**28**(88%), **29**(9%)
18		**30**(10%), **31**(12%)	**30**(0%), **31**(64%)	**30**(0%), **31**(73%)	**30**(0%), **31**(79%)	**30**(36%), **31**(47%)	**30**(23%), **31**(52%)

Titanium tetrachloride is a powerful Lewis acid which has been observed to react with epoxides to provide β-chlorotitanates.[36] The affinity of titanium for an epoxide oxygen, and the acidity of the alcohol-Ti complex, can be tempered by replacing chloride by alkoxy groups, such as isopropoxy. The mildly acidic titanium tetraalkoxides have been shown to be effective in the catalysis of aldol condensations.[36] Stork[37] and Sharpless[16g] have successfully applied $Ti(O\text{-}i\text{-}Pr)_4$ to intramolecular Michael addition and β-OH-epoxide-initiated olefin cyclizations, respectively.

Zinc iodide,[38] the final Lewis acid examined in this study, was selected based on an assumption that the product zinc-alcohol complex, generated during the course of the cyclization, would be a weak protic acid. The correctness of this supposition is illustrated by Marshall's successful closure of an acid-labile diene-aldehyde during his synthesis of occidentalol.[38a]

The substrate epoxy furans were then submitted to cyclization conditions as follows. Oxirane **13** was initially treated by "standard" conditions for polyene cyclizations, 0.33 equiv of $BF_3{\cdot}OEt_2$[13] in CH_2Cl_2 at -25°C. As anticipated, **13** failed to yield the cyclized product **19**. Instead, 62% of allylic alcohol **20** was obtained. Epoxy furans **14a, 14b, 15, 16, 17,** and **18** were then treated with $BF_3{\cdot}OEt_2$, in a similar fashion (Table III). Only the six-membered endocyclic precursor **15** and the 6-exo-epoxy furan **16** provided appreciable quantities of cyclized products, leading to **24** and **26** in 47% and 30% yields, respectively. The majority of the materials recovered from the attempted cyclizations of **14a, 14b, 17,** and **18** were the corresponding allylic alcohols. In all of these cases the material balance was poor, with only about 60% of the starting mass recovered. The general lack of cyclization, coupled with the poor mass balance, clearly demonstrates that the standard cyclization conditions are not generally applicable.

Our study of aluminum based Lewis acids in the cyclization of epoxy furans began with $EtAlCl_2$, and Et_2AlCl. Treatment of epoxy furans **13-18** with two equiv of either $EtAlCl_2$ or Et_2AlCl, in CH_2Cl_2 at -25°C, provided little cyclized materials (Table III). As with $BF_3{\cdot}OEt_2$ only the 6-endo-epoxide **15** yielded appreciable quantities of cyclized products, 16% and 22%, respectively. Smaller quantities of **26** (10%) and **28** (10%) were isolated after treatment of **16** and **17** with Et_2AlCl. However, as is obvious from an inspection of Table III, this modification of the Lewis acid resulted in a marked improvement in the mass balance.

The results from these cyclization studies demonstrated that the majority of the substrate was being diverted to undesired elimination products. Therefore, further moderation of the Lewis acid was required. Stirring epoxy furans **13** and **15-17** with alumina resulted in very high yields (60-90%) of elimination products. Only substrate **15** afforded cyclized product, and **24** was obtained in 32% yield. Again elimination was preferred over cyclization in all of the cases examined.

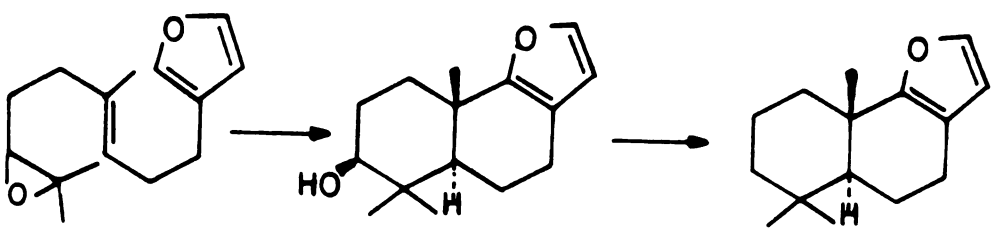
In the titanium series, $Ti(O\text{-}i\text{-}Pr)_4$ was initially examined as a Lewis acid for cyclization of epoxides **13-18**. Exposure of these substances to 3 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 for extended periods at room temperature resulted in quantitative starting material recovery.

The next acid in this series $Ti(O\text{-}i\text{-}Pr)_3Cl$, prepared by the disproportionation of 3 equiv. of $Ti(O\text{-}i\text{-}Pr)_4$ with 1 equiv. $TiCl_4$[36] (1.5 M in CH_2Cl_2), proved to be an efficient and useful promoter of epoxy furan cyclization. As before, oxiranes **13** and **14a** provided only products of elimination, allylic alcohols **20** (80%) and **22** (72%), respectively. Epoxide **14b** could not be induced to react, even after treatment with 3 equiv. of

$Ti(O\text{-}i\text{-}Pr)_3Cl$ (CH_2Cl_2) at room temperature for 24 h. Similar treatment of epoxy furan **15** led to the formation of the desired cyclized adduct **24** in 78% yield, virtually uncontaminated by elimination products. 6-exo-Epoxide **16** and 7-endo-epoxide **17** afforded excellent yields of cyclized products **26** (89%) and **28** (87%), respectively, the latter being accompanied by a modest amount of allylic alcohol **29** (8%). Even epoxide **18**, designated as 7-exo, gave a respectable yield of cyclic product **30** (36%) when exposed to $Ti(O\text{-}i\text{-}Pr)_3Cl$.

Cyclizations of furyl epoxides **13-18** with ZnI_2, the final Lewis acid in this study, were performed in CH_2Cl_2 at room temperature. Treatment of furyl epoxides **11** and **12a** with 3 equiv. of freshly prepared ZnI_2 led to the isolation of high yields of the derived allylic alcohols (Table III). However furyl epoxide **14b** afforded the elusive five-membered cyclic product **21b**, albeit in only 25% yield under similar conditions. Epoxy furans **15-18** provided good to excellent yields of the corresponding cyclic products accompanied by small quantities of allylic alcohols.

A more rigorous test of the epoxy furan cyclization as a route to naturally occurring terpenoids might require the formation of two or more rings during the sequence. Pallescensin-A (**52**)[39] provided an appropriate test. In the event, epoxydendrolasin (**42**)[11] (eq 2) gave 3 - β -OH pallascensin-A (**53**)[40] in 47% yield upon treatment with $BF_3 \cdot OEt_2$ (Figure 14). Zinc iodide



42 53 52

Figure 14 Preparation of Pallascensin A (52)

and triisopropoxytitanium chloride gave even higher yields of **53**, 62% and 65%, respectively, as well as a cleaner reaction mixture. Compound **53** was then smoothly converted to pallescensin-A (**52**) as described by Nasipuri.[40]

These results (Table III) clearly demonstrate the potential of the epoxy furan cyclization for the formation of six- and seven-membered rings. Good to excellent yields of cyclic products can be realized with a judicious choice of Lewis acid. However, closure to form five-membered rings remains problematic. As anticipated, the 5-endo type of closure, represented by epoxide **13**, afforded only elimination products. In this case the overlap necessary for cyclization is precluded by the presence of but a single sp^3 carbon in the forming cycle. The low yield of product **21b** from 5-exo-epoxide **14b** was initially disappointing, since there is ample literature precendent for cyclizations to form five-membered rings with similar steric constraints.[16f,35b,41] However, each of these cases the terminator function is considerably more nucleophilic than a furan. A solution, in principle, to this problem is to increase the nucleophilicity of the furyl terminator by introduction of an electron donating substituent onto the furan ring. Unfortunately few examples of stable, appropriately substituted furans related to organometallics **33** and **32** are known.[9]

ALLYLIC ALCOHOL AND ENONE INITIATED CYCLIZATIONS

Our previous work demonstrated the utility of epoxide initiated furan terminated cationic cyclizations. However, these substrates provided access only to rather simple and relatively unfunctionalized fused-ring systems; and in addition, the difficulties encountered in the preparation of the requisite epoxy-furans reduced the generality of this approach. In an attempt to expand the usefulness of furan terminated cationic cyclizations, we have examined the reaction of furyl dianion equivalent **54** (Figure 15) with a variety of bis-electrophillic synthons **55–57**. The interaction of the active furan side chain nucleophilic center with the bis-electrophile will provide a coupling product; subsequent activation of the second electrophilic center followed by aromatic substitution could provide fused-**58**, spirocyclic-**59** and bridged-**60** ring systems. Manipulation of the furan nucleus (see Figure 4) and other residual functional groups would provide complex intermediates for the preparation of diverse classes of bioactive natural products.

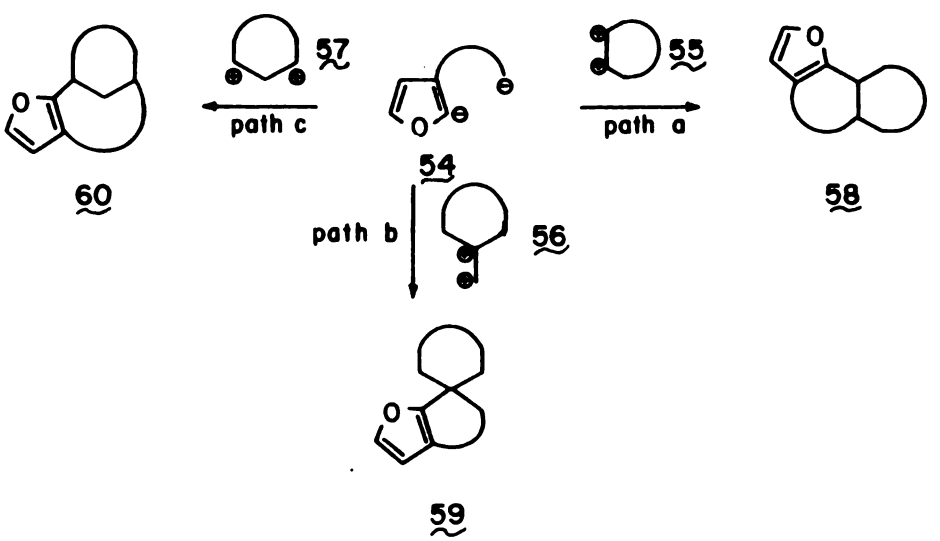


Figure 15 Dianion Couplings

Design and Synthesis of Cyclization Substrates

Of paramount importance to this study was the selection of the bis-electrophilic moieties illustrated in Figure 15. The relative level of reactivity must be arranged so that the active furan side-chain nucleophilic center reacts selectively at one of the electrophilic sites so as to furnish the desired regioisomer upon cyclization. In order to minimize potential selectivity problems in the initial addition, we sought equivalents of bis-electrophiles **55** and **56** (Figure 15, paths A and B) which would reveal a second electrophilic center on the adjacent carbon as a result of the initial addition. Recent reports by Marino[42a,c-f], Wender[42g], and Ziegler[42b] have demonstrated the usefulness of vinyl epoxides[42a-f] and enol ethers of α,β-epoxy ketones in SN_2' type addition of cuprates (Figure 16). In these processes, an allylic alcohol and enone, are created respectively, providing a potential second electrophilic center on the carbon adjacent to the position of initial attack. These results suggest the applicability of α,β-epoxy ketone enol ethers **60** and vinyl spiro-epoxides **61** (Figure 17) as equivalents of the hypothetical **55** in the formation of fused ring compounds (Figure 15, path A). An exo-methylene vinyl epoxide **62** (Figure 18) would provide access to spirocyclic substances as the operational equivalent of **56** (Figure 15, path B). The syntheses of bridged species (Figure 15, path C) in which the distance between the electrophilic centers can be variable is best dealt with on a case-to-case basis. This analysis pinpoints allylic alcohols[12a-h,23v,43], prepared directly from **61** and **62** (Figures 16-18) or by reduction of the enone product of **60**, and/or enones and enals[23v,44] prepared from allylic alcohols, as the initiators in cyclization step.

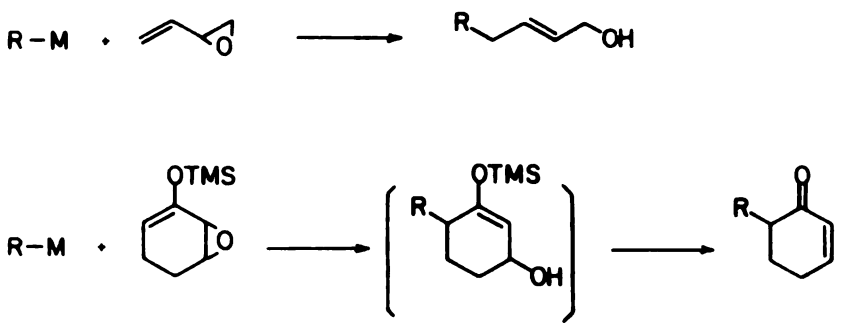


Figure 16 Additions to Vinyl Epoxides

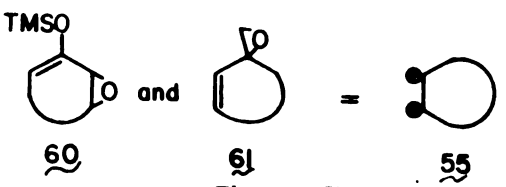


Figure 17

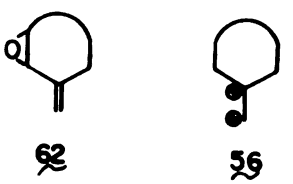
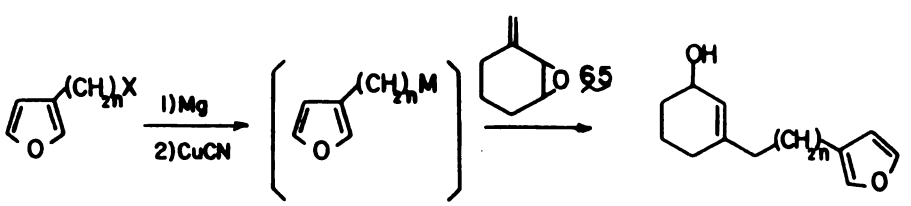


Figure 18

In the event, Grignard reagents prepared from 3-chloromethyl furan **46**[45a], 2-(3-furyl)-1-bromoethane **63**[45b], and 3(3-furyl)-1-bromopropane[45c] **64** were treated with CuCN[7a,c-f] and allowed to react with the readily available vinyl epoxide **65** (Figure 19) to provide allylic alcohols **66–68**, precursors to

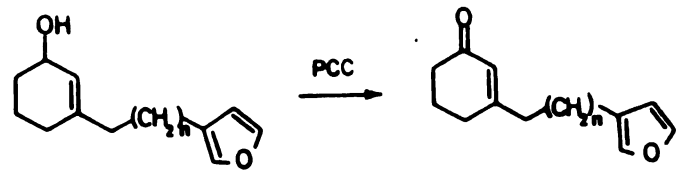


	n	X
46	1	Cl
63	2	Br
64	3	Br

	n	Yield
66	1	82%
67	2	58%
68	3	62%

Figure 19 Preparation of 66-68

spiro-[4.5]decane, [5.5]undecane and [5.6]dodecane systems, respectively, in good to excellent yields. The corresponding enones **69–71** were readily prepared (Figure 20) via oxidation (PCC)[46] of alcohols **66–68**. Additionally, the Grignard

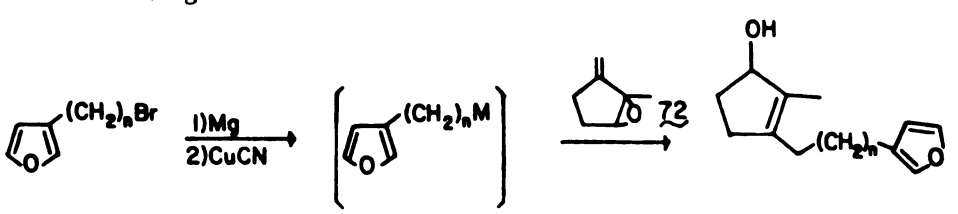


	n
66	1
67	2
68	3

	n	Yield
69	1	87%
70	2	83%
71	3	84%

Figure 20 Oxidation of 66-68

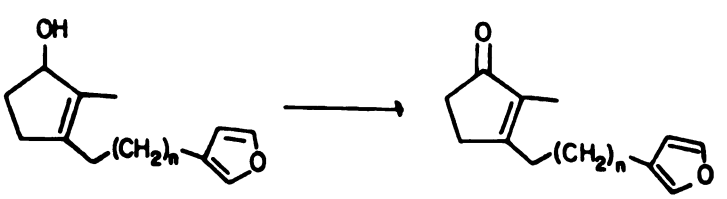
reagents prepared from **63** and **64** were treated with CuCN and coupled with vinyl epoxide **72** (Figure 21) to provide the acid labile allylic alcohols **73** and **74**, precursors to the spiro-[4.5]decane, and [4.6]undecane systems in good yield. The corresponding enones **75** and **76** were prepared by oxidation of the alcohols (Figure 22).



	n
63	2
64	3

	n	Yield
73	2	59%
74	3	63%

Figure 21 Preparation of 73-74



	n
73	2
74	3

	n	Yield
75	2	73%
76	3	74%

Figure 22 Oxidation of 73-74

The synthesis of fused-ring compounds requires **60** and **61** as annulation partners. For this study, cyclohexenone and cyclopentenone were selected as the precursors to **60** and **61** which, when treated with the Grignard reagents derived from **63** and **64**, might lead to fused bicyclo-[4.4.0]-decane and bicyclo-[5.4.0]-undecane ring systems, respectively. Enol ether **77** was easily prepared by the methods of Marino[42f] and Wender[42g] from cyclohexenone; however, enol ether **78** had to be prepared and used in situ. To the best of our knowledge, **79** has not been reported in the literature. A direct approach to **79** using Corey's dimethylsulfonium methylide[47] provided **79** in variable (0-35%)

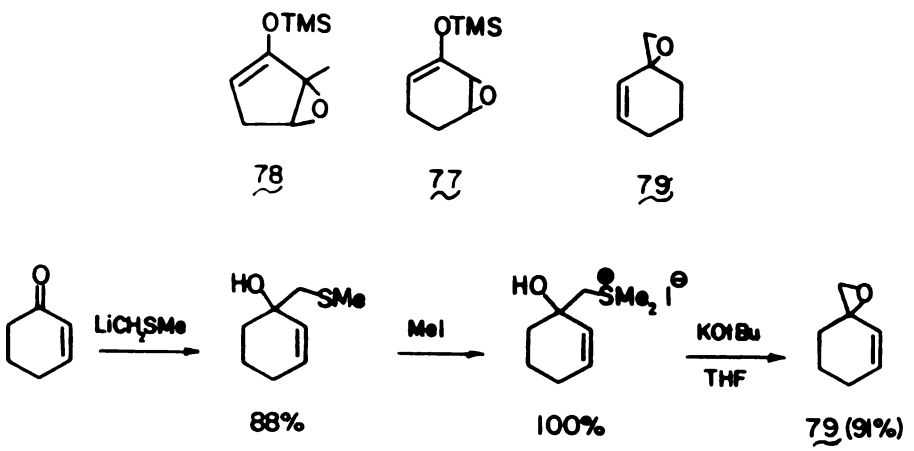
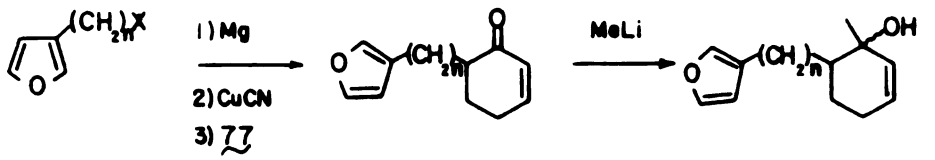


Figure 23 Preparation of 79

yields. We then examined the alternative procedure outlined in Figure 23. The addition of methylthiomethyl lithium[48] to cyclohexenone provided the 3°-allylic alcohol in 88% yield. Methylation at sulfur (CH_3I, 100%) and treatment of the resulting sulfonium salt with KOtBu (THF) provides **79** in 80% overall yield from cyclohexenone.[49] With **71-79** available, the fused-ring cyclization substrates were prepared as described in Figures 24 and 25.

