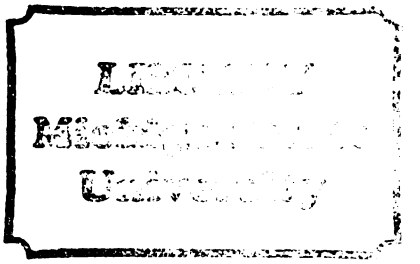
THESIS



This is to certify that the

thesis entitled

A GENERAL APPROACH TO THE SYNTHESIS
OF NATURAL PRODUCTS CONTAINING
FIVE-MEMBERED HETEROCYCLES

presented by

Paul Matthew Herrinton

has been accepted towards fulfillment
of the requirements for

M.S. degree in Chemistry

Major professor

Date 6/25/82

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A GENERAL APPROACH TO THE SYNTHESIS OF NATURAL PRODUCTS CONTAINING FIVE-MEMBERED HETEROCYCLES

By

Paul Matthew Herrinton

A THESIS

Submitted to
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ABSTRACT

A GENERAL APPROACH TO THE SYNTHESIS
OF NATURAL PRODUCTS CONTAINING
FIVE-MEMBERED HETEROCYCLES

By

Paul Matthew Herrinton

Most of the syntheses of natural products containing five-membered heterocycles have been approached by careful construction of a parent carbocycle to which the hetercyclic ring is appended. This study demonstrates a general method which acknowledges the heterocycle as an integral part of the molecule.

Several 3-furyl epoxides were prepared in high yield by either: 1) addition of the Grignard reagent derived from (3-furyl)-chloromethane to halo-olefins and then oxidation with meta-chloroperbenzoic acid, or 2) addition of the organo-lithium reagent derived indirectly from (3-furyl)-chloro-methane to iodoepoxides.

Cyclization of these 3-furyl epoxides was attempted by treatment with Lewis acid. The best Lewis acids for cyclization were found to be zinc iodide or triisopropoxy-titanium chloride. Cyclizations which formed six- and seven-membered rings proceeded smoothly but attempts to form five-membered rings have been unsuccessful.

To my lovely Joan

ACKNOWLEDGMENTS

The author wishes to thank Dr. Steven P. Tanis for his patience, support and guidance throughout this project.

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I wish to thank my parents and family for their love and support without which this work would not have been possible.

Special thanks to my wife Joan for her invaluable assistance in the preparation of this thesis.

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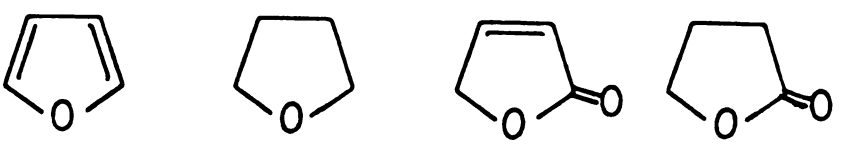
INTRODUCTION

The chemical literature contains numerous reports of various biological activities which are associated with new and interesting skeletal types. The variety of naturally occurring biologically active compounds is as diverse as the systems which produce them. However, upon closer examination, some recurring themes do appear. Many biologically active terpenoids contain five-membered heterocyclic rings.[1] The rings may vary in oxidation state from furan 1, or tetrahydrofuran 2 to butenolide 3 or butyrolactone 4.



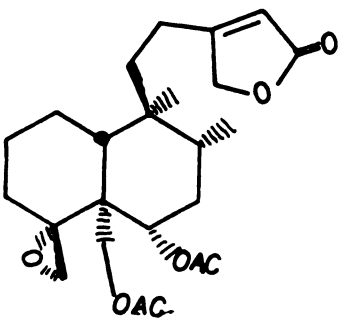
1 2 3 4

Figure 1

Examples of such compounds include the clerodane diterpenes Ajugarin I 5[2] and annonene 6[3], the drimane sesquiterpene confertolin 7[4], the cytotoxic vernolepin 8[5,6] the pseudoguaianolide confertin 9[6], and witchweed germination promoter strigol 10[7].

As a result of the biological activities exhibited by compounds 5-10, which include insect antifeedant, anti-complimental, cytotoxic and germination promotion activities,

as well as antimicrobial, antifungal and antitumor activities these molecules have become attractive targets for total chemical synthesis.



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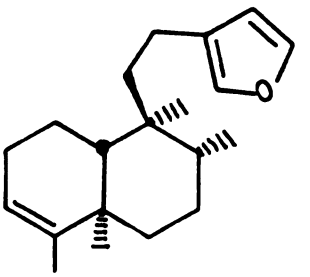

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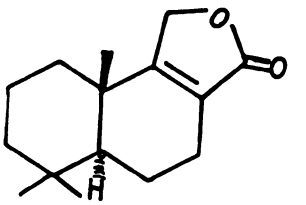

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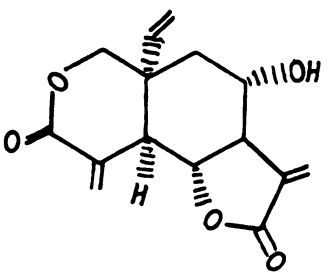

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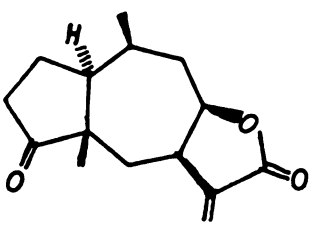

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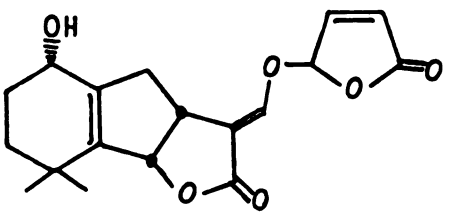

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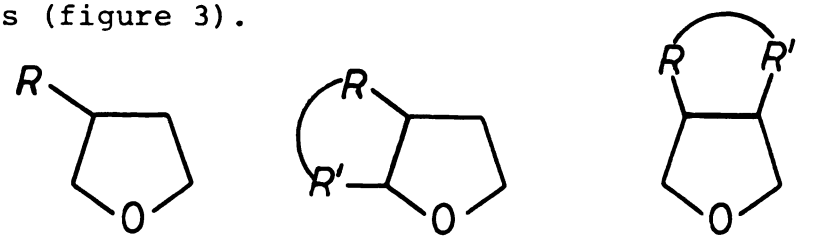
Figure 2

For the most part the syntheses of these terpenoids have been approached by careful, stereocontrolled construction of a parent carbocycle, upon which a furan, butyrolactone, of butenolide is appended. These schemes have not, generally, acknowledged the basic five-membered ring heterocyclic system as an integral part of the molecule which can exert a measure of control upon bond forming reactions. A methodology which would be generally applicable to the synthesis of a terpenoid containing a five-membered heterocyclic ring would therefore be very valuable.

Examination of compounds 5-10 reveals three general substitution patterns about the five-membered heterocyclic rings (figure 3).



A B C

Figure 3

Structure A represents a simple 3-substituted furan equivalent such as compound 5 or 6. Although many methods for the synthesis of 3-substituted furans have been reported most of them require a number of steps and/or proceed in low yields.[8] Recently Tanis reported a convenient high yield synthesis of simple 3-substituted furans.[9]

Structure C represents a 3,4-disubstituted furan equivalent such as compound 7. Oishi et al[10] have demonstrated that type C skeletons may be made by cyclization of a judiciously functionalized furan (figure 4).

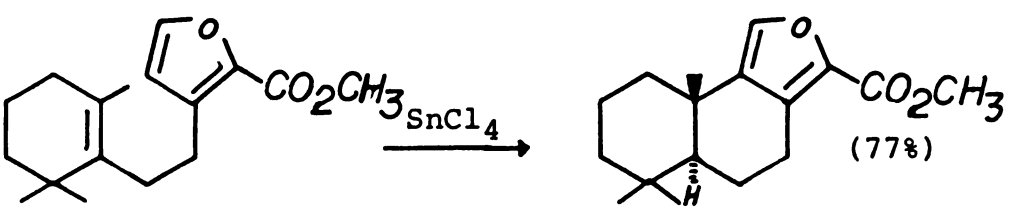
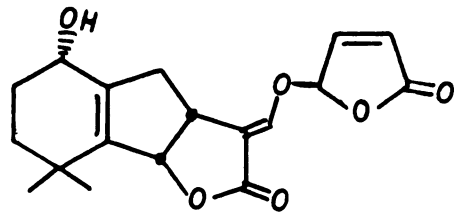


Figure 4

Structure B represents a 2,3-disubstituted furan equivalent. These type-B furans are found as integral parts of numerous natural products. The activities associated with molecules of this structural type range from the germination stimulation activity for the parasite witchweed

exhibited by strigol 10[7], to the cytotoxicity shown by the pseudoguaianolide confertin 9[6], and the fish anti-feedant activities possesed by the sponge, Dysidea fragilis, derived furanosesquiterpenes nakafuran-8 13 and nakafuran-9 14.[11] It was our goal in this study to devise a general methodology for the synthesis of type B ring containing compounds.



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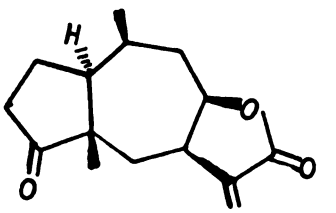

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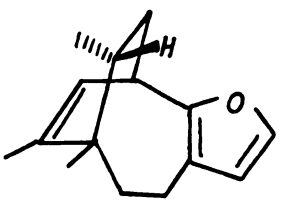

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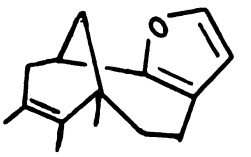

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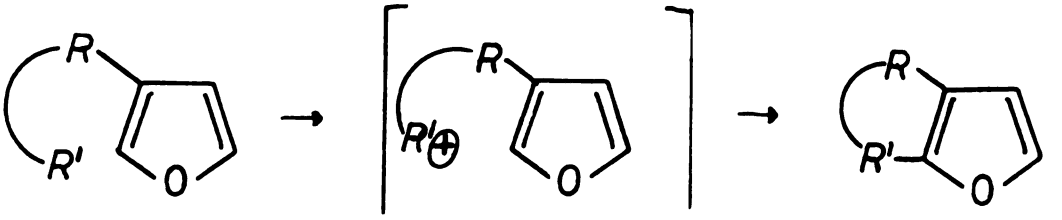
Figure 5

RESULTS AND DISCUSSION

If we consider the usual propensity exhibited by furans for undergoing electrophillic substitution at C-2, the preparation of polycyclic materials related to structure B (figure 3) can be simplified as in figure 6. The generation of an electron deficient center (R'⊕) in the 3-substituted furan 15 should provide compound 16 after cyclization and rearomatization. A simple synthesis of type B furans should then be possible by synthesising a suitably functionalized type A furan. If a latent electrophile is placed in the side chain of a 3-substituted furan and then unmasked it should lead to cyclization at the preferred 2 position.



15 16

Figure 6

Catonic cyclizations of this type have been the object of intense study since 1950.[12] However, there are few examples in which the cyclization terminator is other than a simple olefin or phenyl group. It has been demonstrated by Boeckman [13] that epoxy vinyl ethers 17 could be cyclized by treatment with Lewis acids (figure 7). We wished to demonstrate that this type of cyclization can be routinely performed with furan as the terminator and that five-, six-, and seven-membered rings may be formed.

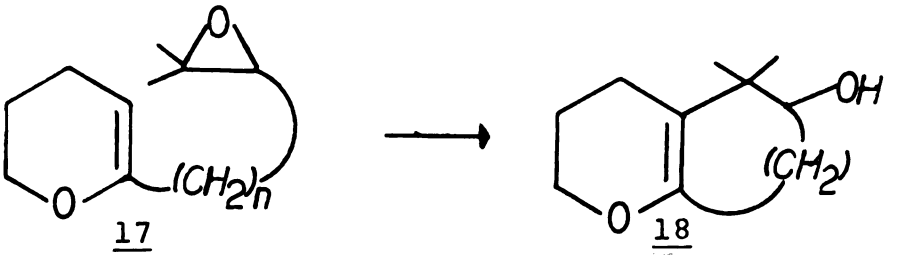


Figure 7

Although furans are known to undergo electrophillic aromatic substitution reactions more easily than benzene, the availability and stability of suitable substrates has limited the exploration of the reactivity and potential synthetic utility of this functional group. We also wished to examine the effect of the placement of the initiating function inside the ring being formed (endocyclic) or outside the ring being formed (exocyclic). According to the study of Baldwin et al,[14] all of the exocyclic closures which generate five-, six-, or seven-membered rings should be favorable while of the endocyclic closures only the formation of a six-membered ring is considered to be favorable.

When using epoxides as cyclization initiators, there is the possibility that either epoxide carbon may serve as the electrophilic center. In order to avoid this type of regiochemical ambiguity in our studies, it was necessary to bias the epoxide functions so that one mode of polarization would be favored over the other. This is possible because of the proposed cationic nature of the reaction intermediate.[12f] When epoxides are treated with Lewis acids one of the carbon oxygen bonds becomes polarized as in figure 8. This results in positive charge being placed on the carbon. If one carbon

of the epoxide can stabilize that positive charge better than the other, then the polarization will be mostly of that carbon oxygen bond. Therefore, by making one side of the epoxide resemble a more stable tertiary carbocation and the other side resemble a less stable primary or secondary cation, we can favor one mode of polarization over the other.

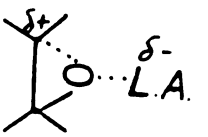


Figure 8

With this in mind, we chose the six epoxy furans in figure 9 as substrates for cyclization.

The cyclization of compound 19 corresponds to a five-membered endocyclic closure to give 25. 20 is representative of a five-membered exocyclic closure to provide 26, cyclization of 21 should proceed via a six-membered endocyclic closure to give 27, and cyclization of 22 should be considered as a six-membered exocyclic closure to give 28. The cyclization of 23 represents a seven-membered endocyclic closure to give 29, and cyclization of 24 corresponds to a seven-membered exocyclic closure to give 30.

Synthesis of epoxy-furans 19-24

The most obvious and simplest path to the desired epoxy-furans was assumed to be epoxidation of the corresponding (3-furyl)-olefins. The necessary olefins may be prepared by coupling the appropriate olefin with a judiciously

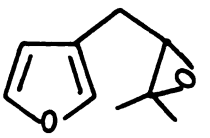
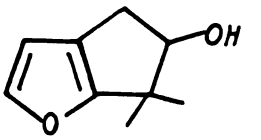
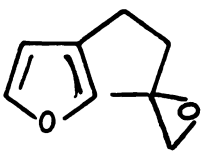
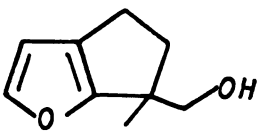
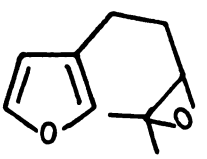
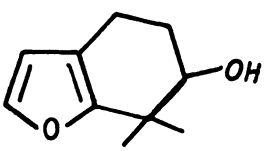
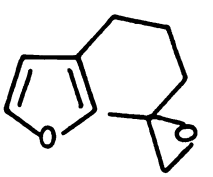
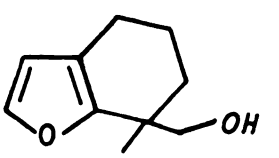
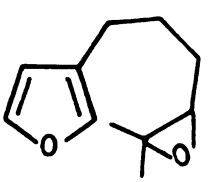
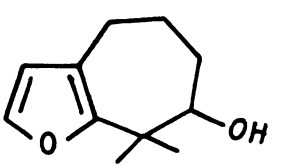
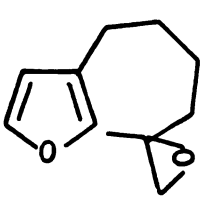
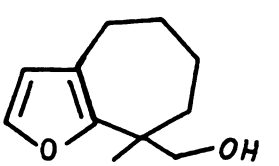
Designation	Epoxide Structure	Desired Cyclization Product
5-endo	 19	 25
5-exo	 20	 26
6-endo	 21	 27
6-exo	 22	 28
7-endo	 23	 29
7-exo	 24	 30

Figure 9

functionalized isoprenoid furyl synthon. Relative to the standard bond forming reactions of such furans, having the furan serve as electrophile and the alkyl group as nucleophile is the "normal" bond forming polarity (path a, figure 10). We have examined the "reverse polarity" bond formation, in which the furyl moiety serves as nucleophile and the alkyl group as electrophile (path b, figure 10).

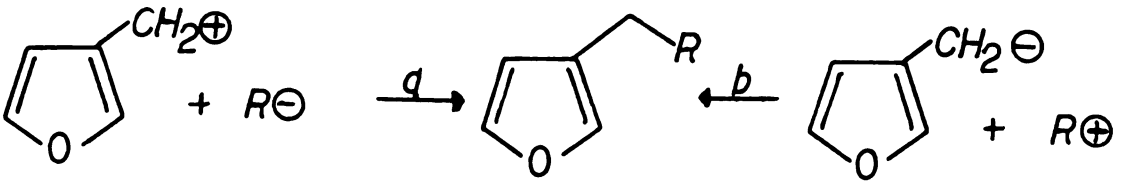
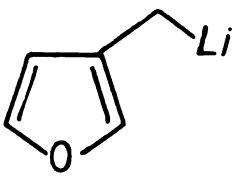


Figure 10

This approach would involve the reaction of furyl organolithum 31 or Grignard reagent 32 with an appropriate electrophile. To the best of our knowledge 31 has been reported only once in the literature. Tanis[9] has demonstrated the utility of 32 in the synthesis of simple 3-substituted furans. The requisite Grignard precursor 33 may be easily prepared from the readily available (3-furyl)-methanol[15] in 80-85% yield by the chlorination procedure of Collington and Meyers.[16]

Treatment of (3-furyl)- chloromethane 33, in tetrahydrofuran (THF), with magnesium, provides the Grignard reagent 32 quantitatively as determined by titration.[17]



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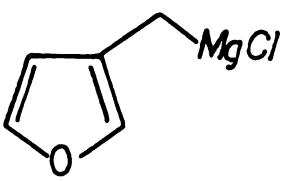

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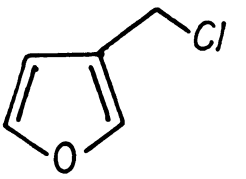


33

A variety of primary, secondary and allylic halides have been reacted with 32 in the presence of Kochi's catalyst Li_2CuCl_4[18] to give uniformly high yields of 3-substituted furans.

The general route to the epoxy-furans would then be the coupling of Grignard reagent 32 with an appropriate haloalkene and then epoxidation of the product furyl olefin. The coupling reactions all proceed smoothly, and in good yield, as indicated in figure 11. The only exception is the coupling of the vinyl bromide 34. There is no reaction between 34 and 32 in the presence of Li_2CuCl_4, however, Kochi notes that vinyl halides react only in the presence of $FeCl_3$, and indeed with ferric chloride as catalyst the coupling proceeds in 82% yield.

Treatment of furyl olefins 39, 41 and 43 under the standard conditions with m-chloroperbenzoic acid results in smooth conversion to the desired epoxy-furans in good to excellent yields, as the only isolated products. Epoxidation of furans 40, 42 and 44 proved more troublesome providing little or none of the desired product epoxides. It became obvious that if the alkene is less than trisubstituted

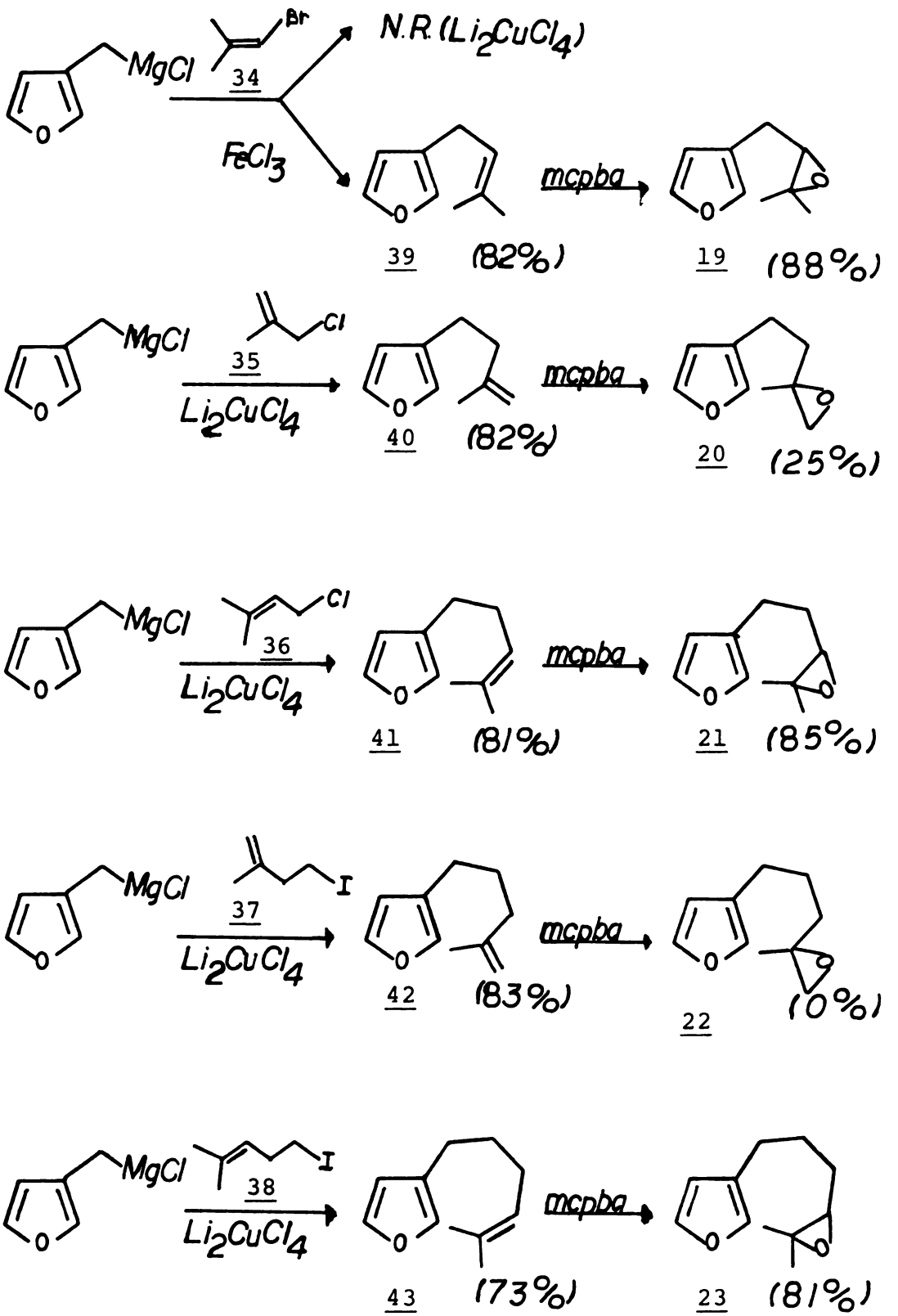
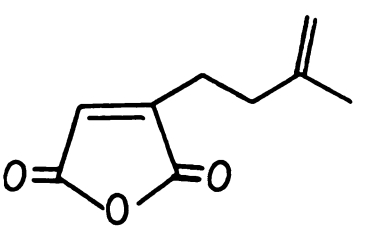