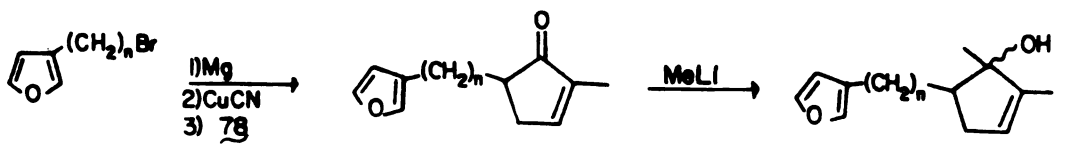


	n	X
63	2	Br
64	3	Br

	n	Yield
80	2	75%
81	3	72%

	n	Yield
82	2	90%
83	3	90%

Figure 24 Preparation of 82-83



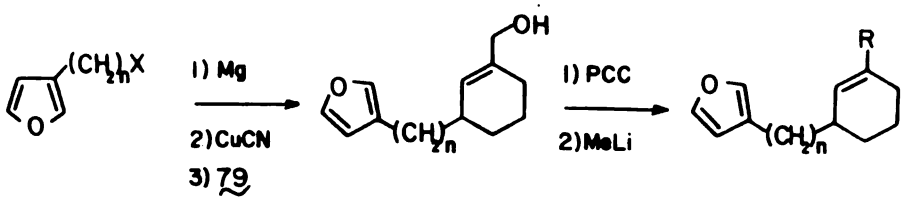
	n
63	2
64	3

	n	Yield
84	2	52%
85	3	54%

	n	Yield
86	2	83%
87	3	78%

Figure 25 Preparation of 86-87

Treatment of the Grignard reagents derived from **63** aqnd **64** with CuCN[7] followed by **79** provided enones **80** and **81** in 75% and 72% yields, respectively. The addition of MeLi afforded 3°-allylic alcohol cyclization substrates **82** and **83** (90%). Similarly, addition to **78** provided the enones **84** (52%) and **85** (55%), which on treatment with methyl lithium afforded the very unstable tertiary allylic alcohols **86** and **87** in 83% and 78% yields respectively. SN_2' addition to spiroepoxide **79** (Figure 25) provided allylic alcohols **88** (78%), **89** (56%), and **90** (58%). Oxidation (PCC) of **88-90** gave enals **91** (79%), **92** (83%), and **93** (78%); the addition of CH_3Li to **92** and **93** afforded 2°-allylic alcohols **94** (90%) and **95** (85%).



	n	X
46	1	Cl
63	2	Br
64	3	Br

	n	Yield
88	1	78%
89	2	56%
90	3	58%

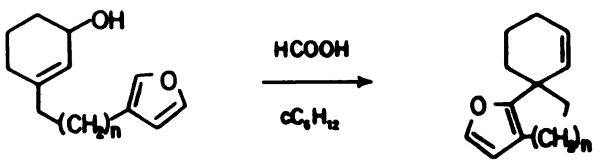
	n	R	Yield
91	1	CHO	79%
92	2	CHO	83%
93	3	CHO	78%
94	2	CH_3CHOH	90%
95	3	CH_3CHOH	85%

Figure 26 Preparation of 88-95

Cyclization Studies

With the desired cyclization substrates available, the ring closing sequence was examined. Given the relatively poor nucleophilic character of the furyl residue relative to standard terminator functions[23,50] and the increased acid lability of the derived product disubstituted furans compared with the starting materials[50], the choice of reaction conditions should have a profound effect in the partitioning of the reaction between a fruitful cyclization pathway and undesired products. During our study of epoxide initiated cyclizations , we observed that the mild Lewis acids $Ti(OiPr)_3Cl$ and $ZnI_2 \cdot OEt_2$ provided the best balance between Lewis and Brønsted acidity of the medium, resulting in high yields of cyclized products. Such Lewis acids, as well as the alkyl aluminum halides examined by Snider[9k] might cause enones **69-71** and **75-76**, and enals **94** and **95** to undergo cyclization. Enones and enals have also been cyclized with acid[44], Ac_2O-H^+[44], and $(CF_3CO)_2O$, CF_3CO_2H[44], however, the fragility of the products and the facility of furan acylation may render these reaction conditions useless. Allylic alcohol

initiators for cationic cyclizations have been extensively examined by Johnson and others [12a-h,43] and the reaction conditions which have been employed generally involve a protic acid of reasonable strength in a solvent in which it is soluble. Of the many conditions reported in the literature, the two-phase mixture of cyclohexane and anhydrous formic acid[43] appeared to be the mildest method for initiating the cyclization of allylic alcohols.

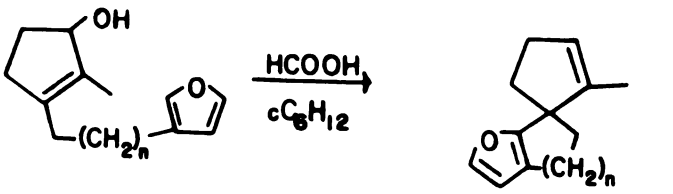


	n
66	1
67	2
68	3

	n	Yield
96	1	0%(formate 84%)
97	2	72%
98	3	58%

Figure 27 Cyclization of 66-68

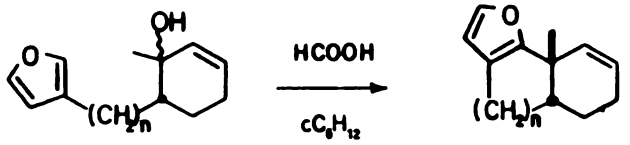
Exposure of allylic alcohols **66-68** (Figure 27) to anhydrous formic acid-cyclohexane for 5-15 minutes at room temperature resulted in the smooth closure of **67** and **68** to provide the corresponding spiro[5.5]undecane **97** (72%) and spiro[5.6]dodecane **98** (58%) ring systems. Allylic alcohol **66**, precursor to a spiro[5.4]decane, failed to provide **96**, yielding instead the formate (84%). The inability of allylic alcohol **96** to form a five-membered ring was expected based upon our earlier experience with epoxy-furans. As we have previously noted with cyclization substrates related to **96**, the overlap required for ring closure to occur is difficult to achieve, as the cation derived from **96**, possesses but two sp^3-hybridized carbon atoms in the forming cycle.[51] Alcohols **73** and **74** were smoothly converted, in good yield, to the spiro[4.5]decene **99** and the spiro[4.6]undecene **100** respectively in good yield (Figure 28).



	n
73	2
74	3

	n	Yield
99	2	58%
100	3	53%

Figure 28 Cyclization of 73-74

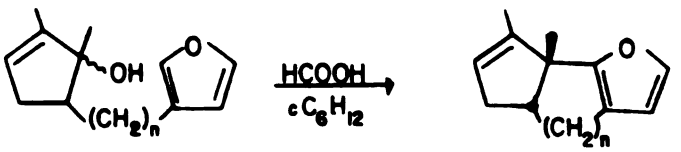


	n
82	2
83	3

	n	Yield
101	2	73%
102	3	56%

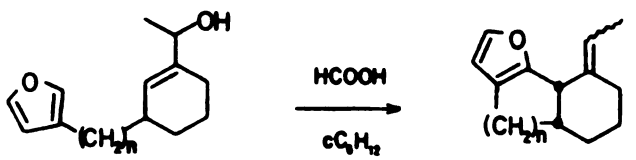
Figure 29 Cyclization of 82-83

Alcohols **82** and **83**, when treated with formic acid and cyclohexane (Figure 29), provide good yields of the fused furan containing bicyclo-[4.4.0]decane **101** (73%) and bicyclo[5.6.0]undecane **102** (56%). The assignment of the cis-ring fusion in **101** and **102** is based upon precedent[12] and is expected from the method of synthesis. Similar exposure of alcohols **86** and **87** (Figure 30) provided the bicyclo[3.4.0]nonene **103** and the bicyclo[3.5.0]decene **104** in good yields. Additionally, treatment of primary allylic alcohols **88, 89** and **90**, also precursors to fused ring systems, with formic acid/cyclohexane, led to the isolation of the corresponding formate esters in excellent (80-90%) yields. However, the related secondary allylic alcohols **94** and **95** cyclized smoothly as is illustrated in Figure 31, affording **103** (68%) and **104** (61%) as a mixture of exo-ethylidene double bond isomers.



	n		n	Yield
86	2	103	2	64%
87	3	104	3	57%

Figure 30 Cyclization of 86-87

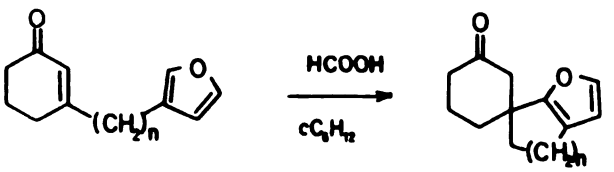


	n		n	Yield
94	2	105	2	68%
95	3	106	3	61%

Figure 31 Cyclization of 94-95

With allylic alcohols firmly established as effective initiators for furan terminated cationic cyclization, we next examined the cyclization of enones **69-71, 75, 76** and enals **91-93.** Compounds **69-71** and **91-93** were exposed to various Lewis acids[52] under numerous sets of reaction conditions to no avail. The more potent Lewis acids $AlCl_3$, $TiCl_4$, BF_3 extensively decomposed substrates **69-71** and **91-93,** however, when milder Lewis acids such as $MgBr_2$, ZnI_2 and $Ti(OiPr)_3Cl$ were employed, the starting materials were recovered in nearly quantitative yields. Acylative-type enone and enal cyclizations similar to those reported by Andersen[44,h], Marshall[44] and Harding[44,i] were then attempted. Treatment of enones **69-71** and enals **91-93** with either Ac_2O,$HClO_4$,EtOAc or $(CF_3CO)_2O$,CF_3CO_2H resulted in a facile and high

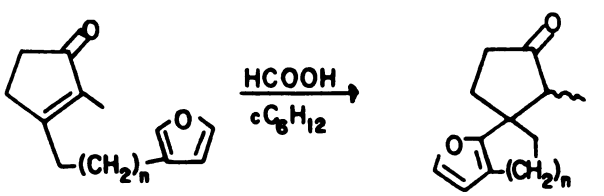
yield acylation of the furyl nucleus at the 2-position. Having failed to cyclize **69-71** and **91-93** under the relatively mild Lewis acid or acylation reaction conditions, we turned to a protic acid mediated closure. Enones **69-71** were each dissolved or suspended in cyclohexane, and formic acid was added to generate a red color. Quenching of the reaction after 5-15 minutes (Figure 32) and analysis of the product mixtures demonstrated that, of the three substrates **69-71**, only **70** had suffered cyclization, providing the furan-containing spiro[5.5]undecane **105** in 60% yield, enones **69** and **70** were recovered quantitatively. Additionally, acid treatment of enones **75** and **76** provided **106** in 61% yield and unreacted **76** respectively. More vigorous reaction conditions led to the complete destruction of **69**, **70** and **76**. Similar treatment of enals **91-93** resulted in starting material recovery; or in cases of harsher treatment, polymerization.



	n
69	1
70	2
71	3

	n	Yield
		NR
107	2	66%
		NR

Figure 32 Attempted Cyclization of 69-71



	n
75	2
76	3

	n	Yield
108	2	72%
	3	NR

Figure 33 Attempted Cyclization of 75-76

In order to investigate the possibility that enone cyclization is reversable and, in the case of seven-membered ring formation, thermo-dynamically unfavorable, the ketone **111**, which would result from cyclization of enone **71**, was prepared from alkene **98** and submitted to the reaction conditions used in the attempted cyclization of **71**. Hydroboration of **98** provided a 10:1 mixture of regioisomers with **109** being the major isomer, produced in 73% yield. Oxidation of **109** with PCC provided an excellent yield of ketone **110**, which, when submitted to the two phase mixture of formic acid-cyclohexane for 1 hour, was recovered unchanged.

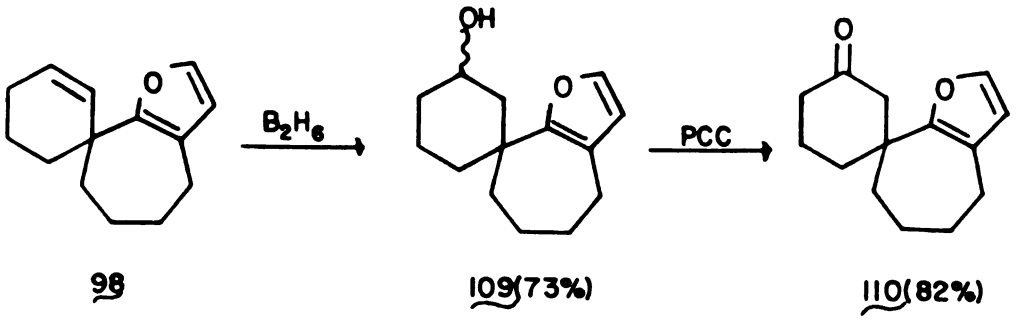


Figure 34 Preparation of 110

The Synthesis of a Bridged System. The Preparation of Nakafuran-9 6.

The construction of bridged-ring systems was demonstrated as part of a synthesis of nakafuran-9 **6**. Nakafuran-9 **6** was recently isolated by Scheuer[7] from the marine sponge Dysidea fragilis and from the nudibranchs Hypselodoris godeffroyana and Chromodoris maridadilus which graze upon D. fragilis. Nakafuran-9 **6** and the closely related nakafuran-8 **5** possess fish antifeedant properties, having been observed to repel predacious reef fishes which feed upon the soft bodied nudibranchs. A retrosynthesis of nakafuran-9 **6**, presented

in Figure 35, suggests that the bicyclo[4.3.1]decane skeleton of **6** ultimately would be available from 3-furyl-methyl dianion and a highly substituted dication.

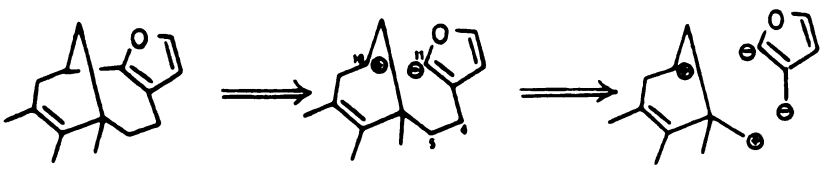


Figure 35 Retrosynthesis of Nakafuran-9

The dication equivalent selected was the vinyl expoxide **111** (Figure 35). The coupling of the Grignard reagent prepared from 3-chloromethyl furan **46** with **11** (CuCN) provided allylic alcohol **112** (62%), thus establishing the C-4, C-5 bond of **6**. Oxidation (PCC, 89%) and treatment of the derived enone with $MeCu{\cdot}BF_3$[53] introduces the C-6-CH_3 group giving ketone **113** (70%) as a 60:40 mixture at pro-C-7 in 62% overall yield from **102**. The second electrophilic center needed for closure at C-10 was introduced smoothly as the enone *via* selenylation[54] of the kinetic enolate followed by oxidation (H_2O_2, Et_3N) and elimination of the selenoxide, giving enone **114** (72%). We found it necessary to perform the oxidation-elimination in the presence of a base (Et_3N) because the phenylseleninic acid produced in the elimination promoted cyclization of **114** providing a mixture of **114** and **115** in greatly reduced yield. Cyclization of **114** was effected with HCO_2H-cC_6H_{12} affording the crucial bicyclo[4.3.1]decanone **115** in excellent (79%) yield as a 60:40 mixture at C-7. All that remained to complete the synthesis of nakafuran-9 **6** was the introduction of a methyl at C-8 and the placement of a double bond at C-7-C-8. A methyl equivalent and double bond were simultaneously introduced *via* a Wittig olefination of **115** using the conditions of Conia[55]

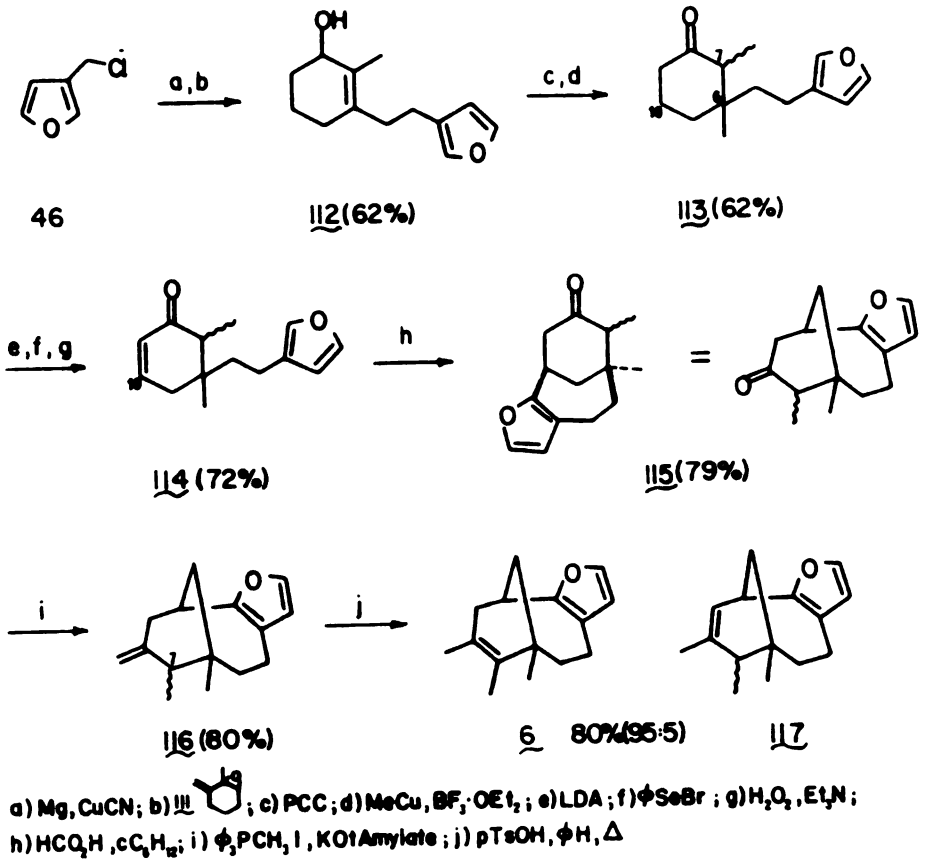


Figure 36 Preparation of Nakafuran-9

(ϕ_3P-CH_3I, K-t-amylate) to give **116** in 80% yield as a 60:40 mixture at C-7. Olefin migration was attempted with $(\phi CN)_2PdCl_2$[56a], $RhCl_3(H_2O)_3$[56b], and $(\phi_3P)_3RhHCl$[22c]; in each case, starting material **116** was recovered unchanged. Acid catalyzed olefin migration was investigated and after extensive experimentation, we found that exposure of **116** to a solution of pTsOH in refluxing benzene for 15 minutes provided a 95:5 mixture of nakafuran-9 **9** and 8,9-isonakafuran-9 **117** in 80% yield. The identity of the extremely acid labile **6** was confirmed by a comparision of spectral data with those of authentic **6**.[57]

SUMMARY AND CONCLUSIONS

Several 3-substituted furans with latent electrophiles in the side chain were prepared as cyclization substrates. 3-Furylmethyl magnesium chloride is readily coupled with a variety of ω-haloalkenes to afford the corresponding 3-substituted furan in good to excellent yields. Epoxidation of the product furyl olefins was found to be effective in producing the desired cyclization substrates only when the olefin was trisubstituted. Less highly substituted epoxy furans were prepared via the coupling of (3-furylmethyl) lithium with ω-iodo epoxides or protected ω-iodo diols followed by closure. The cyclizations of these epoxy furans were examined with a number of Lewis acids. Treatment with $Ti(OiPr)_3Cl$ and ZnI_2 led to the isolation of cyclized products in moderate to excellent yields. Cyclization of 7,8-epoxydendrolasin with $Ti(OiPr)_3Cl$ and ZnI_2 provided 3 β-hydroxypallescensin A in 62% and 65% yields respectively.