MgCl
Br
34
N.R. (Li_2CuCl_4)
$FeCl_3$
mcpba
39 (82%)
19 (88%)
MgCl
Cl
35
Li_2CuCl_4
40 (82%)
mcpba
20 (25%)
MgCl
Cl
36
Li_2CuCl_4
41 (81%)
mcpba
21 (85%)
MgCl
I
37
Li_2CuCl_4
42 (83%)
mcpba
22 (10%)
MgCl
I
38
Li_2CuCl_4
43 (73%)
mcpba
23 (81%)

Figure 11

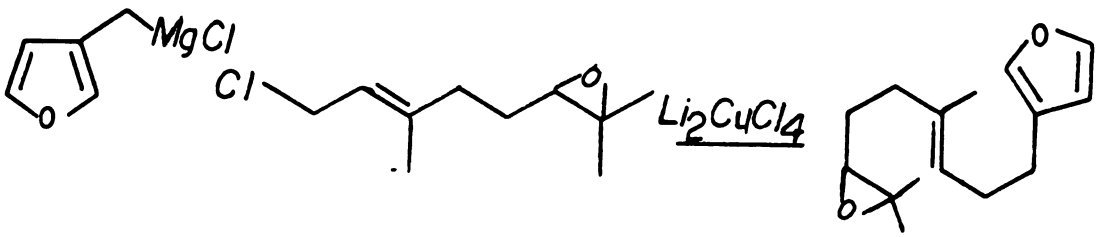
oxidation of the furan ring becomes a competitive reaction. When furyl olefin 40 is reacted with m-chloroperbenzoic acid only 25% of the desired epoxy-furan 20 is recovered. The remainder of material isolated has been tentatively identified as the furan oxidation product 44. Oxidation of olefin 42 provided none of the desired product. Instead, exclusive furan oxidation was observed. Other methods of epoxidation which were tried included: treatment with anhydrous t-butyl hydroperoxide in the presence of various transition metal catalysts ($Mo(CO)_6$, $VO(acac)_2$, $Ti(OiPr)_4$)[19] and oxidation under basic conditions with benzonitrile, hydrogen peroxide and sodium hydroxide.[20] The only set of reaction conditions which provided any product was t-butyl hydrogen peroxide with $Mo(CO)_6$ and that resulted in only a 25% yield of 20 and none of 22.



44

It was then necessary to explore alternate routes to the epoxy furans 22, 24 and 26. Tanis has noted that Grignard reagent 32 will react with an allylic halide containing a remote epoxide function to give the epoxy furan 46 in 79% yield. Products corresponding to attack at the epoxide centers were not observed. It should, therefore, be possible to couple epoxy bromides, iodides or tosylates to yield the

desired epoxy furans. We have discovered, however, that reaction of 32 with 47a, 47b or 47c in the presence of Li_2CuCl_4 resulted only in products which were the result of attack at the epoxide function.



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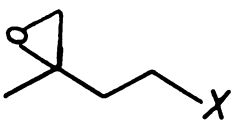
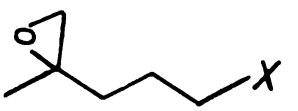


47

a) X=Br
b) X=I
c) X=OTs



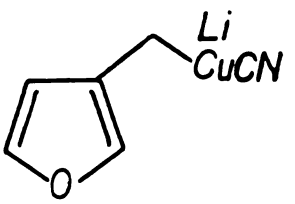
48

a) X=Br
b) X=I
c) X=OTs

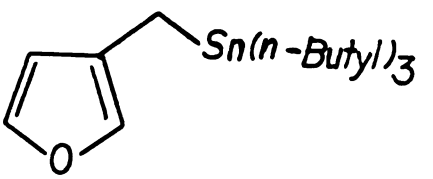
Figure 12

Encouraged by reports[21] that alkyl cuprates could be reacted with epoxy-tosylates to give mixtures of displacement and epoxide opening products, we explored the utility of using the alkyl cuprate 49 in such a coupling reaction. The synthesis of furyl cuprate 49 required the preparation of the furyl organolithium 31. The reactive nature of the halide 33 does not allow a direct metallation and so it was deemed necessary to convert the halide to something less reactive which can still afford 31. The tri(n-butyl) tin compound 50 appeared to be an ideal furyl lithium 31

equivalent. The preparation of 50 was realized upon treatment of chloride 33 with tri(n-butyl) tin lithium according to the procedure of Still.[22] This technique provided the tri(n-butyl)-(3-furyl methyl) stannane 50 in 76% distilled yield. Tin-lithium exchange was accomplished by reaction with n-butyl lithium and the cuprate prepared by the procedure of Marino.[23] Unfortunately, the addition of 49 to bromo, iodo, or tosyl epoxides 47a-c and 48a-c provided only epoxide opening products.



49



50

Direct utilization of the organolithium reagent 31 was initially avoided because of the possibility of an allylic type rearrangement. This sort of behavior has been previously observed in the reaction of this Grignard reagent.[24] However, when the lithium reagent derived from 49, by tin-lithium exchange, was reacted with iodoepoxides 47b and 48b in the presence of hexamethylphosphoramide at -25°C the desired epoxy furans 22 and 24 were obtained in 80 and 68% yields respectively. None of the product which would result from the rearranged anion were detected.

That left only epoxy furan 20 to be prepared in acceptable yield. Reaction of the furyl organolithium reagent

with the appropriate iodoepoxide should provide the deisred compound in good yield. Unfortunately, the requisite iodoepoxide 51 is unknown and thus far has resisted all attempts to affect its preparation. The synthesis of 51 remains under study.

Cyclizations

The chemical literature contains many examples of epoxide initiated biomimetic type cyclizations.[12f-h] The majority of these examples have used simple olefins as the terminator function. To the best of our knowledge there have been few reports of cyclizations utilizing furan as the terminator. We had two major concerns when considering the proposed epoxy-furan cyclizations. The first was the nucleophilicity of the furan terminator. Furans are known to be more reactive toward electrophilic substitution than most aromatics but less nucleophilic than simple olefins. The crucial question is whether the electrophile generated by the Lewis acid-epoxide complex will react with the furan in a cyclization faster than it will yield other undesired products. An important factor in the partitioning of the reaction between the fruitful cyclization pathway and the formation of other products may be the degree of epoxide bond breaking by the Lewis acid. When the epoxide is completely opened the resultant carbocation may eliminate to give an alkene or react in some other undesirable manner before it can react with the weakly nucleophillic furan. On the other hand, when the epoxide is weakly polarized,

the probability of elimination is lowered and cyclization may become the major pathway. Therefore, Lewis acid strength may play an important role in determining product distribution.

The second concern was stability of the cyclization products. The product of the cyclization sequence is a 2,3-disubstituted furan which is decidedly more labile than the starting material. Therefore, the cyclization conditions must be carefully chosen so that the presence of strong protic acid is avoided.

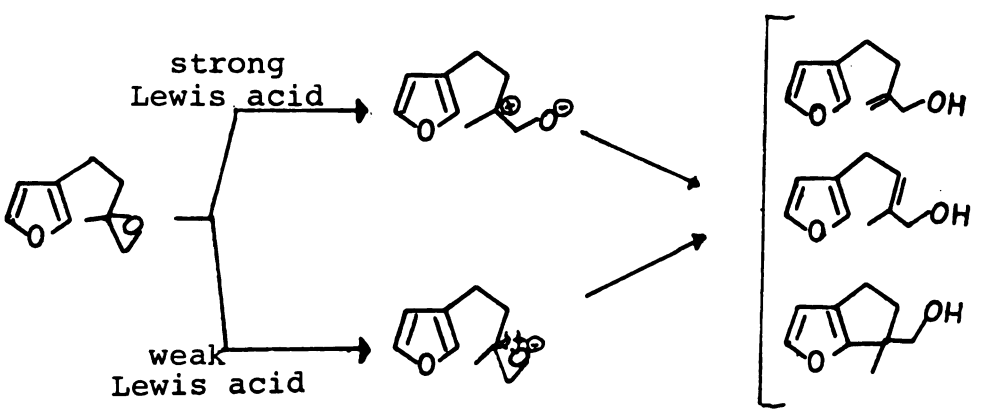


Figure 13

The majority of epoxide initiated cyclizations reported in the literature are carried out by brief exposure to boron trifloride etherate in a non-polar solvent such as methylene chloride. Under this set of conditions the reaction is thought to occur in a concerted manner, that is, little cationic character is ever generated on the electrophilic carbon.[12f] Under these conditions olefin terminated cyclizations proceed smoothly to provide a 20-60% yield of desired product. However, furans are much less nucleophilic than alkenes and these reaction conditions may prove to be too acidic to affect the desired cyclizations.

The first set of conditions which were used were those which appear to be "standard" for polyene cyclizations, that is about 1/3 of an equivalent of boron trifloride etherate in methylene chloride at -25°C. The results of the cyclization attempts under these conditions are summarized in table 1. Only the six-membered endocyclic case 21 provided any of the desired cyclized product. The majority of materials recovered from the attempted cyclizations of 19 (5-endo), 20 (5-exo), 22 (6-exo), 23 (7-endo), and 24 (7-exo) were mixtures of allylic alcohols. The total amount of material recovered from the reaction was only about 50% of the starting material. Evidently, in all cases except the 6-endo, elimination to form allylic alcohols was faster then cyclization. The lack of cyclization in every case except 6-endo, coupled with the poor mass balance clearly demonstrates that the standard cyclization conditions are not generally applicable. Both the formation of the allylic alcohols and cyclization generate protic acid which may destroy labile furanoid products. This could account for the poor mass balance of the reaction.

If the strength of the Lewis acid employed was responsible for the destruction of the reaction products as well as the general lack of cyclization then what was needed was a weaker Lewis acid which would also be able to capture the protic acid released by the reaction. Snider[25] has reported that alkyl aluminum halides act as Lewis acids which react with Bronsted acids liberating alkanes and regenerate a

Table 1. Cyclization Results

	$BF_3 \cdot OEt_2$	$EtAlCl_2$	Et_2AlCl	Al_2O_3	$MgBr_2$	ZnI_2	$Ti(OiPr)_3Cl$
5-endo	0%	0%	0%	0%	-	0%	0
5-exo	0%	-	-	-	-	0%	0%
6-endo	47%	16%	22%	32%	43%	71%	78%
6-exo	30%	0 %	10%	0%	-	64%	89%
7-endo	10%	0%	10%	0%	-	88%	47%
7-exo	0%	0%	0%	0%	-	24%	23%
3-β-hydroxy Pallesencin-A	47%					54%	59%

The difficulty in preparing epoxy-furan 20(5-exo) prevented us from attempting cyclization until we had found a catalyst which appeared to work well. For that reason results are shown for only three catalysts with 5-exo.

Lewis acid. The alkyl aluminum halides cover a wide range of Lewis acitity. Replacing chlorines with alkyl groups has been observed to decrease the Lewis acidity in a predictable fashion. Ethylaluminum dichloride is only slightly less acidic than aluminum trichloride,[22] while diethylaluminum chloride is substantially less acidic and trimethylaluminum is a very mild Lewis acid. The range of Lewis acidity presented by alkylaluminum halides and their ability to absorb protic acids seemed to make them ideal for initiating epoxy-furan cyclizations.

Treatment of the various epoxy-furans with two equivalents of ethylaluminum dichloride at -25°C in methylene chloride provided very disappointing results (table 1). As with boron trifloride etherate, only the six-endo case 21 provided any cyclized material. The majority of the products in all cases were allyclic alcohols resulting from elimination. However, it was noted that the mass balance of the reaction had improved markedly to about 70%.

We appeared to be on the right course using a Lewis acid which is also a base. However, the Lewis acidity was too great and elimination was still faster than nucleophilic attack by furan. Diethylaluminum chloride is much less acidic than ethylaluminum dichloride and so this was the next logical choice as a Lewis acid. Exposure of the epoxy-furans to two equivalents of diethylaluminum chloride at -25°C in methylene chloride led to some cyclization in the six-endo (21), six-exo (22), and seven-endo (23) examples.

The yields of the desired products are very low (10-22%) with the major products being allylic alcohols. However, the material balance of the reaction is very good with 80% of the starting mass being recoverd.

The results from these cyclization attempts seemed to indicate that the Lewis acids being used were still much too strong and we began to search for examples of weaker Lewis acids as catalysts for cyclization. Boeckman[13] has reported success in cyclizing epoxy vinyl ethers by exposure to basic alumina (Al_2O_3, activity I) at room temperature in hexane. Although vinyl ethers are recognized among the most nucleophilic of olefinic bonds[26] and furans are among the least, there are enough similarities to indicate that basic alumina might be a suitable reagent for these cyclizations. Stirring epoxy-furans 19 and 21-24 with alumina in hexane at room temperature for 24 hours resulted in very high yields (80-90%) of elimination products. Only 21 showed any cyclization product and that was obtained in only 23% yield.

Recovering high yields of allylic alcohols and little or no cyclized material was an indication that a milder Lewis acid was necessary. Basic alumina is a mild Lewis acid and that reagent is too potent. Magnesium bromide is a weak Lewis acid which has a high affinity for oxygen and a low affinity for nitrogen. This high affinity for oxygen allows magnesium bromide to be used as a Lewis acid in the presence of tertiary amines such as triethylamine. This system (magnesium bromide, triethylamine) seemed appropriate

for the epoxy-furan cyclization. Exposure of epoxy-furan 21 (6-endo) to three equivalents of magnesium bromide-tetrahydrofuran complex and one equivalent of triethylamine in methylene chloride at room temperature for 24 hours provided 43% of the cyclized product 28 and 53% unreacted starting material. Magnesium bromide, under these conditions appears to be too mild a Lewis acid. Although we have not demonstrated the need for the added triethylamine, since the derived magnesium alkoxide is likely to be an efficient acid scavenger, this system has shown some promise.

Titanium alkoxides have been shown to be effective Lewis acids for the catalysis of aldol condensation.[27] The Lewis acidity of titanium alkoxides may be varied by replacing alkoxides with halogens. Titanium tetrachloride is a very strong Lewis acid which has been observed to react with epoxides to yield β-chlorotitanates (figure 14).[28] Replacing halides by alkoxide groups, such as isopropoxy, lessens the Lewis acidity. Monoalkoxytitanium trichlorides are only slightly less acidic than titanium tetrachloride. Dialkoxytitanium dichlorides and trialkoxytitanium chlorides are intermediate to titanium tetrachloride and the very mild tetraalkoxytitanium compounds (figure 15).

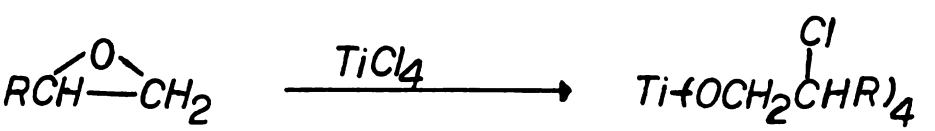


Figure 14

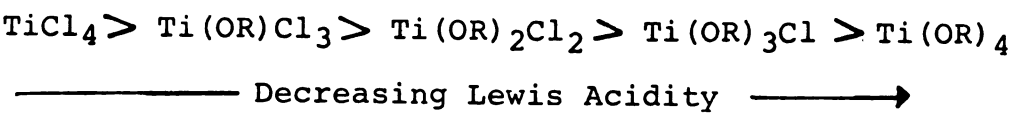


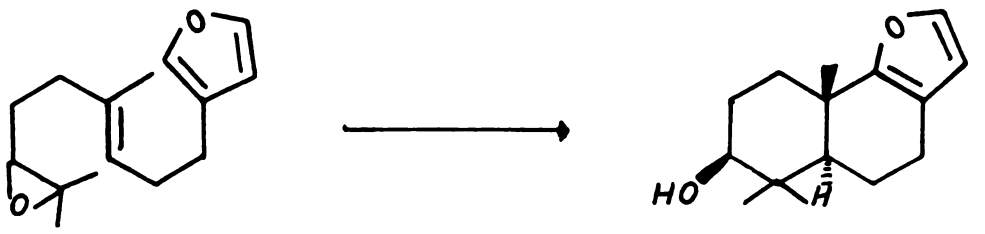
Figure 15

Exposure of epoxy-furan 21 (6-endo) to three equivalents of the very mild Lewis acid titanium tetraisopropoxide in methylene chloride at room temperature for 24 hours resulted in no reaction. The next most acidic compound in the series, triisopropoxytitanium chloride, was prepared by mixing three equivalents of titanium tetraisopropoxide and one equivalent of titanium tetrachloride in methylene chloride.[28] The triisopropoxy titanium chloride was never isolated but simply used as a stock solution in methylene chloride which was stored at -20°C. Stirring epoxy-furan 21 with three equivalents of triisopropoxy titanium chloride in methylene chloride at room temperature for three hours provided 71% of the desired cyclization product. Similar reactions with the remainder of the epoxy-furans provided 64% of the six-exo product 28, 88% of the seven-endo product 29 and 24% of the seven-exo product 30. Both five-membered precursors 19 and 20 failed to provide even trace amounts of the desired products yielding only mixtures of allylic alcohols.

The final Lewis acid employed in this preliminary study was zinc iodide. It has been shown that zinc iodide is useful as a Lewis acid in the addition of allylic acetates

to silyl enol ethers.[29] Stirring epoxides 21-24 with three equivalents of freshly prepared zinc iodide etherate and one equivalent of sodium acetate in methylene chloride for 18 hours at room temperature provided good yields of the cyclized materials 27, 28, 29 and 24% of 30. The two five-membered ring cases 19 and 20 yielded none of the desired materials, but instead a 75-80% of the material was recovered as mixtures of allylic alcohols. Again in this series of reactions the utility of sodium acetate has yet to be demonstrated.

Tanis[30] has noted that treatment of epoxy dendrolasin 46 with boron trifloride etherate provides 47% of 3-β-hydroxy pallesencin A 51. According to our study, this reaction should proceed in higher yield with either zinc iodide-sodium acetate or triisopropoxy titanium chloride as the Lewis acid. Exposure of 2,6-dimethyl-9-(3-furyl)-2,6 nonadiene-oxide-2 46 to 3 quivalents of triisopropoxy titanium chloride for one hour at room temperature provided 57% of 3-β-hydroxy pallesencin A and treatment of 46 with three equivalents of zinc iodide and one equivalent of sodium acetate at room temperature for three hours provided 54% of 51. The yields are actually higher than indicated as the samples of 46 were contaminated with at least 25% epoxy geranyl chloride as determined by ^{1}HNMR. The preparation of larger samples of 46 should allow more efficient purification providing material of much higher purity for future study.



46 51

Figure 16

During the course of this investigation it was necessary to have large amounts of epoxy-furan 24 on hand. The preparation of 5-iodo-2-methyl-2-pentene 38 requires a long and tedious synthesis while 4-chloro-2-methyl-2-butene 36 is readily available by reduction of 3,3-dimethyl acrylic acid and chlorination of the resulting alcohol. Coupling of the readily available 36 with a one carbon homologue of 31 or 32 would provide the furyl olefin 43. This synthon could be used in the preparation of nakafuran-9 14 (figure 17).

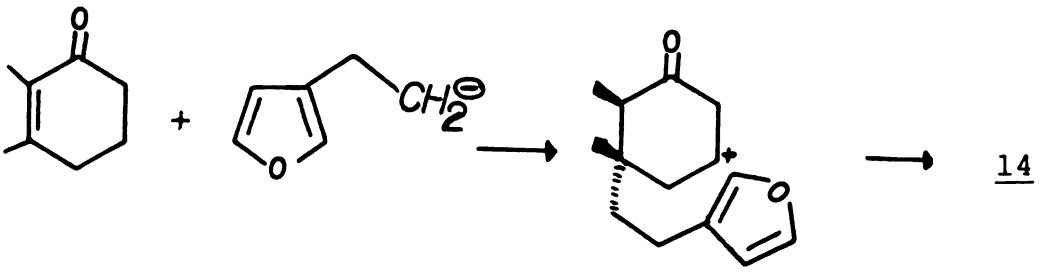
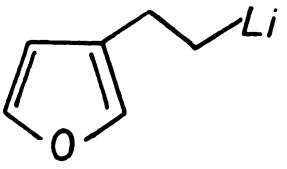


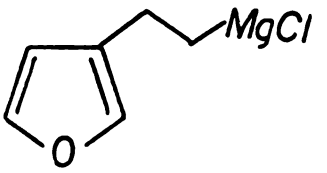
Figure 17

The necessary couplings could be accomplished using either the organo-lithium 51 or Grignard reagent 52 which both may be derived from the corresponding tri-(n-butyl) tin compound 53. The desired one carbon chain extension

has been achieved in 92% yield by the addition of tri-(n-butyl)-iodomethyl stannane[22] to Grignard reagent 32 in the presence of Li_2CuCl_4. The Grignard reagent 52 was then prepared by tin-lithium exchange on 53, with n-butyl lithium, and addition of the organo-lithium to a solution of magnesium bromide in THF. Reaction of the resultant Grignard reagent with 4-chloro-2-methyl-2-butene in the presence of Li_2CuCl_4 provided the desired furyl olefin 43 in 82% yield.



51



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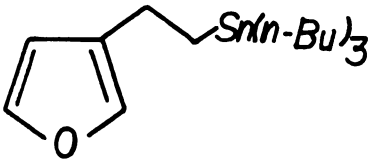


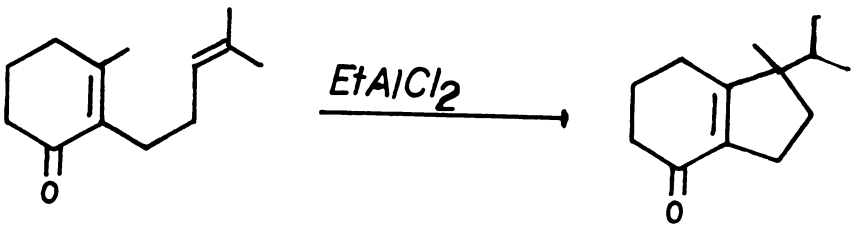
53

CONCLUSIONS

The general method devised for synthesis of type B furans (figure 3) appears to be very promising. The synthesis of the required 3-furyl epoxides proceeds smoothly and in high yield. The only major problem encountered was in the oxidation of the 3-furyl olefins. These reactions do not provide the desired epoxide, if the alkene is not at least trisubstituted. This problem is overcome simply by coupling the organo-lithium reagent 31 with the proper iodo-epoxide. Only 2-methyl-4-(3-furyl)-1-epoxy-butene 20 cannot yet be prepared in at least 65% overall yield. The successful synthesis of 20 requires a convenient, high yield route to the requisite iodoepoxide.

The results of our initial cyclization attempts are surprising in several respects. The first and most disappointing of these results is the failure of both the five-endo and five-exo precurors to undergo cyclizations. Examination of molecular models clearly demonstrates that the type of orbital overlap necessary to effect cyclization is nearly impossible in the five-endo case and therefore, we did not expect cyclization to occur in this case. However, in the five-exo closure the two sp^3 carbons in the ring being formed allow for enough flexibility to make overlap possible and we anticipated a successful closure. There are examples of cyclizations with similar geometry in the literature. Snider[31a] has reported a case (figure 16) in which the ring

being formed contains three sp^2 carbons and two adjacent sp^3 carbons as is the case in the cyclization of 20. This example and examination of molecular models seem to indicate that this cyclization should work but a milder Lewis acid will be required because the poor orbital overlap slows the nucleophilic attach of furan making elimination possible. Sutherland,[31b] and Yamamoto[31c] have reported cyclizations with identical steric constraints.



We had anticipated difficulty in affecting the cyclization of seven-exo precursor 24. As mentioned earlier, the electrophilic carbon and nucleophilic carbon must be brought close enough together to have orbital overlap before cyclization may occur. In the case of 24 there are four sp^3 carbons between the electrophile and nucleophile. The probability that the two required centers are adjacent is very low, requiring a longlived reactive Lewis acid complex if cyclization is to occur. Given the predisposition of these systems to provide allylic alcohols to the exclusion of cyclization, we were pleased to obtain a 24% yield of cyclized product.