Additionally, allylic alcohols and enones derived from the CuCN moderated SN_2' addition of Grignard reagents prepared from 2-(3-furyl)-1-bromoethane and 3-(3-furyl)-1-bromopropane to vinyl epoxides and epoxy-enolethers were employed as cyclization substrates. Treatment of substrate allylic alcohols with a two phase mixture of formic acid and cyclohexane resulted in facile cyclization when the forming ring was 6-, or 7-membered. Enone closures proceeded only when a 6-membered ring was produced or in the case of a bridged system which leads to nakafuran-9.

These results clearly demonstrate the potential of furans as terminators in cationic cyclization. Cyclization of epoxyfurans provides good to excellent yields of simple cyclized products and allylic alcohol initiated cyclizations form fused-, spiro-cyclic, and bridged systems providing reasonably well functionalized products.

The closure to form five membered rings remains problematic. This is analogous to the constraints encountered by Stork[51a] and van Tamelen[51b] in similar work. This result is probably due to the fact that the orbital overlap necessary for closure to occur is difficult to achieve and, therefore, cyclization is slow in comparison to other available pathways.

EXPERIMENTAL SECTION

General. Tetrahydrofuran (THF) was dried by distillation, under nitrogen from sodium benzophenone ketyl; methylene chloride was dried by distillation under nitrogen from calcium hydride; N,N-dimethylformamide (DMF) was dried by distillation at reduced pressure from phosporous pentoxide; hexamethylphosphoramide (HMPA) was dried by distillation at reduced pressure from calcium hydride; pyridine was dried by distillation, under nitrogen, from calcium hydride; diisopropylamine was dried by distillation, under nitrogen, from calcium hydride; formic acid was dried by distillation under argon from phthalic anhydride. Petroleum ether refers to 30-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Mallinkrodt, St. Louis, MO, and used as received. n-Butyllithium and methyllithium in hexane were purchased from Aldrich, Milwaukkee, WI, and titrated by the method of Watson and Eastham.[34] Ethylaluminum dichloride and diethylaluminum chloride were purchased as hexane solutions from Alfa Products, Danvers, MA, and used as received. Magnesium metal turnings were activated by successive washings with 1 N aqueous hydrochloric acid, water, acetone, and ether and dried in a dessicator over phosphorous pentoxide at reduced pressure. All other reagents were used as received unless otherwise stated; all reactions were carried out under a blanket of argon with the rigid exclusions of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrophotometer with polystyrene as standard. Proton magnetic resonance spectra were recorded on a Varian T-60 at 60 MHz or a Bruker WM-250 spectrometer at 250 MHz as indicated, as solutions

in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million of the δ scale relative to a tetramethylsilane internal standard. Data are reported as follows: chemical shift (multiplicity (s = single, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration). ^{13}C magnetic resonance spectra were recorded on a Bruker WM-250 spectrometer (68.9 MHz) and are reported in parts per million from tetramethylsilane on the δ scale. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. High resolution mass spectra were performed by the MSU Department of Biochemistry, Mass Spectroscopy Facility, East Lansing, MI.

Flash chromatography was performed according to the procedure of Still, et al[53] by using the Whatman silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (od) is listed in millimeters.

(3-furyl)-chloromethane (46)[11]. To a mechanically stirred solution of LiCl (2.12 g, 0.05 mmol) in anhydrous DMF (40 mL) was added a mixture of (3-furyl)-methanol (4.9 g, 0.05 mmol) and 2,4,6-trimethylpyridine (6.66 g, 0.055 mol). The resulting solution was cooled to 0°C in an ice-water bath and methanesulfonyl chloride (6.3 g, 0.055 mol, distilled from calcium hydride) was added over a period of 20 minutes. The mixture became bright yellow and a thick suspension. After stirring at 0°C for 2 hours the mixture was cast into ice-water (150 mL) and ether-pentane (1:1, 150 mL). The organic phase was separated and washed with saturated aqueous cupric nitrate (3 x 150 mL), dried (Na_2SO_4) and concentrated <u>in vacuo</u> to give a light yellow liquid. Distillation provided 4.8 g 75%, of product as a colorless liquid B.P. (25mm)

= 40°C. (lit. B.P.$^{32}_{(17mm)}$ = 42-43°C). EI/MS (70 eV): 118 (M^+, 34.5), 81 (base). ^{1}H NMR (60 MHz) δ:7.32 (t, J=2Hz, 2H), 6.28 (d, J=2Hz, 1H), 4.56 (s, 2H).

2-Methyl-4-(2-furyl)-but-2-ene (36). To activated magnesium metal turnings (0.243g, 10 mmol) covered by THF (15mL) was added (3-furyl)-chloromethane (1.16 g, 10 mmol) in one portion. The mixture was allowed to stir at room temperature until all the magnesium had been consumed (about 1 h). The resulting golden solution was cooled to 0° and 1-bromo-2-methylpropene[54] (1.35 g, 10 mmol) was added in one portion followed immediately by anhydrous $FeCl_3$ (16 mg, 0.01 mmol). The resulting deep red reaction mixture was stirred at 0°C for 1 h and then was cast into saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a golden liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 100 g, 50 mm od, ether-petroleum ether 1:99, 30-mL fractions) using the flash technique. Fractions 6-9 provided 1.12 g, 82%, of **36** as a colorless liquid: ^{1}H NMR (250MHz) δ 7.22 (t, J=2 Hz, 1H), 7.04 (m, 1H), 6.13 (br s, 1H), 4.54 (t, J=10 Hz, 1H), 3.10 (d, J=10 Hz, 2H), 2.62 (s, 3H), 2.50 (s, 3H); IR (neat) 2900, 1500, 1450, 1375, 1155, 1070, 1010, 870, 780 cm^{-1}; EI/MS (70 eV) 136 (M^+, base), 121 (42), 93 (41), 91 (37), 77 (36).

GENERAL PROCEDURE FOR PREPARATION OF 3-FURYL OLEFINS

2-Methyl-4-(3-furyl)-but-1-ene (37). To activated magesium metal turnings (0.243g, 10 mmol) covered by THF (15 mL) was added (3-furyl)chloromethane[11] (1.16g, 10 mmol) in one portion. The mixture was stirred at room temperature until all the magnesium had been consumed (about 1 h). The resulting golden solution was cooled to 0°C in an ice-water bath and

3-chloro-2-methyl-propene[55] (0.90g, 10 mmol) was added followed immediately by Li_2CuCl_4 (0.12 mL, 0.1M in THF). The reaction mixture immediately warmed and turned black. After the solution had stirred at 0°C for 30 min., it was cast into saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The organic phase was separated and washed with water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo to yield a colorless liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 100g, 50mm o.d., ether-pet. ether 1:99, 30mL fractions) using the flash technique. Fractions 6-11 provided 1.10g, 81% of **37** as a colorless liquid: ^{1}H NMR (250 MHz):δ=7.28 (t,J=1.8Hz, 1H), 7.13 (m, 1H), 6.19 (brs, 1H), 4.62 (brs, 2H), 2.27 (m, 4H), 1.76 (s, 3H); IR (neat) 2950, 2870, 1500, 1150, 1080, 1025, 900, 890, 780 cm^{-1}; EI/MS (70 eV) 136 (M^+, 15), 121 (11.7), 94 (46.7) 81 (base).

2-methyl-5-(3-furyl)-pent-1-ene (39). 10 mmol of Grignard reagent **32** was reacted with 1.96g (10 mmol) of 4-iodo-2-methyl-1-butene[56] according to the general procedure for the preparation of (3-furyl) olefins to provide 1.24g, 83%, of **38** as a colorless liquid: ^{1}H NMR (250 MHz):δ= 7.25 (t, J=1.8Hz, 1H) 7.08 (m, 1H), 6.15 (br s, 1H), 4.72 (br s, 2H), 2.39 (m, 4H), 1.98 (m, 2H) 1.68 (s, 3H); IR (neat) 2930, 2865, 1500, 1150, 1070, 1025, 900 cm^{-1}; EI/MS (70 eV) 150 (M^+, 19.2), 122 (10.0), 107 (9.8), 95 (15.6), 94 (97), 82 (76.4), 81 (base).

2-methyl-6-(3-furyl)-hex-2-ene (40). 10mmol of Grignard reagent **33** was reacted with (2.10g, 10 mmol) 5-iodo-2-methyl-2-pentene[57] according to the general procedure outlined above to provide 1.19g, 73%, of **40** as a colorless liquid: ^{1}H NMR (250 MHz):δ = 7.29 (t, J=2Hz, 1H), 7.16 (m, 1H), 6.20 (s, 1H), 5.18 (t, J=6Hz, 1H), 2.38 (t, J=6Hz, 2H), 2.36-1.03 (m, 4H), 1.64 (s, 3H), 1.58 (s, 3H); IR (neat) 2950, 2880, 1500, 1160, 1070, 1025, 905, 865, 780 cm^{-1}; EI/MS (70 eV) 164 (M^+, 2) 149 (3), 121 (9.1), 108 (8), 94 (14), 82 (base).

GENERAL PROCEDURE FOR EPOXIDATION OF (3-FURYL) OLEFINS

Preparation 2-methyl-4-(3-furyl)-2-epoxy-butene (13). To a magnetically stirred solution of **36** (1.36 g, 10 mmol) in methylene chloride (30 mL), cooled to 0°C in an ice-water bath, was added a solution of m-chloroperoxybenzoic acid (2.32 g, 11 mmol, 85%) in methylene chloride (50 mL) over a period of 30 min. The resulting mixture was stirred at 0°C for 30 min, the suspension was then filtered, and the filtrate cast into 10% aqueous sodium bisulfite (150 mL) and ether (200 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a light yellow liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 75g, 60 mm od, ether-petroleum ether 1:4, 40 mL fractions) by using the flash technique. Fractions 6-11 provided 1.33 g, 88%, of **13** as a colorless liquid: ^1H NMR (250 MHz):δ=7.42 (t, J=2.8 Hz, 1H), 7.27 (s, 1H), 6.30 (s, 1H), 2.89 (t, J=6 Hz, 1H), 2.70 (dq, J=6, 12 Hz, 2H), 1.42 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$):δ = 144.4, 140.7, 122.0, 112.35, 69.49, 59.77, 26.24, 26.06; IR (neat) 2965, 2925, 1500, 1445, 1375, 1155, 1125, 1020, 870, 780, 760 cm^{-1}; EI/MS (70 eV) 152 (M^+, 4.5), 137 (base), 123 (6.8), 108 (29).

2-Methyl-4-(3-furyl)-1,2epoxybutane (14a). **37** (1.3 g, 10 mmol) was treated with m-chloroperoxybenzoic acid (MCPBA) (2.02 g, 10 mmol, 85%) according to the general procedure for epoxidation of 3-furyl olefins to provide 0.38 g, 25%, of **14a** as a clear colorless liquid: ^1H NMR (250 MHz):δ=7.21 (t, J=2 Hz, 1H), 7.09 (m, 1H), 6.23 (br s, 1H), 2.53 (m, 4H), 1.83 (m, 2H), 1.38 (s, 3H); IR (neat) 2930, 2860, 1500, 1450, 1430, 1390, 1175, 1030, 890 cm^{-1}; EI/MS (70 eV) 156 (M^+, 54.6), 139 (84.3), 121 (43.13), 112 (63.10), 96 (48.7), 81 (67.0), 55 (base).

2-Methyl-5-(3-furyl)-2,3epoxybutane (15). **38**[11] (1.50 g, 10 mmol) was treated with MCPBA (2.02 g, 10 mmol, 85%) according to the general procedure for epoxidation of 3-furyl olefins to provide 1.40 g, 85%, of **15** as a clear colorless liquid: ^{1}H NMR (250 MHz):δ=7.39 (t, J=2 Hz, 1H), 7.22 (s, 1H), 6.29 (s, 1H), 2.78 (t, J=6 Hz, 1H), 2.56 (M, 2H), 1.78 (dd, J=6, 6 Hz, 2H), 1.32 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (CDC1$_3$):δ = 155.8, 141.4, 114.16, 110.00, 76.59, 37.81, 28.64, 24.10, 21.20, 18.99; IR (neat) 2980, 2940, 2880, 1500, 1440, 1380, 1160, 1115, 1025, 925, 875, 790 cm^{-1}; EI/MS (70 eV) 166 (M^+, 7.1), 151 (12), 133 (10), 123 (13.4), 108 (42.8), 95 (39.4), 85 (75.0), 81 (83.4), 72 (38.5), 59 (base). Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.29; H, 8.43. Found: C, 72.25; H, 8.51.

2-Methyl-6-(3-furyl)-2-3epoxybutane (17). **40** (1.64 g, 10 mmol) was reacted with MCPBA (2.02g, 10 mmol, 85%) according to the general procedure for the epoxidation of 3-furyl olefins to epoxides to provide 1.45 g, 81%, of **17** as a clear colorless liquid: ^{1}H NMR (250 MHz):δ=7.28 (t, J=2 Hz, 1H), 7.18 (t, J=2 Hz, 1H), 6.21 (br s, 1H), 2.67 (t, J=6 Hz, 1H), 2.45 (M, 2H), 1.58 (m, 4H), 1.22 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (CDC1$_3$):δ=157.6, 140.2, 114.4, 109.6, 75.81, 38.62, 29.43, 23.21, 24.1, 20.65, 19.34; IR (neat) 2980, 2950, 2880, 1500, 1440, 1390, 1150, 1115, 1020, 915, 875, 790, 720 cm^{-1}; EI/MS (70 eV) 180 (M^+, 1.7), 151 (7.4), 135 (5.6), 121 (14), 107 (11.3), 98 (2), 94 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.40; H, 8.95.

((Tri-n-butylstannyl)methyl)furan (47). To a solution of diisopropylamine (4.44 g, 44 mmol) in anhydrous THF (50 mL) cooled to 0°C in an ice-water bath was added n-butyllithium (1.7 M, 25.8 mL, 44 mmol) over a period of 10 min, and the mixture was allowed to stir for an additional 10 min. after the addition was complete. To the resulting solution was added tri-n-butyltin hydride (11.6 g, 40 mmol) over a period of 10 min and the mixture allowed to stir for an additional 15 min. and then cooled to -25°C in a dry ice-carbon

tetrachloride bath. To the resulting yellow solution was added (3-furyl)-chloromethane (4.55 g, 40 mmol) over a period of 10 min. The cooling bath was removed and the reaction allowed to stir and warm to room temperature over 1 h. The mixture was then cast into ether (300 mL) and saturated aqueous NH_4Cl (200 mL). The organic phase was separated, washed with water (200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. Distillation provided 13.15 g, 89% of **47** as a colorless liquid: bp (0.05 mm) 125°C (lit.[27] bp 116-119 °C (0.55 mm)); ^1H NMR (60 MHz) δ 7.23 (t, J=2 Hz, 1H), 7.18 (m, 1H), 6.21 (s, 1H), 2.0-0.7 (M, 29H); EI/MS (70 eV) 372 (1.3), 355 (6), 315 (10), 291 (28), 235 (32), 201 (19), 179 (base).

3-methyl-but-3-en-1-ol p-toleunesulfonate. To a solution of 3-methyl-but-3-en-1-ol (2.6 g, 30 mmol) in pyridine (20 mL), cooled to 0°C in an ice-water bath, was added freshly crushed p-toluenesulfonyl chloride (7.63 g, 40 mmol) in one portion. The mixture was stirred at 0°C for 1 hour and then placed in a freezer (-20°C) overnight. The resulting suspension was cast into a mixture of ice-water and concentrated hydrochloric acid (50 g - 50 mL) and extracted with ether (150 mL). The organic phase was separated and washed with 1N aqueous hydrochloric acid (100 mL), saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield 6.0 g, 83%, of a viscous yellow liquid which was used without further purification.

3-methyl-3-epoxy-buten-1-ol p-toluenesulfonate (44b). To a solution of 3-methyl-but-3-en-1-ol p-toluenesulfonate (7.62 g, 30 mmol) in methylene chloride (50 mL), cooled to 0°C in an ice-water bath, was added a solution of m-chloroperbezoic acid (8.08 g, 30 mmol, 85%) in methylene chloride (50 mL) over a period of 30 minutes. The mixture was allowed to stir for 3 hours at

0°C and the resulting suspension was then suction filtered and the filtrate was taken up in ether (150 mL) and washed with 10% aqueous sodium bisulfite (2 x 100 mL), saturated aqueous sodium bicarbonate (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a viscous liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 50 g, 40 mm o.d., ether-pet. ether 1:1, 30 mL fractions) using the flash technique. Fractions 8-13 provided 5.52 g, 68%, of **44b** as a colorless liquid. EI/MS (70 eV): 256 (M^+, 2.1), 155 (11), 101 (11.6), 91 (38.5), 84 (24.4), 68 (23.7), 43 (base). ^1H NMR (60 MHz):δ=7.76 (d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H) 4.14 (t, J=6.5Hz, 2H), 2.61 (s, 1H), 1.96 (t, J=6.5Hz, 2H), 1.31 (s, 3H).

4-iodo-2-methyl-1-epoxy-butene (44a). To a solution of 3-methyl-3-epoxy-buten-1-ol p-toluenesulfonate, **44b**, (2.02 g, 7.89 mmol) in acetone (25 mL, dried over $CaCl_2$) was added sodium iodide (1.50 g, 10 mmol) in one portion and the solution heated under reflux for 4 hours. The resulting suspension was cooled to room temperature and suction filtered. The filtrate was diluted with ether (150 mL) and washed with water (100 mL), 10% aqueous sodium bisulfite (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo to yield a colorless liquid. Distillation of the crude product provided 1.47 g, 88%, of **44a** as a clear, colorless liquid. B.P. (25mm)=58°C. EI/MS (70 eV) 212 (M^+, 4.3), 194 (1.13), 110 (14.2), 85 (25.4), 55 (66.1), 43 (base). ^1H NMR (60 MHZ):δ=3.11 (t, J=8Hz, 2H), 2.60 (AB,J=4Hz, 2H), 2.12 (m, 2H), 1.28 (S, 3H). IR(neat): 3000, 2920, 1430, 1375, 1215, 1150, 10650, 895, 790, 720 cm^{-1}.