In this study we have learned a great deal about the range of Lewis acidity which is useful in cyclizing 3-furyl

epoxides. There are many Lewis acids in this range which may prove useful. We are continuing to experiment with magnesium salts and species such as $B(OCH_3)_nCl_{3-n}$ among others. Thus far the only solvent used in the attempted cyclizations has been methylene chloride, other solvents such as ether, THF or acetonitrile may prove useful.

As mentioned earlier, many functionalites have been used as cyclization initiators. We are planning to expand this study by the examination of cyclizations initiated by α,β unsaturated carbonyls and allylic alcohols, etc.

EXPERIMENTAL

General: Tetrahydrofuran (THF) was dried by distillation, under nitrogen from sodium benzophenone ketyl; methylene chloride was dried by distillation under nitrogen from calcium hydride; N-N dimethylformamide (DMF) was dried by distillation at reduced pressure from phosphorous pentoxide; hexamethylphosphoramide (HMPA) was dried by distillation at reduced pressure from calcium hydride; pyridine was dried by distillation, under nitrogen, from calcium hydride; diisopropyl amine was dried by distillation, under nitrogen, from calcium hydride. Pet. ether refers to the 30-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Mallinkrodt Inc., St. Louis, Mo., and used as received. n-Butyl lithium in hexane was purchased from Aldrich Chemical Co., Milwaukee, Wis. and titrated by the method of Watson and Eastham.[17] Ethylaluminum dichloride and diethylaluminum chloride were purchased as hexane solutions from Alfa Products, Danvers, Ma., and used as received. Magnesium metal was activated by successive washings with 1N aqueous hydrochloric acid, water, acetone, ether and dried in a dessicator over phosphorous pentoxide at reduced pressure.

Unless otherwise stated, all reactions were carried out under an atmosphere of argon with the rigid exclusion of moisture from all reagents and glassware.

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 60MHz of a Bruker WM-250 spectrometer at 250MHz as indicated, as solutions in deuterochloroform unless otherwise indicated. Carbon magnetic resonance spectra were recorded on a Bruker WM-250 spectrometer at 68.9MHz. Chemical shifts are reported in parts per million on the δ scale relative to a tetramethylsilane internal standard. In NMR descriptions br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and J=coupling constants in Hertz. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system.

Flash chromatography was performed according to the procedure of Still et al [32] using the Whatman silica gel mentioned and eluted with the solvents mentioned. Analytical thin layer chromatography was run on either Macherey-Nagel Polygram SIL G/UV_{254} precoated plastic sheets or Brinkman Instruments SIL G/UV precoated glass plates. Spots were visualized by either dipping into a solution of Vanillin (1.5g) in absolute ethanol (100ml) and concentrated sulfuric acid (0.5ml) and heating with a heat gun or spraying with a 5% solution of molybdophosphoric acid in absolute ethanol and heating to 120°C.

(3-furyl)-chloromethane (33)[16] - To a mechanically stirred solution of LiCl (2.12g, 0.05 mole) in anhydrous DMF (40ml) was added a mixture of (3-furyl)-methanol (4.9g, 0.05 mole) and 2,4,6-trimethylpyridine (6.66g, 0.055 mole). The resulting solution was cooled to 0°C in an ice-water bath and methanesulfonyl chloride (6.3g, 0.055 mole, 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 (150ml) and ether-pentane (1:1,150ml). The organic phase was separated and washed with saturated aqueous cupric nitrate (3x150ml), dried (Na_2SO_4) and concentrated in vacuo to give a light yellow liquid. Distillation provided 4.8g 76%, of 33 as a colorless liquid B.P.$_{(25mm)}$=40°C. (lit. B.P.$^{24}_{(17mm)}$=42-43°C)

EI/MS (70eV):118(M^++2,11.1), 116(M^+,34.5), 81(base)

^{1}HNMR (60MHz) δ:7.32 (t,J=2Hz,2H), 6.28 (d,J=2Hz,1H), 4.56 (s,2H)

3-methyl-but-2-en-1-ol - To a suspension of lithium aluminum hydride (6.65g, 0.175 mole) in ether (250ml) cooled to 0°C was added a solution of 3,3-dimethyl acrylic acid (5.0g, 0.05 mole) in ether (100ml) over a period of 30 minutes. The suspension was then heated under reflux for 14 hours. The mixture was cooled to 0°C in an ice-water bath and 20% aqueous sodium hydroxide (50ml) was carefully added dropwise. The resulting suspension was filtered through celite 545, the filter cake was rinsed with ether and the combined filtrates were concentrated in vacuo to yield a colorless

liquid. Distillation provided 3.57g, 83%, of 3-methyl-but-2-en-1-ol as a colorless liquid. B.P.$_{(45mm)}$=72°C

^{1}HNMR (60MHz) δ :5.34(m,1H), 4.10(d,J=6Hz,2H), 3.8-3.6 (br s, 1H), 1.88(s,3H), 1.78(s,3H)

4-chloro-2-methyl-but-2-ene (36)[16] - To a mechanically stirred solution of LiCl (2.12g, 0.05 mole) in DMF (40ml) was added a mixture of 3-methyl-but-2-en-1-ol (4.3g, 0.05 mole) and 2,4,6-trimethylpyridene (6.66g, 0.055 mole). The resulting solution was cooled to 0°C and methanesulfonyl cloride (6.3g, 0.055 mole, distilled from calcium hydride) was added over a period of 20 minutes. After stirring at 0°C for 2 hours the mixture was cast into ice-water (150ml) and ether-pentane (1:1,150ml). The organic phase was washed with saturated aqueous cupric nitrate (3x150ml), dried (Na_2SO_4), and concentrated in vacuo to give a yellow liquid. Distillation gave 2.24g, 43% of 36 as a colorless liquid

B.P.$_{(93mm)}$=55°C

^{1}HNMR (60MHz) δ :5.34(m,1H), 4.00(d,J=9Hz,2H), 1.70 (br s,6H)

3-methyl-but-3-en-1-ol p-toluenesulfonate - To a solution of 3-methyl-but-3-en-1-ol (2.6g, 30 mmole) in pyridine (20ml), cooled to 0°C in an ice-water bath, was added freshly crushed p-toluenesulfonyl chloride (7.63g, 40 mmole) 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 (50g-50ml) and extracted with ether (150ml).

The organic phase was separated and washed with 1N aqueous hydrochloric acid (100ml), saturated aqueous sodium bicarbonate (100ml), brine (100ml), dried (Na_2SO_4), and concentrated in vacuo to yield 6.0g, 83%, of a viscous yellow liquid which was used without further purification.

3-methyl-3-epoxy-buten-1-ol p-toluenesulfonate (47c) - To a solution of 3-methyl-but-3-en-1-ol p-toluenesulfonate (7.62g, 30 mmole) in methylene chloride (50ml), cooled to 0°C in an ice-water bath, was added a solution of m-chloroperbenzoic acid (8.08g, 30 mmole, 85%) in methylene chloride (50ml) 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 (150ml) and washed with 10% aqueous sodium bisulfite (2x100ml), saturated aqueous sodium bicarbonate (100ml), water (100ml), brine (100ml), dried (Na_2SO_4), and concentrated in vacuo to yield a viscous liquid. The crude product was purified by chromatography on a column of silical gel (60-230 mesh, 50g, 40mm o.d., ether-pet. ether 1:1, 30ml fractions) using the flash technique. Fractions 8-13 provided 5.52g, 68%, of 47c as a colorless liquid.

EI/MS (70eV):256(M^+,2.1), 155(11), 101(11.6), 91(38.5), 84(24.4), 68(23.7), 43(base)

^{1}HNMR (60MHz) 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 (47b) - To a solution of 3-methyl-3-epoxy-buten-1-ol p-toluenesulfonate, 47c, (2.02g, 7.89 mmole) in acetone (25ml, dried over $CaCl_2$) was added sodium iodide (1.50g, 10 mmole) 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 (150ml) and washed with water (100ml), 10% aqueous sodium bisulfite (100ml), water (100ml), brine (100ml), dried (Na_2SO_4) and concentrated in vacuo to yield a colorless liquid. Distillation of the crude product provided 1.47g, 88%, of 47b as a clear, colorless liquid. B.P.$_{(25mm)}$=58°C

EI/MS (70eV):212(M^+,4.3), 194(1.13), 110(14.2), 85(25.4), 55(66.1), 43(base)

^{1}HNMR (60MHz) δ :3.11(t,J=8Hz,2H), 2.60(AB,J_{AB}=4Hz,2H), 2.12 (m,2H), 1.28(S,3H)

IR(neat): 3000 2920, 1430, 1375, 1215, 1150, 1050, 895, 790, 720cm^{-1}

4-methyl-pent-4-en-1-ol p-toluenesulfonate - To solution of 4-methyl-pent-4-en-1-ol[33] (3.0g,30 mmole) in pyridine (16ml) cooled to 0°C in an ice-water bath was added freshly crushed p-toluenesulfonyl chloride (7.63g,40 mmole) 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 (50g-50ml) and extracted with ether (150ml). The organic phase was washed with 1N aqueous hydrochloric acid (100ml), brine (100ml), dried (Na_2SO_4), and concentrated in vacuo to yield 7.62g,

100% of a viscous yellow liquid. This product was used without further purification.

4-methyl-4-epoxy-penten-1-ol p-toluenesulfonate (48c) - To a solution of 4-methyl-pent-4-en-1-ol p-toluenesulfonate (7.62g, 30 mmole) in methylene chloride (40ml) cooled to 0°C in an ice-water bath was added a solution of m-chloroperbenzoic acid (6.08g, 30 mmole, 85%) in methylene chloride (50ml) 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 (200ml) and washed with 10% aqueous sodium bisulfite (150ml), saturated aqueous sodium bicarbonate (150ml), water (150ml), brine (150ml), 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, 50g, 40mm o.d., ether-pet. ether 1:1, 25ml fractions) using the flash technique. Fractions 10-14 yielded 5.52g, 68% of 48c as a colorless liquid.

^{1}HNMR (60MHz) 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), 1.29(s,3H)

5-iodo-4-methyl-1-epoxy-pentene 48b - To a solution of 4-methyl-4-epoxy-penten-1-ol p-toluenesulfonate, 48c, (5.6g, 20 mmole) in acetone (50ml, dried over $CaCl_2$) was added sodium iodide (3.3g, 22 mmole) 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 (200ml) and ether (200ml). The organic phase was separated and washed with, 10% aqueous

sodium bisulfite (100ml), saturated aqueous sodium bicarbonate (100ml), water (100ml), brine (100ml), dried (Na_2SO_4), and concentrated in vacuo to yield a water white liquid. Distillation of the crude product provided 3.79g, 84.5%, of 48b as a colorless liquid. B.P.$_{(20mm)}$=62°C

^{1}HNMR (60MHz) :3.20(m,2H), 2.58(s,2H), 2.10-1.53(m,4H), 1.29(s,3H)

EI/MS (70eV) 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, 750cm^{-1}

4-methyl-pent-3-en-1-ol - To a suspension of lithium aluminum hydride (0.95g, 25 mmole) in ether (50ml) cooled to 0°C was added a solution of ethyl-4-methyl-3-pentenoate[34] (3.23g, 23 mmole) in ether (50ml) over a period of 30 minutes. The suspension was then heated under reflux for 3 hours. The mixture was cooled to 0°C and 20% aqueous sodium hydroxide (30ml) was carefully added. The resulting suspension was filtered through celite and concentrated in vacuo to yield a colorless liquid. Distillation of the crude product provided 1.47g, 67%, of 4-methyl-pent-3-en-1-ol as a colorless liquid. B.P.$_{(112mm)}$=110°C. (lit. B.P.$^{35}_{(110mm)}$=105°C)

^{1}HNMR (60MHz) δ :5.12(m,1H), 3.60(t,J=7Hz,2H), 2.98(brs,1H), 2.17(M,2H), 1.78(s,3H), 1.73(s,3H)

4-methyl-pent-3-en-1-ol p-toluenesulfonate - To a solution of 4-methyl-pen-3-en-1-ol (3.15g, 37.5 mmole) in pyridine (18ml) cooled to 0°C in an ice-water bath was added freshly crushed p-toluenesulfonyl chloride (7.62g, 40 mmole) in one portion. The mixture was stirred at 0°C for 1 hour and then

stored in the freezer (-20°C) overnight. The mixture was then cast into ice-concentrated hydrochloric acid (50g-50ml) and extracted with ether (150ml). The organic phase was washed with 1N aqueous hydrochloric acid (100ml), saturated aqueous sodium bicarbonate, (100ml), water (100ml), brine (100ml), dried (Na_2SO_4) and concentrated *in vacuo* to yield a viscous yellow liquid which was used immediately in the next reaction.

5-iodo-2-methyl-2-pentene 38 - To a solution of crude 4-methyl-pent-3-en-1-ol p-toluenesulfonate (4.40g, 17.3 mmole) in acetone (50ml) was added sodium iodide (3.0g, 20 mmole) and the solution heated under reflux for 14 hours. The mixture was cooled to 0°C and suction filtered. The filtrate was cast into water (200ml) and ether (150ml). The organic phase was separated and washed with 10% aqueous sodium bisulfite (150ml), water (150ml), brine (150ml) dried (Na_2SO_4), and concentrated *in vacuo* to yield a colorless liquid. Distillation of the crude product provided 3.34g, 92% of 38 as a colorless liquid. $B.P._{(45mm)}$=63°C (lit. $B.P._{(50mm)}^{36}$=72°C

^{1}HNMR (60MHz) δ :5.04(m,1H), 2.50(t,J=8Hz,2H), 1.99(m,2H), 1.66(s,3H), 1.60(s,3H)

tri-(n-butyl)-stanyl methyl furan (50) - To a solution of diisopropyl amine (4.44g, 44 mmole) in anhydros THF (50ml) cooled to 0°C in an ice-water bath was added n-butyl lithium (25.8ml, 44 mmole) over a period of 10 minutes and the mixture was allowed to stir for an additional 10 minutes after the addition was complete. To the resulting solution was added tri-(n-butyl) tin hydride (11.6g, 40 mmole) over a period of 10 minutes and the mixture allowed to stir for an

additional 15 minutes and then cooled to -25°C in a dry ice-carbon tetrachloride bath. To the resulting yellow solution was added (3-furyl)-chloromethane (4.66g, 40 mmole), over a period of 10 minutes. The cooling bath was removed and the reaction allowed to stir at room temperature for 1 hour. The mixture was then cast into ether (300ml) and saturated aqueous NH_4Cl (200ml). The organic phase was separated and washed with water (200ml), brine (200ml), dried (Na_2SO_4) and concentrated in vacuo to yield a yellow liquid. Distillation provided 11.23g, 76%, of a colorless liquid.

B.P.$_{(0.5mm)}$=125°C (lit. B.P.$^{37}_{(0.55mm)}$=116-119°C)

EI/MS (70eV) 372(1.3), 355(6), 315(10), 291(28), 235(32), 201(18), 179(base)

^{1}HNMR (60MHz) δ :7.23(t,J=2,1H), 7.18(m,1H), 6.21(s,1H), 2.0-0.7(m,29H)

2-methyl-4-(3furyl)-but-2-ene (39) - To activated magnesium metal turnings (0.243g, 10 mmole) covered by THF (15ml) was added (3-furyl)-chloromethane (1.16g, 10 mmole) in one portion. The mixture was stirred at room temperature until all the magnesium had reacted (about 1 hour). The resulting golden solution was cooled to 0°C and 1-bromo-2-methyl-propene[38], 34, (1.35g, 10 mmole) was added followed immediately by $FeCl_3$ (16mg, 0.01 mmole). The reaction mixture immediately turned deep red. After the mixture had stirred at 0°C for 1 hour it was cast into saturated aqueous NH_4Cl (100ml) and ether (150ml). The organic phase was separated

and washed with water (100ml), brine (100ml), dried (Na_2SO_4), and concentrated *in vacuo* to yield a golden liquid. The crude product was purified by chromatography in a column of silica gel (230-400 mesh, 100g, 50mm o.d., ether-pet. ether 1:99, 30ml fractions), using the flash technique. Fractions 6-9 provided 1.12g, 82% of 39 as a colorless sweet-smelling liquid.

EI/MS (70eV) 136(M^+, base), 121(42), 93(41), 91(37), 77(36)

^{1}HNMR (250MHz) δ :7.22 (t,J=2Hz,1H0), 7.04(m,1H), 6.13(br s, 1H), 5.24(t,J=10Hz,1H), 3.10(d,J=10Hz,2H), 2.62(s,3H), 2.50(s,3H)

IR(neat): 2900, 1500, 1450, 1375, 1155, 1070, 1010, 870, 780cm^{-1}

2-methyl-4-(3-furyl)-but-1-ene (40) - To activated magnesium metal turnings (0.243g, 10 mmole) covered by THF (15ml) was added (3-furyl)-chloromethane (1.16g, 10 mmole) in one portion. The mixture was stirred at room temperature until all the magnesium had reacted (about 1 hour). The resulting golden solution was cooled to 0°C in an ice-water bath and 3-chloro-2-methyl-propene, 35, (0.90g, 10 mmole) was added followed immediately by Li_2CuCl_4 (0.12ml, 0.1M in THF). The reaction mixture immediately warmed and turned black. After the solution had stirred at 0°C for 1/2 hour it was cast into saturated aqueous NH_4Cl (100ml) and ether (100ml). The organic phase was separated and washed with water (100ml), brine (100ml), 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 40 as a colorless liquid.

^{1}HNMR (250MHz) δ :7.28(t,J=1.8Hz,1H), 7.13(m,1H), 6.19(br s, 1H), 4.62(br s,2H), 2.27(m,4H), 1.76(s, 3H)

EI/MS (70eV) 136(M^+,15), 121(11.7), 94(46.7), 81(base)

IR(neat): 2950, 2870, 1500, 1150, 1080, 1025, 900, 890, 780cm^{-1}

2-methyl-5-(3-furyl)-pent-2-ene (41) - To activated magnesium turnings (0.243g, 0.01 mole) covered by THF (15ml) was added (3-furyl)-chloromethane (1.16g, 0.01 mole) in one portion. The mixture was stirred at room temperature until all the magnesium had reacted (about 1 hour). The resulting golden solution was cooled to 0°C in an ice-water bath and 4-chloro-2-methyl-2-butene, 36, (1.04g,0.01 mole) was added, followed immediately by Li_2CuCl_4 (0.12ml, 0.1M in THF). The reaction mixture immediately warmed and turned black. After the solution had stirred at 0°C for 1/2 hour it was cast into saturated aqueous NH_4Cl (100ml) and ether (100ml). The organic phase was separated and washed with water (100ml), brine (100ml), 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, 100g, 50mm o.d., ether-pet. ether 1:99, 30ml fractions) using the flash technique. Fractions 8-14 yielded 1.23g, 82%, of 41 as a colorless sweet smelling liquid.

EI/MS (70eV) 150(M^+,52), 135(12), 81(67), 69(base)

^{1}HNMR (250MHz) δ :7.32(t,J=2Hz,1H), 7.12(m,1H), 6.23(s,1H), 5.12(t,J=10Hz), 2.6-2.0(m,4H), 1.73(s,3H), 1.65(s,3H)

IR(neat): 2890, 1500, 1440, 1380, 1160, 1080, 1025, 870, 780cm^{-1}

2-methyl-6-(3-furyl)-hex-2-ene (43) - To "activated" magnesium turnings (0.243g, 0.01 mole) covered by anhydrous tetrahydrofuran (15ml) was added (3-furyl)-chloromethane (1.16g, 0.01 mole) in one portion. The mixture was stirred under argon at room temperature until all the magnesium had reacted (about 1 hour). The resulting golden liquid was cooled to 0°C in an ice-water bath and 5-iodo-2-methyl-2-pentene, 38, (2.10g, 0.01 mole) was added, followed immediately by Li_2CuCl_4 (0.12ml, 0.1M, in THF). The reaction mixture warmed and slowly turned black. After the solution had stirred at 0°C for an additional 1 hour it was cast into saturated aqueous NH_4Cl (100ml) and ether (100ml). The organic phase was separated and washed with water (100ml) saturated brine (100ml), 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 (230-400 mesh, 100g, 50mm o.d., ether; pet. ether 1:99, 30ml fractions). Fractions 7-11 were combined and yielded 1.19g (73%) of 43 as a colorless liquid.

EI/MS (70eV): 164(M^+,2), 149(3), 121(9.1), 108(8), 94(14), 82(base)

^{1}HNMR (250MHz) 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, 780cm^{-1}

2-methyl-6-(3-furyl)-hex-2-ene (43) - To activated magnesium metal turnings (0.243g, 0.01 mole) covered by anhydrous THF (10ml) was slowly added 1,2-dibromoethane (1.88g, 0.01 mole). The mixture was stirred at room termerature for 1 hour and then heated under reflux until all the magnesium had reacted (about 1/2 hour). This solution was cooled to 0°C in an ice-water bath. To a solution of 2-(3-furyl) ethyl-tri-(n-butyl) stannane, 53, (3.84g, 0.01 mole), cooled in a dry ice-isopropanol bath was added n-butyl lithium (5.8ml, 0.01 mole, in hexane) over a period of 5 minutes. The solution was allowed to stir at -78°C for 10 minutes and transferred via cannula to the magnesium bromide-THF solution prepared above. This mixture was allowed to stir at 0°C for 1 hour then 4-chloro-2-methyl-but-2-ene, 36, (1.04g, 10 mmole) was added in one portion followed immediately by Li_2CuCl_4 (0.2ml, 0.1M in THF). After 5 minutes the resulting mixture was cast into saturated aqueous NH_4Cl (150ml) and ether (150ml). The organic phase was separated and washed with water (100ml), brine (100ml), 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, 100g, 50mm o.d., pentane, 50ml fractions) using the flash technique. Fractions 8-14 yielded 1.34g, 82%, of 43 as a colorless liquid. For spectral data see previous preparation.

2-methyl-4-(3-furyl)-2-epoxy-butene (19) - To a stirred solution of 2-methyl-4-(3-furyl)-but-2-ene, 39, (1.36g, 0.01 mole) in methlene chloride (30ml) cooled to 0°C in an ice-water bath was added a solution of m-chloroperbenzoic acid (2.23g, 0.011 mole, 85%) in methylene chloride (50ml) over a period of 1/2 hour. The resulting mixture was allowed to stir at 0°C for 1/2 hour. The resulting suspension was suction filtered and the filtrate cast into 10% aqueous sodium bisulfite (150ml) and ether (200ml). The organic phase was separated and washed with saturated aqueous sodium bicarbonate (100ml), water (100ml), brine (100ml), 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, 50mm, o.d., ether-pet. ether 1:4, 40ml fractions) using the flash technique. Fractions 6-11 yielded 1.20g, 79%, of 19 as a colorless liquid.