4-methyl-pent-4-en-1-ol p-toluenesulfonate. To a solution of 4-methyl-pent-4-en-1-ol[58] (3.0 g, 30 mmol) in pyridine (161 mL) cooled to 0°C in an ice-water bath was added freshly crushed p-toluenesulfonyl chloride (7.63 g,

40 mmol) in one portion. The mixture was allowed to stir at 0°C for 1 hour and then placed in the freezer (-20°C) overnight. The mixture was cast into ice-concentrated hydrochloric acid (50 g - 50 mL) and extracted with ether (150 mL). The organic phase was washed with 1N aqueous hydrochloric acid (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield 7.62 g, 100% of a viscous yellow liquid. This product was used without further purification.

4-methyl-4-epoxy-penten-1-ol p-toluenesulfonate (45b). To a solution of 4-methyl-pent-4-en-1-ol p-toluenesulfonate (7.62 g, 30 mmol) in methylene chloride (40 mL) cooled to 0°C in an ice-water bath was added a solution of m-chloroperbenzoic acid (6.08 g, 30 mmol, 85%) in methylene chloride (50 mL) and the resulting suspension was stirred at 0°C for 1 hour and then overnight at room temperature. The mixture was suction filtered and the filtrate was diluted with ether (200 mL) and washed with 10% aqueous sodium bisulfite (150 mL), saturated aqueous sodium bicarbonate (150 mL), water (150 mL), brine (150 mL), dried (Na_2SO_4) and concentrated in vacuo to yield a cloudy colorless liquid. The crude product was purified by chromatography on a column of silica gel (60-230, 50 g, 40 mm o.d., ether-pet. ether 1:1, 25 mL fractions) using the flash technique. Fractions 10-14 yielded 5.52 g, 68% of **45b** as a colorless liquid. ^1H NMR (60 MHz):δ= 7.73 (d, J=7.5Hz, 2H), 7.30 (d, J=7.5Hz, 2H), 4.03 (t, J=6Hz, 2H), 2.44 (s, 3H), 1.63 (m, 4H), 1.23 (s, 3H).

5-iodo-4-methyl-1-epoxy-pentene 45a. To a solution of 4-methyl-4-epoxy-penten-1-ol p-toluenesulfonate, **45b**, (5.6 g, 20 mmol) in acetone (50 mL, dried over $CaCl_2$) was added sodium iodide (3.3 g, 22 mmol) in one portion and the solution was heated under reflux for 6 hours. The resulting suspension was cooled to room temperature and suction filtered. The filtrate was cast into water (200 mL) and ether (200 mL). The organic phase was separated and

washed with 10% aqueous sodium bisulfite (100 mL), saturated aqueous sodium bicarbonate (100 mL), water (100 mL), brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a water white liquid. Distillation of the crude product provided 3.79 g, 84.5%, of **45a** as a colorless liquid. B.P. $_{(20mm)}$=62°C. ^1H NMR (60MHz):δ=3.20 (m, 2H), 2.58 (s, 2H), 2.10-1.53 (m, 4H), 1.29 (s, 3H). EI/MS (70 eV) 227 (M^+, 1.22), 226 (M^+, 8), 199 (26), 141 (14), 100 (82), 43 (base). IR (neat): 3000, 2930, 1460, 1800, 1385, 1225, 1180, 915, 840, 750 cm^{-1}.

2-Methyl-5-(3-furyl)-1,2epoxybutane (16). To a solution of **47** (1.85 g, 5 mmol) in THF (5 mL) cooled to -78°C in a dry ice-2-propanol bath was added n-butyllithium (3.3 mL, 5 mmol, 1.51 M in hexane) over a period of 5 min. The solution was stirred at -78°C for an additional 10 min. and then HMPA (0.90 g, 5 mmol) was added in one portion. The resulting red solution was transferred via cannula into a solution of **44a** (1.06 g, 5 mmol) in THF (10 mL) which was cooled to -25°C in a dry ice-carbon tetrachloride bath. The cooling bath was removed and the mixture stirred at room temperature overnight. The solution was cast into saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 75 g, 40 mm od, ether-petroleum ether 1:4, 25-mL fractions) by using the flash technique. Fractions 12-17 provided 0.60 g, 73%, of **16** as a clear colorless liquid: ^1H NMR (250 MHz):δ=7.32 (t, J=2 Hz, 1H), 7.20 (m, 1H), 6.22 (m, 1H), 3.18 (m, 2H), 2.76-2.50 (m, 2H), 1.77-1.51 (m, 2H), 1.32 (s, 3H); IR (neat) 2925, 2860, 1500, 1450, 1390, 1160, 1070, 1025, 975, 905, 890 cm^{-1}; EI/MS (70 eV) 166 (M^+, 2.3), 149 (8.1), 141 (19), 135 (8.6), 129 (7.8), 121 (12.0), 109 (17.6), 94 (base). Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.29; H, 8.43. Found: C, 72.25; H, 8.51.

2-Methyl-6-(3-furyl)-1,2epoxybutane (18). To a solution of **47** (1.85 g, 5 mmol) in THF (5 mL) cooled to -78°C in a dry ice-2-propanol bath was added n-butyllithium (3.3 mL, 5 mmol, 1.51 M in hexane) over a period of 5 min. The solution was stirred at -78°C for an additional 10 min. and then HMPA (0.896 g, 5 mmol) was added in one portion, and the mixture was stirred at -78°C for an additional 10 min. The resulting solution was transferred via cannula into a solution of **45a** (1.12 g, 5 mmol) in THF (10 mL) cooled to -25°C in a dry ice-carbon tetrachloride bath. The cooling bath was removed and the mixture stirred at room temperature overnight. The solution was cast into saturated aqueous NH_4Cl (100 mL) and ether (150 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 75 g, 40 mm od, ether-petroleum ether 1:4, 25-mL fractions) by using the flash technique. Fractions 8-13 afforded 0.612 g (68%) of **18** as a colorless liquid: ^1H NMR (250 MHz) δ 7.36 (t, J=2 Hz, 1H), 7.21 (t, J=2 Hz 1H), 6.24 (br s, 1H), 3.90 (t, J=9 Hz, 1H), 3.38 (m 1H), 2.58 (m, 2H), 2.42 (t, J=9 Hz, 2H), 1.66-1.38 (m, 4H), 1.31 (s, 3H); IR (neat) 3010, 2990, 2925, 1540, 1500, 1445, 1380, 1150, 1110, 1070, 900, 805, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 12), 163 (11), 149 (14.4), 135 (28), 121 (18.7), 108 (60, 82 (base). Anal. Calcd for $C_{11}H_{16}O_2$; C, 73.33; H, 8.89. Found: C, 73.21; H, 8.96.

1,2-Di-O-isopropylidene-4-(3-furyl)butene-1,2-diol (49). To an activated magnesium metal turnings (0.73g, 30 mmol) covered by THF (40 mL) was added (3-furyl)chloromethane (3.5g, 30 mmol) and the mixture stirred at room temperature until the magnesium was consumed (about 2 h). The resulting golden solution was cooled to 0°C in an ice-water bath and **48**[59] (6.05 g, 25 mmol) was added in one portion followed immediately by Li_2CuCl_4 (0.2 mL,

0.1 M in THF). The mixture was stirred at room temperature for 6 h and then was cast into saturated aqueous NH_4Cl (150 mL) and ether (150 mL). The organic phase was separated, washed with 10% aqueous sodium bisulfite (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 110 g, 50 mm od, ether-petroleum ether 5:95, 40-mL fractions) by using the flash technique. Fractions 18-29 provided 3.57 g, 73%, of **49** as a clear colorless liquid: ^1H NMR (60 MHz) δ 7.28 (t, J=2 Hz, 1H), 7.19 (m, 1H), 6.22 (br s, 1H), 4.06 (t, J=6.5 Hz, 1H), 3.98 (t, J=6.5 Hz, 1H), 3.40 (m, 1H), 2.52 (m, 2H), 1.87 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H); IR (neat) 2990, 2950, 2880, 1500, 1365, 1240, 1165, 1080, 1025, 890, 700 cm^{-1}; EI/MS (70 eV) 196 (M^+, 4.43), 181 (4.33), 138 (5.28), 121 (25.48), 94 (21.56), 82 (53.72), 81 (45.28), 72 (19.0), 53 (18.46) 43 (base).

4-(3-Furyl)-butane-1,2-diol (50). A solution of **49** (1.00 g, 5.10 mmol) in THF-1 N HCl (1;1, 5 mL) was stirred at room temperature for 12 h. The mixture was neutralized by the addition of solid $NaHCO_3$ (0.5 g) and saturated with NaCl. The mixture was extracted with ether (3 X 50 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide 0.51 g, 64%, of a yellow liquid which was used without further purification: ^1H NMR (60 MHz) δ 7.21 (t, J=2 Hz, 1H), 7.12 (m, 1H), 6.12 (br s, 1H), 3.50 (m, 5H), 2.55 (t, J=8 Hz, 2H), 1.83 (br t, J=8 Hz, 2H); IR (neat) 3400 br, 2930, 1500, 1450, 1155, 1060 br, 915, 880 790 cm^{-1}; EI/MS (70 eV) 156 (M^+, 9.37), 107 (5.50), 95 (11.22), 82 (70.1), 81 (base).

4-(3-Furyl)-butane-1,2-diol 1-p-toluenesulfonate (51). To a solution of **50** (0.51 g, 3.2 mmol) in pyridine (5 mL) cooled to 0°C an ice-water bath was added p-toluenesulfonyl chloride (0.61 g, 3.2 mmol) and the resulting mixture

was stirred at 0°C for 6 h. The mixture was then cast into ice-1 N aqueous HCl (30 g, 30 mL) and the solution extracted with ether (100 mL). The organic layer was washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide 0.84 g, 84% of a viscous orange liquid which was used without further purification: ^1H NMR (60 MHz)δ 7.68 (m, 4H), 7.21 (m, 2H), 6.18 (br s, 1H), 3.93 (br s, 1H), 3.74 (m, 3H), 2.68 (m, 2H), 2.35 (s, 3H), 1.85 (m, 2H); IR (neat) 3500 br, 2980, 2875, 1595, 1500, 1440, 1370, 1185, 1100, 990, 875, 820 cm^{-1}; EI/MS (70 eV) 310 (M^+, 4.91), 155 (12.78), 138 (33.87), 120 (21.06), 107 (10.71), 94 (50.85), 81 (base).

4-(3-Furyl)-1,2-epoxybutane (14b). To a suspension of NaH (0.13 g, 2.7 mmol, 50% in oil washed with 5 X 1 mL of dry hexane) in THF (5 mL) was added a solution of **51**, (0.84 g, 2.7 mmol) in THF (5 mL) over a period of 5 min. The resulting mixture was heated under reflux for 2 h. The mixture was allowed to cool to room temperature and was cast into water (50 mL) and ether (50 mL). The organic phase was separated, washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 20 mm od, ether-petroleum ether 1:4, 20-mL fractions) by using the flash technique. Fractions 11-15 provided 0.350 g, 94%, of **14b** as a clear colorless liquid: ^1H NMR (250 MHz)δ 7.39 (t, J=1.8 Hz, 1H), 7.22 (m, 1H), 6.23 (br s, 1H), 2.98 (M, 1H), 2.78 (t, J=4.8 Hz, 1H), 2.57 (m, 1H), 2.48 (dd, J=4.8 Hz, 1H), 1.77 (m, 2H); IR (neat) 2990, 2910, 2860, 2150, 1500, 1450, 1160, 1065, 1025, 910, 870, 780, 720 cm^{-1}; EI/MS (70 eV) 138 (M^+, 18.87), 107 (35.28), 94 (21.23), 81 (base). Anal. Calcd for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.49; H, 7.33.

General Procedure for Cyclization with BF_3·OEt_2 Preparation of 7,7-Dimethyl-6-hydroxy-4,5,6,7-tetrahydrobenzofuran (24). To a solution of **15**

(0.1 g, 0.60 mmol) in CH_2Cl_2 (10 mL) cooled to -25°C in a dry ice-carbon tetrachloride bath was added freshly distilled boron trifluoride etherate (0.28 g, 0.20 mmol). After the mixture had stirred for 5 min at -25°C it was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was cast into ether (50 mL) and the organic phase was separated, washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a dark red liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether-petroleum ether 1:1, 10 mL fractions) by using the flash technique. Fractions 14-17 provided 47 mg, 47%, of **24** as a viscous colorless liquid which affords a white solid on cooling: ^1H NMR (250 MHz):δ = 7.26 (d, J=1.8 Hz, 1H), 6.14 (d, J=1.8 Hz, 1H), 3.83 (br s, 1H), 3.40 (td, J=8, 6 Hz, 2H), 1.92 (m, 2H), 1.38 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$):δ=155.8, 141.4, 114.4, 109.9, 76.3, 37.7, 28.0, 25.5, 21.1, 18.9; IR (neat) 3435 (br), 2900, 1620, 1500, 1470, 1385, 1360, 1280, 1150, 1120, 1085, 1045, 890, 780 cm^{-1}; EI/MS (70 eV) 166 (M^+, 40.4), 151 (9.4), 133 (4.80), 122 (base). Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.29; H, 8.43. Found: C, 72.18; H, 8.54

General Procedure for Cyclization with $EtAlCl_2$. Preparation of 22 and 2-Methyl-6-(3-furyl)-3-hydroxyhex-1-ene (25). To a solution of **15** (0.1 g, 0.60 mmol) in CH_2Cl_2 (10 mL) cooled to -78°C in a dry ice-2-propanol bath was added $EtAlCl_2$ (0.82 mL, 1.2 mmol, 1.47 M in hexane). The mixture was then warmed slowly to -25°C for 30 min and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture warmed to room temperature and cast into ether (50 mL). The organic phase was separated, washed with 1N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30

mm od, ether-petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 9-12 provided 0.057 g, 57%, of **25** as a clear colorless liquid: ^{1}H NMR (250 MHz):δ = 7.23 (t, J=2 Hz, 1H), 7.16 (M, 1H), 6.19 (br s, 1H), 4.88 (br s, 1H), 4.76 (br s, 1H), 4.0 (br s, 1H), 3.38 (M, 1H), 2.36 (M, 2H), 1.98 (m, 2H), 1.98 (m, 2H), 1.78 (s, 3H); IR (neat) 3450 (br), 2990, 2900, 1500, 1470, 1385, 1290, 1160, 1085, 890, 780 cm^{-1}; EI/MS (70 eV) 166 (M^+, 9.7), 135 (base), 82 (47). Fractions 15-18 gave 0.022 g, 22%, of **22**.

General Procedure for Cyclization with Et_2AlCl. Preparation of 24 and 25. To a solution of **15** (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL) cooled to 0°C in an ice-water bath was added Et_2AlCl (0.82 mL, 1.2 mmol, 1.48 M in hexane) and the mixture immediately turned yellow. The solution was stirred at 0°C for 1 h and then was cast into saturated aqueous NH_4Cl (60 mL) and ether (50 mL). The organic phase was separated, washed with 1 N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated <u>in vacuo</u> to yield a yellow liquid. Flash chromatography of the crude product provided 0.049 g, 49%, of **25** and 0.022 g, 22%, of **24**.

General Procedure for Cyclization with Alumina. Preparation of 24 and 25. To a solution of **15** (0.1 g, 0.60 mmol) in dry hexane (15 mL) was added basic alumina (2.0 g, activity I) and the suspension was stirred at room temperature for 24 h. Methanol (10 mL) was added, the mixture was filtered, and the alumina rinsed with methanol (25 mL). The solvent was removed <u>in vacuo</u> to yield a colorless liquid. Flash chromatography of the crude product provided 0.032 g, 32%, of **24** and 0.051 g, 51%, of **23**.

General Procedure for Cyclization with $Ti(O\text{-}i\text{-}Pr)_3Cl$. Preparation of 22. To a solution of **15** (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL) was added $Ti(O\text{-}i\text{-}Pr)_3Cl$[36,60] (2.40 mL, 1.8 mmol, 0.75 M in CH_2Cl_2). The solution was allowed to stir at room temperature for 2 h. The reaction was quenched by

the addition of saturated aqueous NH_4Cl (10 mL) and the resulting two phase mixture was cast into saturated aqueous NH_4Cl (50 mL) and ether (50 mL). The organic phase was separated, washed with 1 N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a light yellow liquid. Flash chromatography of the crude product provided 0.078 g, 78%, of **24**.

General Procedure for Cyclization with ZnI_2. Preparation of 24. To a solution of **15** (0.1 g, 0.50 mmol) in CH_2Cl_2 (10 mL) was added anhydrous sodium acetate (50 mg, 0.60 mmol) followed immediately by $ZnI_2 \cdot OEt_2$[61] (0.70 g, 1.8 mmol). The resulting mixture was stirred in the dark for 3 h. The mixture was then cast into saturated aqueous NH_4Cl (50 mL) and ether (50 mL). The organic phase was separated, washed with 10% aqueous sodium bisulfite (50 mL), water (50 mL), and brine (50 mL), dried (50 mL), and concentrated in vacuo to provide a yellow liquid. Flash chromatography of the crude product provided 0.071 g, 71%, of **24**.

Attempted Cyclization of Epoxy Furan 13 with $BF_3 \cdot OEt_2$. A solution of **13** (0.10 g, 0.66 mmol) in CH_2Cl_2 (10 mL) was reacted with $BF_3 \cdot OEt_2$ (0.031 g, 0.22 mmol) according to the general procedure for cyclization with $BF_3.OEt_2$. The crude product was purified by chromatogrophy on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether-petroleum ether, 1:1, 10-mL fractions) by using the flash technique. Fractions 10-14 provided 0.062 g, 62%, of **20** as a clear colorless liquid: ^1H NMR (250 MHz)δ 7.34 (t, J=2 Hz, 1H), 7.24 (m, 1H), 6.28 (br s, 1H), 4.90 (br s, 1H), 4.79 (br s, 1H), 3.60 (m, 1H), 2.48 (d, J=7.2 Hz, 2H), 1.53 (s, 3H); IR (neat) 3500 (br), 3000, 2980, 1500, 1495, 1170, 1080, 1025, 915, 870, 780 cm^{-1}; EI/MS (70 eV) 152 (M^+, 3.7), 137 (23.4), 117 (8.3), 81 (base).

Attempted Cyclization of Epoxy Furan 13 with Et_2AlCl. A solution of **13** (0.1 g, 0.66 mmol) in CH_2Cl_2 (10 mL) was treated with Et_2AlCl (0.90 mL, 1.32 mmol, 1.47 M in hexane) according to the general procedure for cyclization with Et_2AlCl to provide 0.085 g, 85%, of **20**.

Attempted Cyclization of Epoxy Furan 13 with Alumina. A solution of **13** (0.1 g, 0.66 mmol) in dry hexane (10 mL) was treated with 2.0 g of alumina according to the general procedure for cyclization with alumina to provide 0.083 g, 83%, of **20**.