EI/MS (70eV): δ 152(M^+,4.5) 137(base), 123(6.8), 108(29)

^{1}HNMR (250MHz) :7.42(t,J=3Hz,1H), 7.27(s,1H), 6.30(s,1H), 2.89(t,J=6Hz,1H), 2.70(d of AB,J=6Hz,12Hz,2H) 1.42(s,3H), 1.40(s,3H)

^{13}CNMR (69.8MHz) :144.4, 140.7, 122.0, 112.35, 64.94, 59.77, 26.24, 26.06

IR(neat): 2965, 2925, 1500, 1445, 1375, 1155, 1125, 1020, 870, 780, 760cm^{-1}

2-methyl-4-(3-furyl)-1-epoxy-butene (20) - To a stirred solution of 2-methyl-4-(3-furyl)-but-1-ene, 40, (1.3g, 10 mmole) in methylene chloride (30ml) cooled to 0°C in an ice-water bath was added a solution of m-chloroperbenzoic acid (2.02g, 10 mmole, 85%) in methylene chloride (50ml) over a period of 1/2 hour. The mixture was allowed to stir at 0°C for 1/2 hour. The resulting suspension was suction filtered and the filtrate cast into 10% aqueous sodium bisulfite (150ml) and ether (200ml). The organic phase was separated and washed with saturated aqueous sodium bicarbonate (100ml), water (100ml), brine (100ml), 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, 50mm o.d., ether-pet. ether 1:4, 40ml fractions), using the flash technique. Fractions 6-11 provided 0.38g, 25% of 20 as a colorless liquid.

^{1}HNMR (250MHz) δ :7.21(t,J=2Hz,1H), 7.09(m,1H), 6.23(br s,1H), 2.53(m,4H), 1.83(m,2H), 1.38(s,3H)

EI/MS (70eV):156(M^+,54.6), 139(84.3), 121(43.13), 112(63.10) 93(48.7), 81(67.0), 55(base)

IR(neat): 2930, 2860, 1500, 1450, 1430, 1390, 1175, 1030, 890cm^{-1}

2-methyl-5-(3-furyl)-2-epoxy-pentene (21) - To a solution of 2-methyl-5-(3-furyl)-pent-2-ene, 41, (1.50g, 10 mmole)

in methylene chloride (30ml) cooled to 0°C in an ice-water bath was added a solution of m-chloroperbenzoic acid (2.02g, 10 mmole, 85%) in methylene chloride (50ml) over a period of 1/2 hour. The mixture was allowed to stir at 0°C for 1 hour after the addition was completed. The resulting suspension was suction filtered and the filtrate was cast into 10% aqueous sodium sulfite (150ml) and ether (150ml). The organic phase was separated and washed with saturated aqueous sodium bicarbonate (100ml), water (100ml), brine (100ml), 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, 70g, 50mm o.d., ether-pet 1:4, 30ml fractions) using the flash technique. Fractions 8-13 provided 1.37g, 83% of 21[8b] as a colorless liquid.

EI/MS (70eV):166(M^+,7.1), 151(12), 33(10), 123(13.4), 108 (42.8), 95(39.4), 85(75.0), 81(83.4), 72(38.5), 59(base)

^{1}HNMR (250MHz)δ :7.39(t,J=2Hz,1H), 7.22(s,1H), 6.29(s,1H), 2.78(t,J=6Hz,1H), 2.56(m,2H), 1.78(q,J=8Hz,2H), 1.32(s,3H), 1.21(s,3H)

IR(neat): 2980, 2940, 2880, 1500, 1440, 1380, 1160, 1115, 1025, 925, 875, 790cm^{-1}

^{13}CNMR (69.8MHz)δ :155.8, 141.4, 114.16, 110.00, 76.59, 37.81, 28,64, 21.20, 18.99, 24.1

2-methyl-6-(3-furyl)-2-epoxy-hexene (23) - To a solution of 2-methyl-6-(3-furyl)-hex-2-ene, 43, (1.64g, 10 mmole) in methylene chloride (30ml) cooled to 0°C in an ice-water bath was added a solution of m-chloroperbenzoic acid (2.02g, 10

mmole, 85%) in methylene chloride (50ml) over a period of 1/2 hour. The mixture was allowed to stir at 0°C for 1/2 hour. The resulting suspension was suction filtered and the filtrate was cast into 10% aqueous sodium bisulfite (150ml) and ether (150ml). The organic phase was separated and washed with saturated aqueous sodium bicarbonate (100ml), water (100ml), brine (100ml), 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, 70g, 50mm o.d., ether-pet. ether 1:4, 25ml fractions) using the flash technique. Fractions 8-11 provided 1.40g, 78% of 23 as a colorless liquid.

EI/MS (70eV):180(M^+,1.7), 151(7.4), 135(5.6), 121(14), 107 (11.3), 98(2), 94(base)

^{1}HNMR (250MHz)δ :7.28(t,J=2Hz,1H), 7.18(t,J=2Hz,1H), 6.21 (br s,1H), 2.67(t,J=6Hz,1H), 2.45(m,2H), 1.58 (m,4H), 1.22(s,3H), 1.18(s,3H)

IR(neat): 2980, 2950, 2880, 1500, 1440, 1390, 1150, 1115, 1020, 915, 875, 790, 720cm^{-1}

2-methyl-6-(3-furyl)-1-epoxy-hexene (24) - To a solution of tri-(n-butyl)-stannyl methyl furan, 50, (1.85g, 5 mmole) in anhydrous THF (5ml) cooled to -78°C in a dry ice-isopropanol bath was added n-butyl lithium (3.33ml, 5 mmole, in hexane) over a period of 5 minutes. The solution was allowed to stir at -78°C for 10 minutes, HMPA (0.896g, 5 mmole) was then added in one portion and the mixture stirred at -78°C for 10 minutes. The resulting solution was transferred *via* cannula to a solution of 5-iodo-2-methyl-1-epoxy-pentene, 48b, (1.12g, 5 mmole) in anhydrous THF (10ml) cooled to

-25°C in a dry ice-carbon tetrachloride bath. Upon addition of the organolithium reagent the initially colorless solution turned deep red-brown. The cooling bath was removed and the mixture allowed to stir at room temperature overnight. The solution was cast into saturated aqueous NH_4Cl (100ml) and ether (100ml). The organic phase was separated and washed with water (100ml), brine (100ml), 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, 75g, 40mm o.d., ether-pet. ether 1:4, 25ml fractions) using the flash technique. Fractions 14-18 yielded 0.61g, 68% of 24 as a light yellow liquid.

EI/MS (70eV):180(M^+,12), 163(11), 149(14.4), 135(28), 121 (18.7), 108(60), 82(base)

^{1}HNMR (250MHz) δ :7.36(t,J=3Hz,1H), 7.21(t,J=3Hz,1H), 6.24 (s,1H), 3.90(t,J=9Hz,1H), 3.28(m,1H), 2.58(m,2H), 2.42(t,J=9Hz,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, 780cm^{-1}

7,7-dimethyl-6-hydroxy-4,5-6,7-tetrahydrobenzofuran (27) - To a solution of 2-methyl-5-(3-furyl)-2-epoxy-pentene, 21, (0.1g, 0.60 mmole) in methylene chloride (10ml) cooled to -25°C in a dry ice-carbon tetrachloride bath was added freshly distilled boron trifloride etherate (0.028g, 0.20 mmole). The mixture was quenched (-25°C) with saturated

aqueous NH_4Cl (5ml) and allowed to warm to room temperature. The two phase mixture was cast into ether (50ml) and saturated aqueous NH_4Cl (50ml). The organic phase was separated and washed with water (50ml), brine (50ml), 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, 40g, 30mm o.d., ether-pet. ether 1:1, 10ml fractions) using the flash technique. Fractions 14-17 provided 47mg, 47% of **27** as a light yellow liquid.

EI/MS (70eV):166(M^+,40.4), 151(9.4), 133(4.80), 122(base)

^{1}HNMR (250MHz) δ :7.26(d,J=1.8Hz,1H), 6.14(d,J=1.8Hz,1H), 3.83(br s, 1H), 3.40(t of d, J_t=8Hz, J_d= 6Hz,2H), 1.92(m,2H), 1.38(s,3H), 1.22(s,3H)

^{13}CNMR (69.8MHz) δ:155.8, 141.4, 114.1, 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, 780cm^{-1}

2-methyl-5-(3-furyl)-1-epoxy-pentene (22) - To a solution of tri-(n-butyl)-stanyl methyl furan **50** (1.85g, 5 mmole) in anhydrous THF (5ml) cooled to -78°C in a dry ice-isopropanol bath was added n-butyl lithium (3.33ml, 5 mmole, in hexane) over a period of 5 minutes. The solution was allowed to stir at -78°C for 10 minutes and then HMPA (0.896g, 5 mmole) was added in one portion and the mixture allowed to stir at -78°C for an additional 10 minutes. The resulting solution was transferred *via* cannula into a solution

of 4-ioeo-2-methyl-1-epoxy-butene, 47b, (1.06g, 5 mmole) in THF (10ml) which was cooled to -25°C in a dry ice-carbon tetrachloride bath. Upon addition of the organo-lithium reagent the colorless solution turned deep red-brown. The cooling bath was removed and the mixture allowed to stir at room temperature overnight. The solution was cast into saturated aqueous NH_4Cl (100ml), and ether (100ml). The organic phase was separated and washed with water (100ml), brine (100ml), 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, 75g, 40mm o.d., etherpet. ether, 1:4, 25ml fractions) using the flash technique. Fractions 12-17 provided 0.66g, 80%, of 22 as a light yellow liquid.

EI/MS (70eV):166(M^+,2.3), 149(8.1), 141(19), 135(8.6), 129(7.8), 121(12.0), 109(17.6), 94(base)

^{1}HNMR (250MHz)δ :7.32(t,J=3Hz,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, 905, 975, 890cm^{-1}

Attempted cyclization of 21 with ethylaluminum dichloride - To a solution of 2-methyl-5-(3-furyl)-2-epoxy-pentene 21 (0.1g, 0.60 mmole) in methylene chloride (10ml) cooled to -78°C was added ethylaluminum dichloride (1.22ml, 1.8 mmole, 1.47M in hexane) and the mixture warmed slowly to -25°C. The solution was allowed to stir at -25°C for 1/2 hour and

then quenched by addition of saturated aqueous NH_4Cl (10ml). The reaction was warmed to room temperature and the resulting two phase mixture was cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 1N aqueous hydrochloric acid (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a yellow liquid. Flash chromatography of the crude product provided 0.016g, 16%, of 27 as a light yellow liquid.

Attempted cyclization of 21 with diethylaluminum chloride - To a solution of 2-methyl-5-(3-furyl)-2-epoxy-pentene 21 (0.1g, 0.60 mmole) in methylene chloride (10ml) cooled to 0°C was added diethylaluminum chloride (1.22ml, 1.8 mmole, 1.48M in hexane) and the mixture immediately turned yellow. The solution was allowed to stir at 0°C for 1 hour and then quenched by the addition of saturated aqueous NH_4Cl (10ml). The resulting two phase mixture was cast into saturated aqueous NH_4Cl (50ml), and ether (50ml). The organic phase was separated and washed with 1N aqueous hydrochloric acid, (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a yellow liquid. Flash chromatography of the crude product provided 0.022g, 22%, of 27 as a light yellow liquid.

Attempted cyclization of 21 with alumina - To a solution of 2-methyl-5-(3-furyl)-2-epoxy-pentene, 21 (0.1g, 0.60 mmole) in hexane (15ml, distilled from calcium hydride) was added basic alumina (2.0g, activity I) and the suspension stirred

at room temperature for 24 hours. Methanol (10ml) was added and the mixture suction filtered and the alumina rinsed with methanol (15ml). The solvent was removed in vacuo to yield a colorless liquid. Flash chromatography of the crude product provided 0.032g, 32% of 27 as a light yellow liquid.

Attempted cyclization of 21 with magnesium bromide - To a solution of 2-methyl-5-(3-furyl-2-epoxy-pentene 21 (0.10g, 0.60 mmole) in methylene chloride (10ml) was added magnesium bromide-THF complex (0.317g, 1.2 mmole) followed immediately by triethyl amine (0.061g, 0.60 mmole, distilled under nitrogen from calcium hydride). The mixture was allowed to stir at room temperature for 24 hours. The reaction was quenched by addition of 1N aqueous hydrochloric acid (10ml) and the resulting two phase mixture cast into 1N aqueous hydrochloric acid (50ml) and ether (50ml). The organic phase was separated and washed with water (50ml), brine (50ml), dried (Na_2SO_4), and concentrated in vacuo to yield a light yellow liquid. Flash chromatography of the crude product provided 0.043g, 43% of 27 as a light yellow liquid.