Attempted Cyclization of Epoxy Furan 14a with BF_3·OEt_2. A solution of **14a** (0.10 g, 0.66 mmol) in CH_2Cl_2 (10 mL) was treated with BF_3·OEt_2 (0.031 g, 0.22 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether-petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 9-12 provided 0.053 g, 53%, of **22** as a mixture of isomers: ^1H NMR (60 MHz) δ 7.26 (t, J=2 Hz, 1H), 7.18 (m, 1H), 6.21 (br s, 1H), 5.48 (m, 0.5 H), 4.94 (s, 0.5 H), 4.83 (s, 0.5 H), 4.0 (br s, 1H), 3.49 (br s, 1H), 3.12 (d, J=6 Hz, 2H), 2.40 (m, 4H), 1.86 (s, 1.5 H); IR (neat 3450 (br), 2990, 2980, 2780, 1500, 1380, 1165, 1070, 1030, 925, 880, 790 cm^{-1}; EI/MS (70 eV) 152 (M^+, 5.3), 137 (17.6), 121 (41.3), 106 (10.9), 82 (base).

Attempted Cyclization of Epoxy Furan 14b with BF_3·OEt_2. A solution of **14b** (0.10 g, 0.73 mmol) in CH_2Cl_2 (10 mL) was treated with BF_3·OEt_2 (0.034 g, 0.24 mmol) according to the general procedure for cyclization with BE_3·OFt_2. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether-petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 10-12 provided 0.49 g, 49%, of **23** as a mixture of isomers: ^1H NMR (250 MHz) 7.35 (t, J=2 Hz,

1H), 7.22 (m, 1H), 6.22 (br s, 1H), 4.58 (m, 2H), 3.30 (m, 2H), 2.54 (m, 2H); IR (neat) 3450 (br), 2995, 2890, 1500, 1410, 1150, 1090, 1015, 890, 780 cm^{-1}; EI/MS (70 eV) 138 (M^+, 28.8), 121 (14.4), 95 (21.7), 81 (base).

Cyclization of Epoxy Furan 14b with ZnI_2·OEt_2. Preparation of 23 and 6-(Hydroxymethyl)-4,5-dihydro-6H-cyclopenta[b]furan (21b). A solution of **14b** (0.10 g, 0.73 mmol) in CH_2Cl_2 (10 mL) was reacted with ZnI_2·OEt_2 (0.86 g, 2.19 mmol) and sodium acetate (60 mg, 0.73 mmol) according to the general procedure for cyclization with ZnI_2.OEt_2. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether-petroleum ether, 1:1, 10 mL fractions) by using the flash technique. Fraction 8-11 provided 0.044 g, 44%, of **23** and fractions 13-14 provided 0.025 g, 25%, of **21b** as a clear colorless liquid: ^1H NMR (250 MHz):δ= 7.22 (d, J=1.8 Hz, 1H), 6.41 (d, J=1.8 Hz, 1H), 3.19 (m, 2H), 2.78 (m, 5H); IR (neat) 3480 (br), 2900, 1500, 1425, 1120, 1080, 1050, 1010, 890, 780 cm^{-1}; EI/MS (70 eV) 138 (M^+, 23.4), 121 (8.3), 109 (8.51), 94 (base), Anal. Calcd for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.54; H, 7.27.

Cyclization of Epoxy Furan 16 with BF_3·OEt_2. Preparation of 7-Methyl-7-(hydroxymethyl)-4,5,6,7-tetrahydrobenzofuran 26 and Alcohols 27. A solution of **16** (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL) was reacted with BF_3·OEt_2 (0.28 g, 0.20 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether petroleum-ether, 1:1, 10 mL fractions) by using the flash technique. Fractions 10-12 provided 0.01 g, 10%, of **27** as a mixture of isomers: ^1H NMR (250 MHz):δ= 7.26 (t, J=2.0Hz, 1H), 7.16 (m, 1H), 6.19 (br s, 1H), 5.52 (t, J=8 Hz, 0.5H), 4.90 (br s, 0.5 H), 4.82 (br s, 0.5 H), 3.56 (br s, 1H), 2.36 (m, 5H), 1.78 (s, 1.5 H); EI/MS (70 eV) 166 (M^+, 12.3), 151 (8.3), 135 (43.1), 120 (10.3), 94 (14.9), 82 (base). Fractions 13-17 provided

0.03 g, 30%, of **26** as a pale yellow liquid: ^{1}H NMR (250 MHz)δ 7.21 (d, J=1.8 Hz, 1H), 6.15 (d, J=1.8 Hz, 1H), 3.52 (s, 2H), 2.38 (m, 2H), 1.96 (m, 2H), 1.24 (s, 3H); IR (neat) 3440 (br), 2940, 1500, 1380, 1205, 1160, 1040, 890, 740 cm^{-1}; EI/MS (70 eV) 166 (M^+, 8.8), 149 (4.4), 135 (base). Anal. calcd for $C_{10}H_6O_2$: C, 72.29; H, 8.43. Found: C, 71.96; H, 8.51.

Attempted Cyclization of Epoxy Furan 17 with BF_3-OEt_2. Preparation of 2-Methyl-6-(3-furyl)-3-hydroxyhex-1-ene(29). A solution of **17** (0.10 g, 0.55 mmol) in CH_2Cl_2 (10 mL) was reacted with BF_3·OEt_2 (0.25 g, 0.18 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 70 g, 40 mm od, ether-petroleum ether, 1:1, 25-mL fractions) by using flash technique. Fractions 11-13 provided 0.041 g, 41% of **29**: ^{1}H NMR (60 MHz)δ 7.39 (t, J=2 Hz, 1H), 7.21 (m, 1H), 6.24 (br s, 1H), 4.85 (s, 1H), 4.80 (s, 1H), 4.10 (m, 1H), 3.62 (br s, 1H), 2.60 (M, 2H), 2.44 (m, 4H), 1.61 (s, 3H); IR (neat) 3450 (br), 2990, 1500, 1450, 1390, 1290, 1150, 1090, 890, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 10.6), 162 (8.3), 139 (28.3), 94 (43.2), 82 (base).

Cyclization of Epoxy Furan 17 with Et_2AlCl. Preparation of 8,8-Dimethyl-7-hydroxy-4,5,6,7-tetrahydro-6H-cyclohepta[b]furan 28 and 29. A solution of **17** (0.10 g, 0.55 mmol) in CH_2Cl_2 (10 mL) was treated with Et_2AlCl (0.75 mL, 1.10 mmol, 1.47 M in hexane) according to the general procedure for cyclization with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 45 g, 30 mm od, ether-petroleum ether, 1:1, 10-mL fractions) by using the flash technique. Fractions 9-12 provided 0.069 g, 69%, of **29** and fractions 15-17 provided 0.01 g, 10%, of **28** as a pale yellow liquid: ^{1}H NMR (250 MHz)δ 7.24 (d, J=1.8 Hz, 1H), 6.13 (d, J=1.8 Hz, 1H), 3.73 (t, J=4.2 Hz, 1H), 2.47 (m, 2H, 1.91 (m, 6H), 1.30 (s, 3H), 1.22 (s, 3H); IR (neat) 3430 (br), 2980, 1620, 1500, 1470, 1380,

1360, 1285, 1160, 1115, 1090, 1030, 890, 730 cm^{-1}; EI/MS (70 eV) 180 (M^+, 5.28), 166 (32.2), 151 (12.6), 149 (17.9), 122 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.80. Found: C, 73.32; H, 8.83.

Cyclization of Epoxy Furan 18 with BF_3·OEt_2. Preparation of 8-Methyl-8-(hydroxymethyl)-4,5,7,8-tetrahydro-6H-cyclohepta[b]furan 30 and Alcohol 31. A solution of **18** (0.10 g, 0.55 mmol) in CH_2Cl_2 (10 mL) was reacted with BF_3·OEt_2 (0.25 g, 0.18 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 30 mm od, ether petroleum-ether, 1:1, 10 mL fractions) by using the flash technique. Fractions 9-12 provided 0.012 g, 12%, of **31** as a mixture of isomers: ^1H NMR (250 MHz)δ 7.28 (t, J=2 Hz, 1H), 7.16 (br s, 1H), 6.18 (br s, 1H), 4.96 (s, 0.5 H), 4.80 (s, 0.5 H), 4.10 (m, 0.5 H), 3.10 (br s, 1H), 3.28 (m, 2H), 2.86 (m, 2H), 2.23 (m, 5H), 1.83 (s, 1.5 H); IR (neat) 3450 (br), 2900, 1500, 1460, 1320, 1290, 1160, 1075, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 9.2), 165 (10.5), 149 (23.6), 139 (10.3), 94 (32.6) 82 (base). Fractions 14-16 provided 0.010 g, 10%, of **30** as a clear liquid: ^1H NMR (250 MHz)δ 7.17 (d, J=1.8 Hz, 1H), 6.12 (d, J=1.8 Hz, 1H), 3.79 (d, J=11.1 Hz, 1H), 3.58 (d, J=11.1 Hz, 1H), 2.47 (m, 2H), 1.96-1.31 (br m, 6H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$)δ 155.6, 141.1, 113.9, 109.8, 76.6, 37.7, 28.0, 25.7, 21.3, 19.0; IR (neat) 3470 (br), 2920, 1500, 1460, 1385, 1290, 1210, 1165, 1090, 890, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 10.0), 150 (11.7), 149 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.40; H, 8.99.

Cyclization of Epoxydendrolasin (42) with $Ti(O\text{-}i\text{-}Pr)_3Cl$. Preparation 3β-Hydroxypallescensin A (53). A solution of epoxydendrolasin **(42)**[10] (0.20 g, 0.85 mmol) in CH_2Cl_2 (10 mL) was treated with $Ti(O\text{-}i\text{-}Pr)_3Cl$ (3.4) mL, 2.55 mmol, 0.75 M in CH_2Cl_2) according to the general procedure for cyclization with $Ti(O\text{-}i\text{-}Pr)_3Cl$. The crude product was purified by chromatography on a

column of silica gel (230-400 mesh, 70 g, 50 mm od, ether-petroleum ether 1:3, 25-mL fractions) by using flash technique. Fractions 16-19 provided 0.124 g, 62%, of **53** as a white solid: mp 120-122 °C (lit.[40] mp 122-122.5 °C); ^{1}H NMR (250 MHz):δ = 7.13 (d, J=1.8 Hz, 1H), 6.02 (d, J=1.8 Hz, 1H), 3.31 (m, 3H), 3.43 (m, 4H), 2.22 (m, 1H), 1.5-2.1 (m, 4H), 1.18 (s, 3H), 1.07 (s, 3H), 0.89 (m, 3H); EI/MS (70 eV) 234 (M^+, 46.4), 219 (82), 201 (base).

Preparation of 2-(3-furyl)-1-bromoethane (63). A solution of 2-(3-furyl) ethanol[45b] (3.35 g, 30 mmol) in pyridine (25 mL) was cooled to 0°C (ice-water) and p-toluenesulfonyl chloride (6.29 g, 33 mmol) was added all in one portion. The resulting yellow mixture was stirred at 0°C for four hours. The suspension was cast into ice-conc. HCl (50 g - 50 mL) and ether (250 mL). The organic phase was separated and washed with 1N aq. HCl (200 mL), water (200 mL), brine (200 mL), and dried ($MgSO_4$). The solvent was removed in vacuo to provide a viscous yellow liquid which was immediately taken up in dry acetone (150 mL) and LiBr (3.5 g, 40 mmol) was added. The mixture was heated under reflux for 12 hours; after cooling to room temperature, the solvent was removed in vacuo and the residue dissolved in water (200 mL) and ether (200 mL). The organic phase was washed with saturated aqueous sodium bicarbonate (200 mL), brine (200 mL), dried ($MgSO_4$) to provide 4.64 g, 88%, of a light red liquid which was used without further purification. ^{1}H NMR (60 MHz):δ = 7.24 (m, 2H); 6.21 (d, J=1.7 Hz, 1H); 3.42 (t, J=5.1 Hz, 2H); 2.93 (t, J=5.1 Hz, 2H). EI/MS (70 eV): 176 (22.9), 174 (25.1), 95 (49.7), 81 (base). IR (neat): 2995, 2980, 1505, 1435, 1385, 1280, 1170, 1075, 1030, 880, 790 cm^{-1}.

Preparation of 3-(3-furyl)-1-bromopropane (64). To a solution of triphenyl-phosphine (7.41 g, 30 mmol) in ether (50 mL) cooled to 0°C in an ice bath was added carbon tetrabromide (10.05 g, 30 mmol)[62] all in one portion

and the resulting suspension stirred at 0°C for 30 minutes. A solution 3-(3-furyl)propan-1-ol[45c] (1.89 g, 15 mmol) in ether (10 mL) was added all in one portion and the mixture heated under reflux for 4 hours. The resulting suspension was cooled to room temperature and cast into hexane (150 mL) and was cooled (0°C) for 30 minutes. The mixture was filtered through celite and the solvent removed in vacuo to provide a yellow liquid. The product was purified by chromatography on a column of silica gel (60-230 mesh, 50 g, 40 mm. od, pet. ether, 25 mL fractions) using the flash technique. Fractions 4-9 provided 2.04 g, 72%, of the bromide **64** as a clear, colorless, sweet-smelling liquid. ^{1}H NMR (60 MHz): δ=7.18 (t, J=1.7 Hz, 1H); 7.07 (m, 1H); 6.17 (m, 1H); 3.36 (t, J=6.2 Hz, 2H); 2.68 (t, J=6.6 Hz, 2H); 2.08 (m, 2H). EI/MS (70 eV): 190 (21.9), 188 (23.9), 109 (6.1), 95 (4.5), 82 (base). IR (neat): 2990, 2890, 1500, 1430, 1380, 1280, 1170, 1030, 880, 780 cm^{-1}.

Preparation of 2-methylene-7-oxabicyclo-[4.1.0]-heptane (65). To a solution of methyltriphenylphosphonium bromide (35.7 g, 0.1 mmol) in anhydrous THF (150 mL), cooled to -23°C (dry ice - CCl_4) was added diisopropylamine (10.1 g, 0.1 mol) followed immediately by the addition n-butyllithium over a period of 15 minutes. The resulting red solution was stirred at -22°C for 1 hour and then warmed to 0°C for 1 hour. A solution of 7-oxabicyclo [4.1.0] heptan-2-one[63] (7.8 g, 0.07 mol) in THF (50 mL) was added to the red solution over a period of 5 minutes and the resulting suspension stirred at 0°C for 1 hour and then at room temperature for 2 hours. The suspension was cast into hexane (500 mL) and cooled to 0°C for 3 hours. The ϕ_3PO was removed by filtration through a pad of celite and the hexane was removed by distillation. The residue was distilled under reduced pressure to provide 5.4 g, 70%, of **65** as a clear, colorless oil. B.P.$_{29mm}$ = 62-63°C. ^{1}H NMR (250MHz): δ=5.23 (d, J=1.4 Hz, 1H); 5.10 (m, 1H); 3.42 (d, J=3.9 Hz, 1H); 3.38 (m, 1H); 2.26 (m,

1H); 2.02 (m, 2H); 1.83 (m, 1H); 1.57 (m, 1H); 1.42 (m, 1H). EI/MS (70 eV): 110 (M^+, 12.1), 95 (17), 81 (25.4), 67 (31), 55 (55), 40 (base). IR (neat): 3050, 2900, 3895, 1645, 1440, 1400, 940, 910, 835, 755 cm^{-1}. MS: M^+ calc. 110.073160, obs. 110.07323.

1-methyl-2-methylene-6-oxabicyclo-[3.1.0]-hexane (72). To a liquid ammonia (30 mL), cooled to -78°C (dry ice-isopropanol), was added sodium metal (0.5 g, 22 mmol) and the mixture stirred until all the sodium had dissolved (about 30 minutes). Several crystals of ferric nitrate were added and the solution stirred until the color became a light grey. Methyltriphenyl-phosphonium bromide (8.08 g, 20 mmol) was added and the ammonia allowed to evaporate as the mixture was slowly warmed to room temperature. Anhydrous ether was added and the resulting orange suspension heated under reflux for 30 minutes. The ether was decanted into a clean dry 50 mL round bottom flask and a solution of 1-methyl-6-oxabicyclo [3.1.0.]-hexan-2-one[63] (1.6 g, 15 mmol) in ether (10 mL) was added dropwise. The resulting mixture was stirred at room temperature for 2 hours. The mixture was cast into pentane (50 mL), cooled to 0°C and filtered through a pad of celite. The filtrate was washed with saturated aqueous NH_4Cl (50 mL), brine (50 mL), dried ($MgSO_4$) and the solvent removed by distillation. The residue was purified by chromatography on a column of silica gel (60-230 mesh, 40 g, 30 mm o.d., 10% ether-pet. ether 15 mL fractions) using the flash technique. Fractions 9-12 provided 0.52 g, 32% of **72** as a clear, colorless, sweet smelling liquid. ^1H NMR (60 MHz): δ =5.0 (br m, 2H); 3.32 (brs, 1H); 2.14 (m, 2H); 1.96 (m, 2H); 1.43 (s, 3H). EI/MS (70 eV): 110 (M^+, 12.7), 95 (134, 69 (17.7), 55 (33.8), 43 (base).

1-methyl-2-methylene-7-oxabicyclo[4.1.0]-heptane (111). According to the above procedure for the preparation of vinyl epoxides 1-methyl-7-

oxabicyclo[4.1.0]hepan-2-one[63] (9.0 g, 70 mmol) provided 4.6 g, 53%, of **111**; BP_{25mm} = 65-70°C. ^1H NMR (60 MHz): δ= 5.19 (d, J=1.3 Hz, 1H); 5.07 (m, 1H); 3.11 (t, J=2.1 Hz, 1H); 1.92 (m, 6H); 1.42 (s, 3H). EI/MS (70 eV): 124 (M^+, 1.5), 97 (13.7), 81 (30.6), 67 (19.7), 57 (22.1), 43 (base). IR (neat); 3070, 2980, 2790, 1650, 1440, 940, 910, 835, 760 cm^{-1}.

GENERAL PROCEDURE FOR THE PREPARATION OF ALLYLIC ALCOHOLS

3-(2-(furyl)-ethyl)-cyclohex-2-en-1-ol (66). To magnesium turnings (0.36 g, 15 mmol) covered by THF (15 mL) was added (3-furyl)-chloromethane [10a] (1.74 g, 15 mmol) and the mixture stirred at room temperature until all the magnesium had been consumed (about 2 hours). The resulting golden solution was cooled to -78°C (dry ice - isopropanol) and copper (I) cyanide (1.34 g, 15 mmol) was added all in one portion. The mixture became a yellow-green suspension which was stirred at -78°C for 30 minutes. To this suspension was added a solution of vinyl epoxide **65** (1.20 g, 10 mmol) in THF (10 mL) over 5 minutes and the resulting yellow suspension was allowed to slowly warm to room temperature over 4 hours. The mixture was cast into saturated aqueous NH_4Cl (100 mL) and ether (150 mL). The organic phase was separated and washed with 1N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), dried $MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50 g, 40 mm o.d., 2:5 ether-pet. ether, 25 mL fractions) using the flash technique. Fractions 9-15 provided 1.57 g, 82.3%, of the product as a viscous, colorless oil. ^1H NMR (250 MHz): δ= 7.34 (dd, J=1.6, 1.4 Hz, 1H); 7.21 (m, 1H); 6.26 (brs, 1H); 5.52 (t, J=1.5 Hz, 1H); 4.19 (brs, 1H); 2.55 (dd, J=8.3, 7.3 Hz, 2H); 2.22 (dd, J=8.3, 7.3 Hz, 2H); 1.95 (m, 2H); 1.5-1.7 (m, 4H). EI/MS (70 eV): 192 (M^+, 10.4), 174 (33.4), 110 (62.1), 97 (45), 91 (19), 81 (base). IR

(neat): 3400, 2970, 2900, 1675, 1510, 1460, 1170, 1080, 1035, 975, 885, 790, 740 cm^{-1}.

3-(3-(3-furyl)-propyl)-cyclohex-2en-1-ol (67). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from 2-(3-furyl)-1-bromethane (2.6 g, 15 mmol) was reacted (CuCN) with vinyl epoxide **65** (1.1 g, 10 mmol) to provide 1.19 g, 58%, of **67** as a colorless oil. ^1H NMR (250 MHz): δ = 7.22 (dd, J=1.7, 1.4 Hz, 1H); 7.06 (m, 1H); 6.18 (m, 1H); 5.36 (brs, 1H); 4.20 (br, 1H); 4.09 (m, 1H); 2.41 (t, J=6.8 Hz, 2H); 1.42 (m, 10H). EI/MS (70 eV): 206 (M^+, 6.6), 123 (45.1), 110 (14.2), 97 (base). IR (neat): 3400 (br), 3050, 2970, 2900, 1675, 1500, 1460, 1170, 1055, 975, 850, 790 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.72; H, 8.73. Found: C, 75.56; H, 8.62.

3-(4-(3-furyl)-butyl)-cyclohex-2en-1-ol (68). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from 3-(3-furyl)-1-bromethane (2.8 g, 15 mmol) was reacted (CuCN) with vinyl epoxide **65** (1.10 g, 10 mmol) to provide 1.36 g, 62%, of **68** as a colorless oil. ^1H NMR (250 MHz): δ 7.38 (dd, J=1.7, 1.4 Hz, 1H); 7.22 (m, 1H); 6.25 (m, 1H); 5.49 (d, J=1.4 Hz, 1H); 4.18 (m, 1H); 2.23 (t, J=6.3 Hz, 2H); 2.1-1.35 (m, 12H). EI/MS (70 eV): 220 (M^+, 6.33), 218 (22.2), 202 (29.3), 136 (85), 123 (55), 110 (44), 97 (48), 81 (base). IR (neat): 3500 (br), 3010, 2980, 2900, 1670, 1500, 1430, 1170, 975, 850, 780 cm^{-1}.

3-(3-(3-furyl)-propyl)-2-methylcyclopent-2-en-1-ol (73). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from 2-(3-furyl)-1-bromoethane (0.53 g, 3 mmol) was reacted (CuCN) with vinyl epoxide **72** (0.11 g, 1 mmol) to provide 120 mg, 59% of **73** as a clear, colorless oil. ^1H NMR (250 MHz) δ =7.17 (dd J=1.4, 1.2 Hz, 1H), 7.09 (m, 1H), 6.00 (m, 1H), 4.42 (t, J=8.5 Hz, 1H), 2.26 (t, J=6.6 Hz, 2H), 1.89 (m,

2H), 1.75 (m, 2H). EI/MS (70 eV): 206 (M^+, 4.53); (188, 32.4); 120 (14.3); 94 (base). IR (neat): 3450 (br, 3040, 2980, 1500, 1460, 1170, 1080, 890 cm^{-1}.

3-(4-(3-furyl)-butyl)-2-methylcyclopent-2-en-1-ol (74). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from 3-(3-furyl)-1-bromopropane (0.26 g, 1.4 mmol) was reacted (CuCN) with vinyl epoxide **72** (0.75 g, 0.68 mmol) to provide 95 mg, 63% of **74** as a clear, colorless oil. ^1H NMR (250 MHz): δ=7.18 (dd, J=1.4, 1.2 Hz, 1H), 7.07 (m, 1H), 6.04 (m, 1H), 4.42 (t, J=8.2 Hz, 1.H), 2.26 (t, J=6.6 Hz, 2H), 1.98 (m, 4H), 1.77 (m, 2H), 1.60 (brs, 3H), 146 (m, 4H). EI/MS (70 eV): 220 (M^+, 5.68), 202 (18.4), 120 (base). IR (neat): 3440 (br), 3045, 2980, 1500, 1465, 1170, 1080, 780 cm^{-1}.

GENERAL PROCEDURE FOR THE PREPARATION OF 2-EN-1-ONES AND 2-EN-1-ALS

3-(2-(3-furyl)-ethyl)-cyclohex-2-en-1-one (69). To a solution of allylic alcohol **66** (1.92 g, 10 mmol) in CH_2Cl_2 (10 mL) was added Na_2CO_3 (0.1 g, 1 mmol) and the mixture cooled in an ice water bath. Pyridinium chlorochromate (3.23 g, 15 mmol) was added in small portions over 10 minutes. The resulting red-brown suspension was stirred at 0°C for 30 minutes and cast into 1N HCl (50 mL) and ether (100 mL). The organic phase was separated and washed with 1N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), water (50 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 55 g, 40 mm o.d., 1:1 ether-pet. ether, 25 mL fractions) using the flash technique. Fractions 8-11 provided 1.65 g, 87%, of the **69** as a colorless, sweet-smelling oil. ^1H NMR (250 MHz): δ=7.37 (dd, J=1.7, 1.4 Hz, 1H); 7.21 (brs, 1H); 6.24 (brs, 1H); 5.88 (s, 1H); 2.63 (t, J=6.3Hz, 2H), 2.43 (t, J=6.4 Hz,

2H); 2.28 (m, 4H); 2.01 (m, 2H). EI/MS (70 eV): 190 (M^+, 19.6), 172 (15.1), 134 (12), 81 (base). IR (neat): 2990, 2790, 1680 (s), 1500, 1230, 1180, 1040, 880, 800 cm^{-1}.

3-(3-(3-furyl)-propyl)-cyclohex-2-en-1-one (70). According to the general procedure for the preparation of 2-en-1-ones, allylic alcohol **67** (2.06 g, 10 mmol) was treated with PCC (3.23 g, 15 mmol) to provide 1.7 g, 83%, of **70** as a light yellow oil. ^1H NMR (250 MHz): δ =7.28 (dd, J=1.7, 1.5 Hz, 1H); 7.18 (m, 1H); 6.19 (brs, 1H); 5.76 (s, 1H); 2.58 (t, J=6.8 Hz, 2H); 2.36 (m, 4H); 2.28 (m, 2H); 1.98 (m, 4H). EI/MS (70 eV): 204 (M^+, 22.8), 188 (66), 147 (73), 123 (20.2), 110 (32.8), 94 (65.7), 82 (base). IR (neat): 2980, 2790, 1685 (br), 1500, 1245, 1170, 1030, 880, 800 cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.44; H, 7.81.

3-(4-(3-furyl)-butyl)-cyclohex-2-en-1-one (71). According to the general procedure for the preparation of 2-en-1-ones, allylic alcohol **68** (2.20 g, 10 mmol) was treated with PCC (3.23 g, 15 mmol) to provide 1.83 g, 85%, of **71** as a light yellow oil. ^1H NMR (250 MHz): =7.38 (dd, J=1.2, 1.5 Hz, 1H); 7.20 (m, 1H); 6.23 (brs, 1H); 5.83 (s, 1H); 2.46 (t, J=6.4 Hz, 2H); 2.38 (t, J=7.2 Hz, 2H); 2.21 (m, 2H); 1.98 (m, 4H); 1.68 (m, 4H). EI/MS (70 eV): 218 (M^+, 37), 175 (7.17), 126 (17.8), 94 (28.7), 82 (base). IR (neat): 2980, 2795, 1680 (br), 1630, 1260, 1195, 1030, 875, 880 cm^{-1}.

2-methyl-5-[2-(3-furyl)ethyl]-cyclopent-2-en-1-one (75). To a solution of oxalyl chloride (175 mg, 1.38 mmol) in dichloromethane (2 mL) cooled to -60°C in a dry ice-chloroform bath was added dimethylsulfoxide (215 mg, 2.75 mmol) and the solution stirred at -60°C. After 30 minutes, a solution of alcohol **73** (100 mg, 0.5 mmol) in dichloromethane (2 mL) was added and the solution stirred at -60°C for 1 hour. Triethylamine (0.5 g, 5 mmol) was added and the mixture warmed to room temperature for 30 minutes. The solution was

cast into dichloromethane (25 mL) and water (25 mL). The organic phase was separated and washed with 1N HCl (25 mL), saturated aqueous $NaCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 15 g, 20 mm o.d., 1:1 Et_2O/pet. ether, 10 mL fractions) using the flash technique. Fractions provided 72 mg, 73% of **75** as a clear colorless oil. ^1H NMR (250 MHz): δ =7.21 (m, 1H); 7.08 (m, 1H); 6.09 (m, 1H); 2.23 (m, 2H); 2.05 (m, 4H); 1.95 (m, 4H); 1.80 (m, 4H); 1.76 (brs, 3H). EI/MS (70 eV): 204 (M^+, 15.5); 161 (600); 149 (47.5); 123 (72.9); 110 (45.6); 95 (86.01); 82 (base). IR (neat): 2990, 2980, 1685(s), 1500, 1450, 1230, 1040, 980, 780 cm^{-1}.

2-methyl-5-[3-(3-furyl)propyl]-cyclopent-2-en-1-one (76). According to the general procedure for the preparation of 2-en-1-ones allylic alcohol **74** (100 mg, 0.45 mmol) was treated with PCC (0.29 g, 1.36 mmol) to provide 73 mg, 74% of **76** as a light yellow oil. ^1H NMR (250 MHz): δ=7.24 (m, 1H); 7.08 (m, 1H); 6.04 (m, 1H); 2.18 (t, J=8.2 Hz, 2H); 2.01 (m, 2H); 1.92 (m, 4H); 1.80 (m, 4H); 1.66 (brs, 3H). EI/MS (70 eV): 218 (M^+, 11.7); 204 (3.5); 159 (6.7); 136 (56.9); 123 (44.5); 110 (49.0); 95 (70.8); 81 (base). IR (neat): 2995, 2980, 1690, 1500, 1245, 1040, 980, 780 cm^{-1}.

6-(4-(3-furyl)-ethyl)-cyclohex-2-en-1-one (80). To magnesium metal (0.24 g, 10 mmol) covered by THF (10 mL) was added 2-(3-furyl)-1-bromethane **63** (1.75 g, 10 mmol) and the mxiture stirred at room temperature until all the magnesium had been consumed (about 2½ hours). The resulting golden yellow solution was cooled to -78°C (dry ice - isopropanol) and copper (I) cyanide (0.89 g, 10 mmol) was added in one portion. The resulting green suspension was stirred at -78°C for 30 minutes and a solution of **77**[42f] (1.47 g, 8 mmol) in THF (5 mL) was added over a period of 5 minutes. The resulting yellow-brown suspension was stirred at -78°C for 2 hours. The mixture was cast

into saturated aqueous NH_4Cl (50 mL) and ether (75 mL). The organic phase was separated, washed with 1N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50 g, 40 mm o.d., 1:1 ether:hexane) using the flash technique. Fractions 7-9 provided 1.14 g, 75%, of **80** as a light yellow liquid. ^1H NMR (250 MHz): δ=7.37 (dd, J=1.6, 1.4 Hz, 1H); 6.25 (m, 1H); 6.92 (dt, J=8.1, 3.5 Hz, 1h); 6.32 (brs, 1H); 6.00 (dt, J=8.1, 2.1 Hz, 1H); 2.49 (m, 2H); 2.37 (m, 2H); 1.79 (m, 2H); 1.58 (m, 2H). EI/MS (70 eV): 190 (M^+, 7.37), 167 (2.56), 96 (base), 81 (24.6). IR (neat): 2940, 2880, 1685, 1500, 1450, 1390, 1030, 880, 800 cm^{-1}.

6-(3-(3-furyl)-propyl)-cyclohex-2-en-1-one (81). To magnesium metal (0.12 g, 5 mmol) covered by THF (3 mL) was added 3-(3-furyl)-1-bromopropane[10c] (0.94 g, 5 mmol) and the mixture stirred at room temperature until all the magnesium had been consumed (about 2 hours). The resulting golden yellow solution was cooled to -78°C (dry ice - isopropanol) and copper (I) cyanide (0.45 g, 5 mmol) was added in one portion. The resulting green suspension was stirred at -78°C for 30 minutes and a solution of **77** (0.73 g, 4 mmol) in THF (3 mL) was added over a period of five minutes and the resulting brown suspension stirred at -78°C for 2 hours. The mixture was cast into saturated aqueous NH_4Cl (25 mL) and ether (50 mL). The organic phase was separated, washed with 1N HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50 g, 40 mm o.d., 1:1 ether:hexane) using the flash technique. Fractions 10-14 provided 0.72 g, 72%, of **81** as a clear, colorless liquid. ^1H NMR (250 MHz): δ=7.18 (dd, J=1.6, 1.4 Hz, 1H); 6.99 (m, 1H); 6.68 (dt, J=9.8,

3.92 Hz, 1H); 6.03 (brs, 1H); 5.73 (dt, J=9.8, 2.4 Hz, 1H); 2.22 (t, J=8.2 Hz, 2H); 2.14 (m, 3H); 1.90 (m, 2H); 1.75-1.2 (m, 4H). EI/MS (70 eV): 204 (M^+, 6.5), 159 (11.7), 122 (17.7), 108 (base), 96 (54), 81 (48). IR (neat): 2950, 2880, 1685, 1500, 1445, 1380, 1140, 1030, 880, 800 cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.45; H, 7.84.

1-methyl-6-(2-(3-furyl)-ethyl)-cyclohex-2-en-1-ol (82). To a solution of **80** (0.38 g, 2 mmol) in THF (3 mL) cooled to -78°C (dry ice -isopropanol) was added methyl lithium (3.07 mL), 1.3M, 4 mmol) in one portion and the mixture stirred at -78°C for 30 minutes. The resulting solution was cast into saturated aqueous NH_4Cl (20 mL) and ether (20 mL). The organic phase was separated, washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 30 mm o.d., 1:4 ether-hexane, 10 mL fractions) using the flash technique. Fractions 14-18 provided 0.37 g, 90%, of **82** as a clear, colorless liquid which is a 3:2 mixture of isomers by capillary GLC. ^1H NMR (250 MHz): δ=7.36 (dd, J=1.6, 1.4 Hz, 1H); 7.22 (m, 1H); 6.28 (m, 1H); 5.72-5.53 (m, 2H); 2.47 (m, 2H); 2.06 (m, 2H); 1.76 (m, 2H); 1.29 (s, 1.2H): 1.18 (s, 1.8H). EI/MS (70 eV): 206 (M^+, 4.2), 188 (3.4), 108 (10.3), 94 (20.7), 82 (base). IR (neat): 3500 (br), 3010, 2980, 2900, 1665, 1500, 1430, 1165, 975, 780 cm^{-1}.

1-methyl-6-(3-(3-furyl)-propyl)-cyclohex-2-en-1-ol (83). To a solution of **81** (0.15 g, 0.75 mmol) in THF (2 mL) cooled to -78°C (dry ice -isopropanol) was added methyl lithium (2.85 mL, 1.3M, 3.7 mmol) in one portion and the mixture stirred at -78°C for 30 minutes. The resulting solution was cast into saturated aqueous NH_4Cl (10 mL) and ether (10 mL). The organic phase was separated, washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by

chromatography on a column of silica gel (230-400 mesh, 30 g, 40 mm o.d., 1:1 ether-hexane, 25 mL fractions) using the flash technique. Fractions 7-10 provided 146 mg, 90%, of **83** as a 3:2 mixture of isomers by GLC. ^{1}H NMR (250 MHz): δ=7.35 (dd, J=1.6, 1.4 Hz, 1H); 7.21 (m, 1H); 6.29 (brs, 1H); 5.79-5.50 (m, 2H); 2.47 (m, 2H); 2.03 (m, 2H); 1.81-1.38 (m, 4H); 1.29 (s, 1.8H); 1.17 (s, 1.2H). EI/MS (70 eV): 220 (M^+, 3.16), 202 (2.75), 167 (39.2), 157 (22.9), 120 (11.2), 108 (14.8), 93 (39.0), 84 (base). IR (neat): 3500 (br), 3010, 2990, 2890, 1670, 1500, 1430, 1170, 975, 880, 780 cm^{-1}.

2-methyl-5-[2-(3-furyl)ethyl]cyclopent-2-en-1-one (84). To magnesium metal (0.05 g, 2 mmol) covered by THF (1 mL) was added 2-(3-furyl)-1-bromoethane (0.35 g, 2 mmol) and the mixture stirred at room temperature until all the magnesium had reacted (about 1 hour). The resulting golden solution was cooled to -78°C (dry ice-isopropanol) and copper (I) cyanide (0.18 g, 2 mmol) was added and the green suspension stirred at -78°C for 30 minutes. To a solution of diisopropyl amine (0.1 g, 1 mmol) in THF (1 mL) cooled to -78°C (dry ice-isopropanol) was added n-BuLi (0.4 mL), 2.5 m, 1.0 mmol) and the mixture stirred at -78°C for 15 minutes. To this solution was added 1-methyl-6-oxabicyclo [3.1.0]hexane-2-one (0.11 g, 1mmol) and the mixture stirred for 30 minutes at -78°C. To this solution was added trimethyl chlorosilane (0.13 g, 1.25 mmol) and the mixture warmed to 0°C. After 30 minutes, this mixture was slowly added via syringe to the cuprate prepared above and the suspension stirred at -78°C for 2 hours. The resulting suspension was cast into 1N HCl (10 mL) and ether (10 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated <u>in vacuo</u> to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 15 g, 20 mm o.d., 1:1 Et_2O: hexane, 10 mL fractions) using the flash

technique. Fractions 9-14 provided 105 mg, 55% of **84** as a light yellow oil. ^{1}H NMR (250 MHz): δ=7.28 (dd, J=1.4, 1.2 Hz); 7.15 (m, 1H); 7.10 (m, 1H); 6.21 (m, 1H); 2.78 (m, 1H), 2.73 (m, 1H); 2.57 (m, 2H), 2.24 (m, 3H); 1.88 (m, 3H). EI/MS (70 eV): 190 (M^+, 17.7); 169 (5.18); 109 (5.08); 96 (base).

2-methyl-5-[3-(3-furyl)propyl)cyclopent-2-en-1-one (85). According to the procedure outlined for the preparation of **84**, 3-(3-furyl)-1-bromopropane (0.38 g, 2 mmol) was reacted with 1-methyl-6-oxabicyclo[3.1.0]hexan-2-one (0.11 g, 1 mmol) to provide 110 mg, 54% of **85** as a clear oil. ^{1}H NMR (250 MHz): δ=7.21 (dd, J=1.6, 1.2 Hz, 1H); 7.16 (m, 1H); 7.09 (m, 1H); 6.17 (m, 1H); 4.02 (m, 1H); 3.43 (m, 2H); 2.38 (m, 4H); 1.64 (brs, 3H); 1.49 (m, 2H). EI/MS (70 eV): 204 (M^+, 21.2); 185 (8.13), 122 (37.9), 108 (base).