Triisopropoxytitanium chloride - To a solution of titanium tetraiopropoxide (6.39g, 22.5 mmole) in methylene chloride (40ml) was added titanium tetrachloride (1.42g, 7.5 mmole). This mixture was stored at -20°C.

Attempted cyclization of 21 with triisopropoxytitanium chloride - To a solution of 2-methyl-5-(3-furyl)-2-epoxy-pentene, 21, (0.10g, 0.60 mmole) in methylene chloride (10ml) cooled to 0°C in an ice water bath was added triisopropoxytitanium chloride (2.40ml, 1.8 mmole, 0.75M in

methylene chloride). The mixture was allowed to stir at 0°C for 1 hour and then at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture was cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 1N aqueous hydrochloric acid (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a light yellow liquid. Flash chromatography of the crude product provided 0.078g, 78%, of 27 as a light yellow liquid.

Zinc Iodide - To zinc metal (3.26g, 50 mmole, 30 mesh) covered by ether (30ml), was added a solution of iodine (12.7g, 50 mmole) in ether (80ml) over a period of 1 hour. The resulting mixture was heated to reflux until all brown color had disappeared (about 2 hours). The solvent was removed in vacuo and the residue dried in a dessicator over phosphorous pentoxide at reduced pressure to provide (19.0g, 99%) of zinc iodide-ether complex.

Attempted cyclization of 21 with zinc iodide - To a solution of 2-methyl-5-(3-furyl)-2-epoxy-pentene, 21, (0.10,g, 0.60 mmole) in methylene chloride (10ml) was added anhydrous sodium acetate (50mg, 0.60 mmole) followed immediately by zinc iodide-ether complex (0.47g, 1.2 mmole) and the mixture allowed to stir in the dark for 3 hours. The reaction was quenched by addition of saturated aqueous NH_4Cl (10ml)

and the resulting two phase mixture cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 10% aqueous sodium bisulfite (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a light yellow liquid. Flash chromatography of the crude product provided 0.071g, 71%, of 27 as a light yellow liquid.

7-methyl-7-hydroxmethyl-4,5-6.7-tetrahydrobenzofuran (28) - To a solution of 2-methyl-5-(3-furyl)-1-epoxy-pentene, 22, (0.10g, 0.60 mmole) in methlene chloride (10ml) cooled to 0°C was added stock titanium catalyst (2.40ml, 1.8 mmole, 0.75M in methylene chloride). The mixture was allowed to stir at 0°C for 1 hour and then at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 1N aqueous hydrochloric acid (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a light yellow liquid. The crude product was purified on a column of silica gel (230-400 mesh, 40mm o.d., ether-pet. ether 1:1, 25ml fractions) using the flash technique. Fractions 13-17 provided 0.089g, 89%, of 28 as a light yellow liquid.

EI/MS (70eV):166(M^+, 8.8), 149(4.4), 135(base)

^{1}HNMR (250MHz) δ :7.21(d,J=1.8Hz,1H), 6.15(d,J=8Hz,1H), 3.52(s,2H), 2.38(m,2H), 1.96(m,2H), 1.24 (s,3H)

IR(neat): 3440, 2940, 1500, 1380, 1205, 1160, 1040, 890, 740cm^{-1}

8,8-dimethyl-7-hydroxy-4,5-7,8-tetrahydrocyclohepta-6H-[b] furan 29 - To a solution of 2-methyl-6-(3-furyl)-2-epoxy-hexene (0.10g, 0.55 mmole) in methylene chloride (10ml) was added anhydrous sodium acetate (0.045g, 0.55 mmole) followed immediately by zinc iodide-ether complex (0.648g, 1.5 mmole) and the mixture allowed to stir in the dark for 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 10% aqueous sodium bisulfite (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a light yellow liquid. The crude product was purified on a column of silica gel (230-400 mesh, 70g, 40mm o.d., ether-pet. ether 1:1, 24ml fractions) using the flash technique. Fractions 15-20 provided 0.088g, 88%, of 29 as a light yellow liquid.

EI/MS (70eV):166(M^+,32.2), 151(12.6), 149(17.9), 133(7.4), 122(base)

^{1}HNMR (250MHz) δ :7.24(d,J=1.98Hz,1H), 6,13(d,J=1.98Hz,1H) 3.73(d of d, J=4.21Hz,1H), 2.47(m,2H), 1.91(m,6H), 1.30(s,3H), 1.22(s,3H)

IR(neat): 3430, 2980, 1750, 1620, 1500, 1470, 1380, 1360, 1285, 1160, 1115, 1090, 1030, 890, 730, 705cm^{-1}

Fractions 11-12 provided 9mg, 9%, of a mixture of allylic alcohols

^{1}HMNR (60MHz) δ :7.39(t,J=3Hz,2H), 7.21(t,J=3Hz,2H), 6.24 (s,2H), 4.85(s,1H), 4.80(s,1H), 4.10(m,1H), 3.62(br m 2H), 3.28(m,2H), 2.60(m,4H),

2.44(t,J=9Hz,4H), 1.31(s,6H).

8-methyl-8-hydroxymethyl-4,5-7,8-tetrahydrocyclohepta-6H-[b]-furan 30 - To a solution of 2-methyl-6-(3-furyl)-1-epoxy-hexene (0.10g, 0.55 mmole) in methylene chloride (10ml) was added anhydrous sodium acetate (0.045g, 0.55 mmole) followwed immediately by zinc iodide-ether complex (0.648g, 1.5 mmole) and the mixture stirred in the dark for 6 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 10% aqueous sodium bisulfite (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a yellow liquid. The crude product was purified on a column of silica gel (230-400 mesh, 70g, 40 mm o.d., ether- pet. ether 1:1, 30ml fractions) using the flash technique. Fractions 14-16 provided 0.023 g, 23% of 30 as a light yellow liquid.

EI/MS (70eV):180(M^+,10.0), 150(11.7), 149(base)

^{1}HNMR (250MHz) δ :7.17(d,J=1.7Hz,1H), 6.12(d,J=1.7Hz,1H), 3.79 d,J=11.1Hz,1H), 3.58(d,J=11.1Hz,1H), 2.47 (m,2H), 1.96-1.31(br m,6H), 1.22(s,3H)

^{13}CNMR (69.8MHz) δ :155.6, 141.1, 113.9, 109.8, 76.6, 37.7, 28.0, 25.7, 21.3, 19.0

Fractions 9-12 provided 52mg, 52% of a mixture of allylic alcohols.

^{1}HNMR (250MHz) :7.28(t,J=2Hz,2H), 7.16(s,2H), 6.18(s,2H), 4.96(s,1H), 4.80(s,1H), 3.90(br s, 1H),

3,80(t,J=6Hz,2H), 3.38(m,4H), 2.28(m,4H),
2.10-108(m,6H)

3-β-hydroxy-pallesencin-A (51) - To a solution of 2.6-dimethyl-9-(3-furyl)-2,6 nonadiene-oxide-2 (0.20g, 0.85 mmole, prepared according to procedure of S.P. Tanis) in methylene chloride (10ml) cooled to 0°C was added stock titanium catalyst (3.4ml, 2.55 mmole, 0.75M in methylene chloride). The mixture was allowed to stir at 0°C for 1 hour and then at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture cast into saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 1N aqueous hydrochloric acid (50ml), water (50ml), brine (50ml), dried (Na_2SO_4) and concentrated in vacuo to yield a yellow liquid. The crude product was purified on a column of silica gel (230-400 mesh, 70g, 50mm o.d., ether-pet. ether 1:3, 25 ml fractions) using the flash technique, fractions 16-19 provided 0.118g, 59% of 51 as a white solid. m.p. 120-122°C (lit. m.p.[30]=122-122.5°C)
EI/MS (70eV):234(M^+,46.6), 219(82), 201(base)
^{1}HNMR (250MHz) δ :7.13(d,J=1.6Hz,1H), 6.02(d,J=1.6Hz,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)
IR(neat): 3490, 2900, 1500, 1450, 1370, 1200, 1080, 1020cm^{-1}

Attempted cylization of 19 with triisopropoxytitanium chloride - To a solution of 2-methyl-4-(3-furyl)-2-epoxybutene, 19, (0.10g, 0.66 mmole) in methylene chloride (10ml) cooled to 0°C in an ice-water bath was added triisopropoxytitanium chloride (2.40ml, 1.8 mmole, 0.75M in methylene chloride). The mixture was allowed to stir at 0°C for 1 hour and then at room temperature for 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture was cast into saturated aqueous NH_4Cl(40ml) and ether (40ml). The organic phase was separated and washed with 1N hydrochloric acid (50ml), water (50ml), brine (50ml), dried (Na_2SO_4), and concentrated in vacuo to provide a light yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40g, 30mm o.d., ether-pet. ether 1:1, 10ml fractions) using the flash technique. Fractions 10-14 provided 80mg, 80% of a mixture of allylic alcohols.

^{1}HNMR (250MHz) δ :7.34(t,J=3Hz,2H), 7.24(s,2H), 6.28(s,2H), 4.90(s,1H), 4.79(s,1H), 3.60(d,J=6Hz,2H), 2,48(m,4H), 1.53(s,3H), 1.48(s,3H).

Attempted cyclization of 20 with triisopropoxytitanium chloride - To a solution of 2-methyl-4-(3-furyl)-1-epoxybutene, 20, (0.10g, 0.66 mmole) in methylene chloride (10ml) cooled to 0°C in an ice-water bath was added triisopropoxytitanium chloride (2.40ml, 1.8 mmole, 0.75M in methylene chloride). The mixture was allowed to stir at 0°C for 1 hour and then at room temperature for 3 hours. The reaction was

quenched by the addition of saturated aqueous NH_4Cl (10ml) and the resulting two phase mixture was cast into saturated aqueous NH_4Cl (50ml) and ether (50ml). The organic phase was separated and washed with 1N hydrochloric acid (50ml, water (50ml), brine (50ml), 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, 40g, 30mm o.d., ether pet-ether 1:1, 10ml fractions) using the flash technique. Fractions 9-12 provided 0.072g, 72%, of a mixture of allylic alcohols.

^{1}HNMR (60MHz) δ :7.26(t,J=2Hz,2H), 7.18(M,2H), 5.48(t,J=8Hz,1H), 4.94(s,1H), 4.83(s,1H), 4.0(br s,2H), 3.49 (s,2H), 3.12(d,J=6Hz,4H), 2.40(m,8H), 1.86 (2,3H), 1.63)s,3H).

2-(3-furyl)-ethyl-tri-(n-butyl) stannane 53 - To activated magnesium turnings (0.243g, 0.01 mmole) covered by THF (15ml) was added (3-furyl) chloromethane (1.16g, 0.01 mole) and the mixture allowed to stir at room temperature until all the magnesium had reacted (about 1 hour). The resulting golden liquid was cooled to 0°C in an ice-water bath and iodomethyl-tributyl stannane[22] (3.23g, 7.5 mmole) was added in one portion followed immediately by Li_2CuCl_4 (0.2ml, 0.1M in THF). The reaction mixture immediately became solid. The mixture was diluted with saturated aqueous NH_4Cl (100ml) and cast into pentane (100ml). The organic phase was washed with water (100ml), brine (100ml), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. Distillation gave 2.65g, 92%, of 53 as a pale

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yellow liquid. B.P.$_{(0.5mm)}$=150°C.

EI/MS (70eV):384(M^+,1.2), 325(7.2), 329(30), 291(33), 235(34), 201(13), 177(95.5), 121(80), 81(62.39), 41(base)

^{1}HNMR (250MHz)δ :7.24(m,1H), 7.18(m,1H), 6.23(s,1H), 2.8-2.4(m,2H), 2.0-0.7(m,29H)

IR(neat): 3000, 2960, 2890, 1500, 1470, 1380, 1175, 1070, 1035, 880, 780cm^{-1}

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