1,2-dimethyl-5-[2-(3-furyl)ethyl]cyclopent-2-en-1-ol (86). To a solution of **84** (50 mg, 0.25 mmol) in THF (1 mL), cooled to -78°C (dry ice-isopropanol) was added methyl lithium (1.0 mL, 1.3 M, 1.3 mmol) in one portion and the mixtured was stirred at -78°C for 30 minutes. The resulting solution was cast into saturated aqueous NH_4Cl (10 mL) and ether (10 mL). The organic phase was separated and washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide 41.3 mg, 78% of a yellow liquid which was used without further purification. ^{1}H NMR (250 MHz): δ=7.21 (m, 1H); 7.09 (m, 1H); 6.10 (m, 1H); 5.24 (m, 1H); 2.24 (m, 4H); 1.98 (m, 6H); 1.85 (brs, 3H); 123 (m, 3H). EI/MS (70 eV): 206 (M^+, 14.2), 188 (61.5), 173 (43.0), 157 (12.4), 149 (25.5), 123 (37.0), 109 (73.9), 94 (97.0), 81 (base).

1,2-dimethyl-5-[3-(3-furyl)propyl]-cyclopent-2-en-1-ol (87). To a solution of **85** (50 mg, 0.25 mmol) in THF (1 mL), cooled to -78°C (dry ice-isopropanol) was added methyl lithium (1.0 mL, 1.3 M, 1.3 mmol) in one portion and the mixture stirred at -78°C for 30 minutes. The resulting solution was cast into saturated aqueous NH_4Cl (10 mL) and ether (10 mL). The organic phase was

separated and washed with brine (10 mL), dried $MgSO_4$) and concentrated in vacuo to provide 46 mg, 83% of a yellow liquid which was used without further purification. ^1H NMR (250 MHz): δ=7.19 (m, 1H); 7.06 (m, 1H); 6.09 (m, 1H); 5.22 (m, 1H); 2.24 (m, 6H); 1.95 (m, 4H); 1.80 (brs, 3H); 1.21 (m, 3H). EI/MS (70 eV): 220 (M^+, 4.5); 202 (13.1), 185 (16.9), 169 (13.6), 15.7 (151), 120 (53.5), 108 (58.3), 95 (48.9), 81 (61.6), 43 (base).

1-(methylthiomethylene)cyclohex-2-en-1-ol. To n-butyl lithium (28.6 mL, 1.75 M in hexane, 50 mmol) chilled in an ice-water bath was added tetra methylethylenediamine (TMEDA 5.8 g, 50 mmol). The mixture was warmed to room temperature and allowed to stir for 30 minutes. The mixture was cooled to 0°C and dimethyl sulfide[13] (3 g, 48.4 mmol) was added. The resulting pale yellow solution was stirred for 3.5 hours at room temperature, cooled to -78°C (dry ice - isopropanol) and a solution of 2-cyclohexen-1-one (4.85 g, 50 mmol) in THF (30 mL) was added over 5 minutes. The mixture was warmed to room temperature, cast into ether (150 mL) and saturated aqueous (NH_4SO_4) and concentrated in vacuo to provide a viscous yellow liquid. The crude product was purified by distillation. $B.P._{0.007mm}$ = 65-68°C to provide 6.7 g, 88%, of 1-(methylthiomethylene)cyclohex-2-en-1-ol as a colorless, viscous liquid. ^1H NMR (250 MHz): δ = 5.85 (ddd, J=10, 4, 3.15 Hz, 1H); 5.66 (dddd, J=9.5, 2.4, 2.0, 0.77 Hz, 1H); 2.75 (d, J=13.4 Hz, 1H); 2.67 (d, J=13.4 Hz, 1H); 2.50 (brs, 1H); 2.20 (s, 3H); 1.95-2.09 (m, 2H); 1.57-1.85 (m, 4H). EI/MS (70 eV): 158 (M^+, 6.65), 141 (32.3), 97 (base). IR (neat): 3470 (br), 3050, 2950, 2855, 1645, 1435, 1220, 1185, 1055, 1000, 965 (br), 740 cm^{-1}.

1-(dimethylsulfonium methylene)—cyclohex-2-en-1-ol. To a solution of allylic alcohol (3.16 g, 20 mmol) in dry acetone (10 mL) was added methyl iodide (5.67 g, 40 mmol). The mixture was allowed to stir at room temperature overnight and then concentrated in vacuo to provide 6.0 g, 100%, of the

sulfonium salt as a white solid, M.P. = 155° (dec), which was used without further purification.

8-oxaspiro[5.2]-oct-2-ene (79). To a suspension of the sulfonium salt (6.0 g, 20 mmol) in 250 mL of THF was added 2.9 g (25.9 mmol) of freshly sublimed KOtBu. The mixture was allowed to stir at room temperature for 4 hours, quenched with saturated aq. $NaHCO_3$ (50 mL), and was cast into ether (250 mL). The aqueous phase was separated, extracted with ether (4 x 100 mL), and the combined organic extracts were washed with saturated aq. $NaHCO_3$ (0.5 L), brine (0.5 L), and dried ($MgSO_4$, K_2CO_3). The solvent was removed by distillation at atmospheric pressure and the residue was purified by distillation, $B.P._{37mm}$ = 70-72°C to provide 2.0 g, 91%, **79** as a colorless liquid. ^1H NMR (250 MHz): δ = 6.12 (dd, J=10.07, 3.97, 3.66 Hz, 1H); 5.25 (brd, J=10.07 Hz, 1H); 2.84 (d, J=4.88 Hz, 1H); 2.79 (d, J=4.88 Hz, 1H); 1.5-2.3 (m, 6H). EI/MS (70 eV): 110 (M^+, 83), 93 (51), 79 (base). IR (neat): 3080, 3020, 1460, 950, 810, 760 cm^{-1}. MS: M^+ calc. for $C_7H_{10}O$; 110.073160; M^+ found 110.07320.

1-hydroxymethyl-3-(3-furylmethyl)-1-cyclohexene (88). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from (3-furyl)-chloromethane[10a] (1.7 g, 15 mmol) was reacted (CuCN) with vinyl epoxide **79** to provide 1.5 g, 78%, of **88** as a clear, colorless liquid. ^1H NMR (250 MHz): δ = 7.35 (dd, J=1.7, 1.4 Hz, 1H); 7.22 (dd, J=1.7, 0.77 Hz, 1H); 6.27 (m, 1H); 5.58 (brs, 1H); 3.98 (brs, 2H); 2.38 (m, 2H); 2.30 (brs, 1H); 1.98 (brs, 2H); 1.77 (m, 1H); 1.58 (m, 1H); 1.52 (m, 1H); 1.20 (m, 1H). EI/MS (70 eV): 192 (M^+, 1.44), 174 (6.8), 161 (1.72), 128 (1.60), 111 (69), 93 (base). IR (neat): 3400 (br), 2965, 2895, 1515, 1460, 1175, 1080, 1040, 890, 800, 785, 745 cm^{-1}.

1-hydroxymethyl-3-(2-(3-furyl)-ethyl)-1-cyclohexene (89). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from 2-(3-furyl)-1-bromoethane[10b] (2.6 g, 15 mmol) was reacted (CuCN) with vinyl epoxide **79** to provide 1.15 g, 56%, of **89** as a colorless oil. ^{1}H NMR (250 MHz): δ= 7.35 (dd, J=1.7, 1.4 Hz, 1H); 7.24 (m, 1H); 6.25 (m, 1H); 5.43 (brs, 1H); 3.83 (brs, 2H); 2.41 (t, J=6.3 Hz, 2H); 2.33 (m, 2H); 1.98-1.23 (m, 7H). EI/MS (70 eV): 206 (M^+, 1.34), 175 (36), 188 (19.0), 124 (10), 95 (16), 82 (base. IR (neat): 3400 (br), 2965, 2895, 1500, 1460, 1175, 1080, 1040, 890, 800, 780 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.72; H, 8.73. Found: C, 75.66; H, 8.74.

1-hydroxymethyl-3-(3-(3-furyl)-propyl)-1-cyclohexene (90). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived from 3-(3-furyl)-1-bromoethane[10c] (2.8 g, 15 mmol) was reacted (CuCN) with vinyl epoxide **79** to provide 1.27 g, 58%, of **90** as a light yellow oil. ^{1}H NMR (250 MHz): δ=7.38 (dd, J=1.7, 1.6 Hz, 1H); 7.21 (m, 1H); 6.29 (brs, 1H); 5.58 (brs, 1H); 3.98 (s, 2H); 2.40 (t, J=6.1 Hz, 2H); 2.18-2.00 (m, 4H); 1.8-1.3 (m, 7H). EI/MS (70 eV): 220 (M^+, 10.8), 202 (27.5), 189 (10.8), 120 (46.1), 111 (23.7), 95 (70.1), 81 (base). IR (neat): 3500 (br), 2980, 2895, 1500, 1450, 1190, 1060, 1045, 800, 750 cm^{-1}.

3-(3-furylmethyl)-cyclohex-1-en-1-carboxaldehyde (91). According to the general procedure for the preparation of 2-en-1-als, allylic alcohol **88** (1.92 g, 10 mmol) was oxidized with PCC (3.23 g, 15 mmol) to provide 1.5 g, 78.9%, of **91** as a clear, colorless liquid. ^{1}H NMR (250 MHz): δ= 9.41 (s, 1H), 7.31 (dd, J=1.6, 1.4 Hz, 1H), 7.22 (m, 1H), 6.64 (brs, 1H), 2.52 (m, 2H), 1.2-8.18 (m, 8H). EI/MS (70 eV): 190 (M^+, 20), 172 (1.12), 161 (2.57), 108 (9), 81 (base). IR (neat): 2980, 2880, 2710, 1685, 1630, 1450, 1390, 1180, 1020, 880, 800 cm^{-1}.

3-(2-(3-furyl)-ethyl)-cyclohex-1-ene-1-carboxaldehyde (92). According to the general procedure for the preparation of 2-en-1-als, allylic alcohol **89** (2.06 g, 10 mmol) was oxidized with PCC (3.23 g, 15 mmol) to provide 1.7 g, 83%, of **92** as a pale yellow oil. ^{1}H NMR (250 MHz): δ= 9.23 (s, 1H); 7.21 (dd, J=1.6, 1.4 Hz, 1H); 7.10 (m, 1H); 6.52 (brs, 1H); 6.18 (m, 1H); 2.54 (t, J=5.8 Hz, 2H); 2.1 (t, J=5.7 Hz, 2H); 1.8-1.6 (m, 7H). EI/MS (70 eV): 204 (M^+, 25.8), 186 (12.7), 173 (26.3), 123 (23.9), 95 (13.2), 82 (base). IR (neat): 3140 (w), 2980, 2880, 1690, 1630, 1500, 1450, 1190, 1070, 1030, 880, 780 cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84. Found: C, 76.34; H, 7.88.

3-(3-(3-furyl)-propyl)-cyclohex-1-ene-1-carboxaldehyde (93). According to the general procedure for the preparation of 2-en-1-als, allylic alcohol **90** (2.20 g, 10 mmol) was oxidized with PCC (3.23 g, 15 mmol) to provide 1.7 g, 78%, of **93** as a yellow oil. ^{1}H NMR (250 MHz): δ= 9.26 (s, 1H); 7.34 (dd, J=1.6, 1.5 Hz, 1H); 7.21 (m, 1H); 6.23 (brs, 1H); 6.31 (m, 1H); 2.43 (t, J=7.3 Hz, 2H); 2.38 (m, 2H); 2.08 (m, 2H); 1.98-1.16 (m, 7H). EI/MS (70 eV): 218 (M^+ 11.2), 189 (5.8), 147 (6.9), 136 (base), 107 (12.6), 95 (19.2), 81 (33.4). IR (neat): 2980, 2880, 2720, 1690, 1630, 1500, 1450, 1380, 1185, 1020, 880, 790 cm^{-1}.

1-(1-hydroxyethyl)-3-(2-(3-furyl)-ethyl)-1-cyclohexene (94). To a solution of **92** (0.102 g, 0.5 mmol) in THF (3 mL) cooled to -78°C (dry ice-isopropanol) was added a solution of methyllithium in hexane (1.15 mL, 1.3 M, 1.5 mmol) in one portion and the mixture stirred at -78°C for 20 minutes. The mixture was cast into saturated aqueous NH_4Cl (10 mL) and ether (10 mL). The organic layer was separated and washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40 g, 40 mm o.d., 1:4 Et_2O/Hex, 25 mL fractions) using the flash

technique. Fractions 5-8 proviced 99 mg, 90%, of (**94**) as a clear, colorless liquid. ^{1}H NMR (250 MHz): δ = 7.20 (dd, J=1.6, 1.4 Hz, 1 H); 7.10 (m, 1H); 6.13 (m, 1H); 5.43 (brs, 1H); 3.98 (q, J=7.3 Hz, 1H); 2.42 (t, J=6.3 Hz, 2H); 2.0-1.3 (m, 5H); 1.14 (d, J=7.3 Hz, 3H). EI/MS (70 eV): 220 (M^+, 0.5), 202 (19.9), 138 (5.5), 123 (6.2), 95 (49.1), 82 (base). IR (neat): 3400 (br), 2995, 2890, 1500, 1460, 1185, 1060, 1045, 800, 760 cm^{-1}.

1-(1-hydroxyethyl)-3-(3-(3-furyl)-propyl)-1-cyclohexene (95). To a solution of **93** (0.218 g, 1 mmol) in THF (5 mL) cooled to -78°C (dry ice-isopropanol) was added a solution of methyllithium in hexane (2.3 mL, 1.3 M, 3 mmol) in one portion and the mixture stirred at -78°C for 30 minutes. The mixture was cast into saturated aqueous NH_4Cl (25 mL) and ether (25 mL). The organic layer was separated and washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 75 g, 50 mm o.d., 1:4 Et_2O/Hex, 25 mL fractions) using the flash technique. Fractions 7-11 provided 0.20 g, 85%, of **34** as a clear, colorless liquid. ^{1}H NMR (250 MHz): δ = 7.34 (dd, J=1.6, 1.4 Hz, 1 H); 7.21 (m, 1H); 6.24 (m, 1H); 5.54 (brs, 1H); 4.15 (q, J=7.2 Hz, 1H); 2.40 (t, J=6.3 Hz, 2H); 2.0 (m, 4H); 1.8-1.4 (m, 8H); 1.24 (d, J=7.2 Hz, 3H). EI/MS (70 eV): 234 (M^+, 4.2), 216 (23.9), 190 (5.1), 173 (7.9), 147 (13.5), 134 (90.4), 121 (14.9), 107 (50.5), 95 (70.9), 81 (base). IR (neat): 3400 (br), 2990, 2890, 1670, 1500, 1420, 1380, 1185, 1020, 880 cm^{-1}.

GENERAL PROCEDURE FOR THE CYCLIZATION OF ALLYLIC ALCOHOLS

Cyclization of Alcohol 67. To a solution of allylic alcohol **67** (0.1 g, 0.53 mmol) in cyclohexane (2 mL) was added anhydrous formic acid (0.5 mL) and the two-phase mixture was stirred rapidly at room temperature for 10

minutes. The resulting purple (lower layer) and colorless (upper layer) mixture was cast into water (10 mL) and ether (10 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 30 mm o.d., 1:4 ether-hexane, 10 mL fractions) using the flash technique. Fractions 5-7 provided 65 mg, 72%, of olefin **97** as a clear, colorless oil. ^1H NMR (250 MHz): δ= 7.23 (d, J=1.2 Hz, 1H); 6.17 (d, J=1.2 Hz, 1H); 5.82 (dt, J=10.4, 4.16 Hz, 1H); 5.53 (brd, J=10.4 Hz, 1H); 2.42 (t, J=5.2Hz, 2H); 2.08 (m, 2H); 1.96 (m, 2H); 1.8-1.6 (m, 6H). EI/MS (70 eV): 188 (M^+, 36.2), 160 (base), 145 (20.9), 131 (33.7), 117 (22.3), 105 (12.4), 91 (31.6), 77 (22.4). IR (neat): 3040, 2980, 2980, 1505, 1450, 1170, 1045, 895, 730 cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O$: C, 82.97; H, 8.51. Found: C, 82.90; H, 8.52.

Cyclization of Alcohol 68. According to the general procedure for the cyclization of allylic alcohols, **68** (0.1 g, 0.45 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 15 minutes to provide 53 mg, 58%, yield of olefin **98** as a clear, colorless liquid. ^1H NMR (250 MHz): δ= 7.18 (d, J=1.2 Hz, 1H); 6.16 (d, J=1.2 Hz, 1H); 5.83 (dt, J=9.8, 4.03 Hz, 1H); 5.66 (brd, J=9.89 Hz, 1H); 2.50 (m, 2H); 2.19 (m, 2H); 2.05 (m, 2H); 1.87 (m, 2H); 1.8-1.5 (m, 6H). EI/MS (70 eV): 202 (M^+, 74.3), 174 (base), 159 (77.0), 145 (46.3), 131 (79.9), 115 (28.8), 91 (39.9), 78 (21.3). IR (neat): 3040, 2995, 2880, 1500, 1120, 1050, 895, 730 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O$: C, 83.16; H, 8.91. Found: C, 82.91; H, 8.92.

Cyclization of Alcohol 73. According to the general procedure for the cyclization of allylic alcohols' **73** (50 mg, 0.24 mmol) in cyclohexane (2 mL) was treated with formic acid (1 mL) for 10 minutes to provide 26 mg, 58% of **99** as a colorless oil. ^1H NMR (250 MHz):δ=7.21 (d, J=1.2 Hz, 1H); 6.19 (d,

J=1.2 Hz, 1H); 5.53 (m, 1H), 2.42 (dd, J=8.1, 6.5 Hz, 2H); 2.37 (m, 2H); 2.12 (m, 2H); 1.93 (m, 2H); 1.53 (brs, 3H). EI/MS (70 eV): 188 (M^+, 79.8), 173 (39.4), 160 (base).

Cyclization of Alcohol 74. According to the general procedure for the cyclization of allylic alcohols, **74** (50 mg, 0.23 mmol) in cyclohexane (2 mL) was treated with formic acid (0.5 mL) for 15 minutes to provide 24 mg, 53% of **100** as a colorless oil. ^{1}H NMR (250 MHz): δ=7.19 (d, J=1.2 Hz, 1H); 6.18 (d, J=1.2 Hz, 1H); 5.03 (m, 1H); 2.59 (m, 2H); 2.42 (m, 2H); 2.01 (m, 4H); 1.98 (m, 4H); 1.58 (brs, 3H). EI/MS (70 eV): 202 (M^+, 34.9), 187 (12.2), 173 (16.9), 159 (19.2), 145 (10.2), 131 (11.8), 115 (10.7), 91 (17.8), 77 (12.1), 67 (12.4) 57 (15.1) 40 (base).

Cyclization of Alcohol 82. According to the general procedure for the cyclization of allylic alcohols, **82** (0.1 g, 0.48 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 30 minutes to provide 68 mg, 73%, yield of olefin **101** as a light yellow oil. ^{1}H NMR (250 MHz): δ = 7.18 (d, J=1.2 Hz, 1H); 6.08 (d, J=1.2 Hz, 1H); 5.75 (d, J=9.80 Hz, 1H); 5.54 (dt, J=9.81, 3.43 Hz, 1H); 2.33 (m, 3H); 1.92 (m, 2H); 1.71 (m, 4H); 1.30 (s, 3H). EI/MS (70 eV): 188 (M^+, 16.3), 173 (base), 131 (13.3), 91 (21.7), 77 (13.8). IR (neat): 3040, 2990, 2885, 1500, 1440, 1165, 1030, 890, 780 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$: C, 82.97; H, 8.51. Found C, 82.87; H, 8.50.

Cyclization of Alcohol 83. According to the general procedure for the cyclization of allylic alcohols, **83** (0.1 g, 0.46 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 15 minutes to provide 52 mg, 56%, yield of olefin **102** as a clear, colorless oil. ^{1}H NMR (250 MHz): δ=7.18 (d, J=1.2 Hz, 1H); 6.08 (d, J=1.2 Hz, 1H); 5.82 (dt, J=9.44, 1.3 Hz, 1H); 5.75 (dt, J=9.45, 4.12 Hz, 1H); 2.50 (m, 3H); 2.09 (m, 2H); 1.95-1.40 (m, 6H); 1.32 (s, 3H). EI/MS (70 eV): 202 (M^+, 16.4), 187 (base), 131 (10.6), 121 (26.3), 91

(18.7), 77 (15.3). IR (neat): 3035, 2985, 2880, 1500, 1440, 1165, 1030, 890, 780 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O$: C, 83.16; H, 8.91. Found: C, 83.00; H, 8.86.

Cyclization of Alcohol 86. According to the general procedure for the cyclization of allylic alcohols, **86** (50 mg, 0.24 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 5 minutes to provide 29 mg, 64% of **103** as a clear colorless oil. ^1H NMR (250 MHz):δ=7.13 (d, J=1.2 Hz, 1H); 6.17 (d, J=1.2 Hz, 1H); 5.24 (m, 1H); 2.51 (m, 2H); 2.33 (m, 2H); 2.10 (m, 1H); 1.92 (brs, 3H); 1.89 (m, 2H); 1.37 (s, 3H). EI/MS (70 eV): 188 (M^+, 20.9); 173 (base). IR (neat): 3040, 2985, 2880, 1500, 1440, 1105, 1030, 890, 780 cm^{-1}.

Cyclization of Alcohol 87. According to the general procedure for the cyclization of allylic alcohols, **87** (50 mg, 0.23 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 5 minutes to provide 26 mg, 57% of **104** as a clear colorless liquid. ^1H NMR (250 MHz):δ=7.12 (d, J=1.2 Hz, 1H); 6.02 (d, J=1.2 Hz, 1H); 5.26 (m, 1H); 2.41 (m, 2H); 2.18 (m, 4H); 1.92 (m, 3H); 1.89 (brs, 3H); 1.37 (s, 3H). EI/MS (70 eV): 202 (M^+, 17.2); 187 (55.3); 145 (11.0); 131 (15.1); 117 (11.3), 95 (38.5); 81 (base).

Cyclization of Alcohol 94. According to the general procedure for the cyclization of allylic alcohols, **94** (0.1 g, 0.45 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 20 minutes to provide 62 mg, 68%, yield of olefin **105** as a clear, colorless oil. ^1H NMR (250 MHz): δ =7.10 (d, J=1.2 Hz, 1H); 6.08 (d, J=1.2 Hz, 1H); 5.01 (m, 1H); 3.38 (m, 2H); 2.49 (t, J=6.2 Hz, 2H); 2.04 (m, 2H); 1.8-1.4 (m, 6H); 1.78 (s, 1.5H); 1.63 (s, 1.5H). EI/MS (70 eV): 202 (M^+, 51.6), 187 (15.2), 173 (76.7), 162 (base). IR (neat): 3035, 2990, 2880, 1500, 1450, 1165, 1040, 890, 750 cm^{-1}. MS: M^+ calcd. for $C_{14}H_{18}O$, 202.13576; M^+ Found, 202,13569.

Cyclization of Alcohol 95. According to the general procedure for the cyclization of allylic alcohols, **95** (0.1 g, 0.43 mmol) in 2 mL of cyclohexane was reacted with formic acid (0.5 mL) for 20 minutes to provide 53 mg, 61%, of **106** as a clear, colorless oil. ^{1}H NMR (250 MHz): δ=7.20 (d, J=1.2 Hz, 1H); 6.13 (d, J=1.2 Hz, 1H); 5.23 (m, 1H); 3.62 (m, 2H); 2.59 (m, 2H); 2.40 (m, 4H); 1.90-1.23 (m, 6H); 1.82 (s, 1.5H); 1.73 (s, 1.5H). EI/MS (70 eV): 216 (M^+, 64.5), 187 (base), 173 (33.4), 159 (21.5), 145 (20.5), 131 (34.6), 91 (30.9), 77 (16.2). IR (neat): 3035, 2990, 2880, 1510, 1450, 1165, 1040, 890, 800 cm^{-1}. MS: M^+ calcd. for $C_{15}H_{20}O$, 216.15141; M^+ Found, 216.15139.

Cyclization of Enone 70. To a solution of en-one **70** (0.1 g, 0.49 mmol) in cyclohexane (2 mL) was added anhydrous formic acid (0.5 mL) and the mixture stirred vigorously for 20 minutes. The two-phase mixture was cast into water (10 mL) and ether (10 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (15 g, 20 mm o.d., 20% ether-hexane, 10 mL fractions) using the flash technique. Fractions 8-11 provided 66 mg, 60%, of ketone **107** as a clear, colorless liquid. ^{1}H NMR (250 MHz): δ = 7.26 (d, J=1.2 Hz, 1H); 6.15 (d, J=1.2 Hz, 1H); 2.40 (m, 4H); 2.18 (m, 2H); 1.89 (m, 4H), 1.68 (m, 4H). EI/MS (70 eV): 204 (M^+, 40.8), 161 (35.7), 147 (base), 134 (32.5), 91 (20.8). IR (neat): 3010, 2990, 2980, 1715, 1500, 1380, 1260, 1180, 1040, 880, 800 cm^{-1}. MS: M^+ calcd. for $C_{13}H_{16}O_2$ 204.11502; M^+ found, 204.11522.

Cyclization of Enone 75. According to the procedure outlined for the cyclization of enone **70, 75** (30 mg, 0.14 mmol) in 1 mL of cyclohexane was reacted with formic acid (0.5 mL) for 15 minutes to provide 21 mg, 72% of **108** as a colorless oil. ^{1}H NMR (250 MHz): δ=7.11 (d, J=1.2 Hz, 1H); 6.09 (d, J=1.2

Hz, 1H); 2.58 (m, 2H); 2.39 (m, 2H); 2.30 (m, 2H); 2.03 (m, 1H); 1.79 (m, 4H); 0.77 (d, J=7.2 Hz, 3H). EI/MS (70 eV): 204 (M^+, 71.1); 160 (8.4); 147 (base).

Preparation of Alcohol 109. To a solution of alkene **98** (0.2 g, 1 mmol) in THF (1 mL) cooled to 0°C in an ice water bath was added borane in THF (2.0 mL, 1M, 2.0 mmol) dropwise. The resulting solution was warmed to room temperature and stirred for 18 hours. The reaction was quenched by the careful addition of water (1 mL) followed by 20% aqueous NaOH (1 mL) and 30% H_2O_2 (1 mL). The resulting mixture was stirred at room temperature for 1 hour and cast into saturated aqueous $NaHCO_3$ (10 mL) and ether (10 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo to provide a clear, colorless oil. The crude produce was purified on a column of silica gel (230-400 mesh, 15 g, 20 mm o.d., 1:1 ether-hexane, 10 mL fractions) using the flash technique. Fractions 7-9 provide 18 mg, 8% of the minor regio isomer and fractions 11-14 provided 160 mg, 73% of the major isomer **109**.

Minor Isomer

^1H NMR (250 MHz): δ= 7.10 (d, J=1.2 Hz, 1H); 6.03 (d, J=1.2 Hz, 1H); 4.22 (dd, J=8.55, 4.22, 1H); 2.48 (m, 2H), 2.37 (m, 2H), 2.00-1.2 (brm, 12H). EI/MS (70 eV): 220 (M^+, 48.0); 192 (17.6), 161 (45.3), 148 (65.5), 135 (base).

Major Isomer

^1H NMR (250 MHz): δ= 7.16 (d, J=1.2 Hz, 1H); 6.04 (d, J=1.2 Hz, 1H); 4.02 (m, 1h); 2.51 (m, 2H), 2.08 (m, 2H), 1.92 (m, 4H), 1.48 (m, 4H), 1.24 (m, 4H). EI/MS (70 eV): 220 (M^+, 28.3); 177 (29.9), 161 (19.3), 148 (26.8), 135 (base).

Oxidation of Alcohol 109. To a solution of alcohol **109** (0.1 g, 0.45 mmol) in methylene chloride (1 mL) was added PCC (135 mg, 0.63 mmol) all in one portion and the mixture stirred at room temperature of 30 minutes. The resulting suspension was cast into 1N HCl (10 mL) and ether (10 mL).

The organic phase was separated and washed with 1N HCl (5 mL), saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow oil. The crude product was purified on a column of silica gel (230-400 mesh, 15 g, 20 mm o.d., 1:1 ether-hexane, 10 mL fracitons) using the flash technique. Fractions 7-9 provided 80 mg, 82% of the ketone **110** as a colorless oil. ^1H NMR (250 MHz): δ =7.17 (d, J=1.2 Hz, 1H), 6.11 (d, J=1.2 Hz, 1H), 2.93 (dd, J=1.4, 1.6 Hz, 1H), 2.81 (dd, J=1.4, 1.6 Hz, 1H), 2.43 (m, 2H), 2.20 (m, 4H), 1.96 (m, 4H), 1.74 (m, 4H). EI/MS (70 eV): 218 (M^+, 18.9), 175 (31.9), 161 (99.6), 148 (base).

3-(2-(3-furyl)-ethyl)-2-methylcyclohex-2-en-1-ol (112). According to the general procedure for the preparation of allylic alcohols, the Grignard reagent derived (3-furyl)-chloromethane (2.3 g, 20 mmol) was reacted (CuCN) with vinyl epoxide **111** (2.5 g, 20 mmol) to provide 2.5 g, 62% of **112** as a clear, colorless oil. ^1H NMR (250 MHz): δ = 7.22 (dd, J=1.6, 1.4 Hz, 1H); 7.18 (m, 1H); 6.21 (m, 1H); 3.98 (br, 1H); 2.46 (m, 3H); 2.05 (m, 4H); 1.87 (m, 4H); 1.78 (s, 3H). EI/MS (70 eV): 204 (M^+, 2.15), 128 (14.7), 110 (23.8), 95 (38.6), 81 (base). IR (neat): 3400 (br), 3045, 2970, 2880, 1670, 1500, 1465, 1170, 1060, 880, 800 cm^{-1}. Anal. calcd. for $C_{13}H_{18}O_2$: C, 75.72; H, 8.73. Found: C, 75.54; H, 8.61.

3-(2-(3-furyl)-ethyl)-2-methylcyclohex-2-en-1-one. According to the general procedure for the preparation of 2-en-1-ones, allylic alcohols **112** (3.09 g, 15 mmol) was oxidized with PCC (4.85 g, 22.5 mmol) to provide 2.72 g, 89%, of the desired enone as a clear, colorless liquid. ^1H NMR (250 MHz): δ = 7.28 (dd, J=1.4, 1.2 Hz, 1H); 7.17 (m, 1H); 6.22 (m, 1H); 2.59 (brs, 2H); 2.36 (m, 4H); 2.05 (m, 4H); 1.79 (s, 3H). EI/MS (70 eV): 204 (M^+, 12.9), 186 (9.32), 133 (5.91), 108 (11.5), 91 (5.02), 81 (base). IR (neat): 2995, 2875, 1685, (s),

1500, 1460, 1230, 1180, 1030, 880, 880 cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O_2$; C, 76.47; H, 7.84. Found: C, 76.51; H, 7.73.

2,3-dimethyl-3-(2-(3-furyl)-ethyl)-cyclohexanone (113). To a slurry of cooper (I) iodide (3.8 g, 20 mmol) in anhydrous ether (20 mL) cooled to 0°C in an ice-water bath was added a solution of methyl lithium in hexane (15.4 mL, 1.3 M, 20 mmol) over a period of 10 minutes and the suspension stirred at 0°C for 20 minutes. The resulting yellow suspension was cooled to -78°C in a dry ice-isopropanol bath and boron trifluoride etherate (2.8 g, 20 mmol) was added dropwise.[19] The mixture lightened in color and was stirred at -78°C for 20 minutes. A solution of enone (2.04 g, 10 mmol) in ether (15 mL) was added over a period of 10 minutes and the suspension was allowed to warm to room temperature over 5 hours. The mixture was cast into 1N HCl (100 mL) and ether (100 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50 g, 40 mm o.d., 1:1 ether-hexane, 25 mL fractions) using the flash technique. Fractions 10-14 provided 1.54 g, 70%, of ketone as a 60:40 mixture of epimers. ^1H NMR (250 MHz): δ= 7.36 (dd, J=1.4, 1.5 Hz, 0.6H); 7.33 (m, 0.4H); 7.20 (m, 0.6H); 7.18 (m, 0.4H); 6.28 (m, 0.6H); 6.23 (m, 0.4H); 2.38 (m, 3H); 1.90 (m, 4H); 1.86 (m, 4H); 1.09 (s, 1.2H); 1.00 (d, J=6.89 Hz, 1.2H); 0.97 (d, J=7.6 Hz, 1.8H); 0.80 (s, 1.8H). EI/MS (70eV): 220 (M^+, 8.36), 148 (4.70), 125 (49.0), 111 (17.2), 95 (70.2), 81 (base). IR (neat): 2995, 2980, 1720, 1500, 1380, 1260, 1175, 1030, 880 cm^{-1}. MS: M^+ calcd. for $C_{14}H_{20}O_2$ 220.14632, M^+ found 220.14627.

5,6-dimethyl-5-(2-(3-furyl)-ethyl)-cyclohex-2-en-1-one (114). To a solution of diisopropylamine (0.60 g, 6 mmol) in THF (6 mL) cooled to -78°C in

a dry ice-isopropanol bath was added n-butyllithium (2.4 mL, 2.5 M in hexane, 6 mmol) over 5 minutes and the solution stirred at -78°C for 30 minutes. Ketone **113** (1.12, 5 mmol) in THF (5 mL) was added over 15 minutes and the resulting yellow solution stirred at -78°C for 30 minutes. To the solution was added phenyl selenyl bromide[20] (1.4 g, 6 mmol) in THF (3 mL). The resulting yellow solution was stirred at -78°C for 2 hours and cast into saturated aqueous NH_4Cl (50 mL) and ether (50 mL). The organic phase was separated and washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow liquid. The yellow residue was taken up in methylene chloride (10 mL) and triethylamine (2 mL) was added followed immediately by aqueous hydrogen peroxide (6 mL, 30%). The mixture was vigorously stirred at room temperature for 30 minutes and cast into 1N HCl (50 mL) and ether (50 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50 g, 40 mm o.d., 1:1 ether:hexane, 25 mL fractions) using the flash technique. Fractions 11-15 provided 0.78 g, 72%, of enone **114** as a 60:40 mixture of epimers. ^1H NMR (250 MHz): δ = 7.38 (dd, J=1.6, 1.4 Hz, 1H); 7.19 (m, 1H); 5.89 (m, 1H); 6.25 (m, 1H); 5.99 (brd, J=11.4 Hz, 1H); 2.39 (m, 3H); 2.20 (m, 2H); 1.62 (m, 2H); 1.08 (m, 4.2H); 0.95 (s, 1.8H). EI/MS (70eV): 218 (M^+, 8.39), 135 (10.4), 123 (base), 109 (10.5), 95 (30.0), 81 (49.7). IR (neat): 3010, 2900, 1680, 1500, 1460, 1180, 1060, 990, 780 cm^{-1}.

Cyclization of Enone 114. To a solution of **114** (0.5 g, 2.3 mmol) in cyclohexane (5 mL) was added anhydrous formic acid (1.5 mL) and the mixture stirred vigorously for 15 minutes at room temperature. The biphasic mixture was cast into water (25 mL) and ether (25 mL). The organic phase was

separated and washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow liquid. The crude product was purified on a column of silica gel (230-400 mesh, 40 g, 33 mm o.d., 1:1 ether:hexane, 25 mL fractions) using the flash technique. Fractions 8-10 provided 0.4 g, 79%, of **115** (60:40) as a white solid. M.P. = 58-60°C. ^1H NMR (250 MHz): δ = 7.08 (m, 1H); 6.08 (m, 1H); 3.77 (m, 1H); 2.75 (m, 1H), 2.59 (m, 1H); 2.39 (m, 3H); 2.09 (m, 2H); 1.76 (m, 2H); 1.17 (m, 4H); 1.02 (s, 2H). EI/MS (70eV): 218 (M^+, 64.3), 203 (17.9), 147 (base), 131 (14.1), 109 (46.1), 91 (32.3), 77 (31.8).

Δ8,13-isonakafuran-9 116. To a suspension of methyl tripenyl phosphonium iodide (1.41 g, 3.5 mmol) in benzene (5 mL) was added a solution of potassium t-amylate (2.8 mL, 1.25M, 3.5 mmol) in benzene[21] and the mixture was stirred at room temperature until the phosphonium salt had dissolved (about 1.5 hours). Ketone **115** (0.218 g, 1 mmol) in benzene (2 mL) was added and the resulting solution was stirred at room temperature for 3 hours. The mixture was cast into saturated aqueous NH_4Cl (25 mL) and pentane (25 mL). The organic phase was separated and washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL), dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by rapid chromatography on a column of silica gel (230-400 mesh, 8 g, 20 mm o.d., hexane, 8 mL fractions) using the flash technique. Fractions 6-8 provided 0.173 g, 80%, of olefin **116** as a clear, colorless, sweet smelling liquid. The material was shown by capillary GLC to be a 80:20 mixture of epimers. ^1H NMR (250 MHz): δ = 7.10 (d, J=1.2 Hz, 1H); 6.01 (m, 1H); 4.62 (t, J=2.1 Hz, 0.8H); 4.59 (t, J=2.2 Hz, 1H); 4.56 (t, J=2.1 Hz, 0.2H); 2.43 (m, 4H); 2.78 (m, 2H); 2.25 (m, 2H); 1.06 (d, J=6.07, 0.6H); 1.01 (d, J=6.09 Hz, 2.4H); 0.98 (s, 2.4H); 0.86 (s, 0.6H). EI/MS (70eV): 216 (M^+, 59.3), 201 (21.3), 147 (base). IR (neat): 3050, 2990, 2890, 1500,

1430, 1050, 890, 800 cm^{-1}. MS: M^+ calcd. for $C_{15}H_{20}O$ 216.15141, M^+ found 216.14147.

Preparation of Nakafuran-9 6. To a refluxing solution of olefin **116** (0.1 g, 0.46 mmol) in benzene (3 mL) was added p-toluenesulfonic acid decahydrate (2 mg) and the mixture heated under reflux for 20 minutes. The mixture was cooled, cast into saturated aqueous $NaHCO_3$ (10 mL) and ether (10 mL). The organic phase was separated, dried ($MgSO_4$) and concentrated in vacuo to provide 80 mg, 80%, of a 95:5 (capillary GLC) mixture of nakafuran-9 **6** and 8,9-isonakafuran-9 **117**. Compound **6** was identical in all respects (^1H-NMR, IR, EI/MS) when compared with data provided by Professor Scheuer.[7,64]

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