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FURAN TERMINTED N-ACYLIMINIUM ION CYCLIZATIONS IN THE SYNTHESIS OF FUSED-, SPIROCYCLIC-, AND BRIDGED-RING CONTAINING ALKALOIDS

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BY

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ABSTRACT

FURAN TERMINATED N-ACYLIMINIUM ION CYCLIZATIONS IN THE SYNTHESIS OF FUSED-, SPIROCYCLIC-, AND BRIDGED- RING CONTAINING ALKALOIDS

BY

LISA ANN DIXON

In an ongoing investigation of furans as terminators in cationic cyclization, we have examined the use of N-acyliminium ions as the initiators. This approach has proven to be successful in the preparation of the linearly fused, bridged, and spirocyclic ring systems present in many alkaloids.

We had hoped to utilize furans in both the cyclization sequence, and as resident functionality to facilitate completion of chosen natural product syntheses. Several questions had to be addressed during this study: 1) could the required furan containing cyclization precursors be prepared, 2) would the furans withstand the cyclization conditions, 3) would both the 2- to 3-furyl mode of closure as well as the relatively more reactive 3- to 2 furyl closure be viable processes, 4) could the furans be manipulated to provide useful synthetic intermediates, and 5) could the intermediates be transformed into the targeted alkaloids.

Studies directed towards answering these questions will be presented. To summarize we will describe the successful preparation of 5,6 and 6,6 linearly fused ring systems through the 2- to 3- furyl closure, and 5,6; 6,6; 5,7; and 6,7 linearly fused ring systems through the 3- to 2- furyl closure. The 6,6 fused

system (2- to 3- furyl closure) has been employed in a total synthesis of (+/-)-epi-lupinine. The spiropiperidine ring system present in histrionicotoxin and perhydrohistrionicotoxin has been prepared, and applied to a formal total synthesis of the later. Finally, two bridged ring containing systems, the aza[3.2.1]bicyclooctane, present in cocaine and the aza[4.2.1]bicyclononane, present in anatoxin-a have been prepared.

DEDICATION

To Mom and Dad

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INTRODUCTION

INTRODUCTION

As part of a general program in furan chemistry , we have been examining furan terminated cyclizations as a method for the construction of linearly-fused, spirocyclic, and bridged-carbocyclic ring systems.[1] We have found that by using enones[1e], epoxides[1d], and allylic alcohols[1d] as cationic initiators, the above mentioned ring systems may be readily prepared (Figure 1). Our interest in developing substituted furans as bis-nucleophilic synthons in annulative processes stemmed from the variety of useful functional groups which might be realized from the relatively unreactive furyl nucleus (Figure 2). We have utilized this concept to accomplish a total synthesis of nakafuran-9[1d] and a formal total synthesis of (+/-)- and (+)-aphidicolin[1c]. Should a nitrogen containing initiator be employed, similar methodology might provide an entry into alkaloid natural products containing the ring systems mentioned above. Possible initiators include the iminium ion and the N-acyliminium ion (Figure 3).[2]

In choosing between these two initiators we need to consider several factors, including the relative reactivity and stability of the two moieties. There is very little quantitative data available concerning N-acyliminium vs iminium ions; nonetheless, it is possible to make some qualitative distinctions.

As would be expected, substitution of an acyl group on an iminium ion results in a more electron poor carbon. This was demonstrated by Wurthwein and coworkers using ^{13}C spectroscopy (Figure 4).[3] They observed a significant downfield shift when the nitrogen was substituted with an electron withdrawing

carbonyl group. The implication here is that the N-acyliminium ion would be more electrophilic and more reactive than the simple iminium ion. This prediction is borne out experimentally as Figure 5 demonstrates.[4] In this example an olefinic terminator, which is a relatively unreactive nucleophile, which is also quite hindered, succeeds in participating in the cyclization only when an N-acyliminium ion is used as the initiator. In general, iminium ions

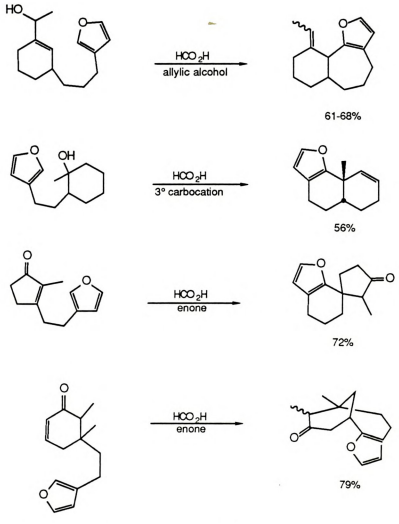


Figure 1: Some Representative Examples of Furan-Terminated Cationic Cyclizations

require either very reactive terminators or very strongly acidic conditions[5] to participate in cyclization sequences. There are exceptions, such as when a stable carbenium ion intermediate is formed upon termination.[6] N-acyliminium ions, on the other hand, rarely require extremely harsh conditions and need much less reactive terminators for successful cyclizations.[2]

Another rationale for the synthetic utility of N-acyliminium ions may lie in the types of products formed. After generation of either type of ion they are usually

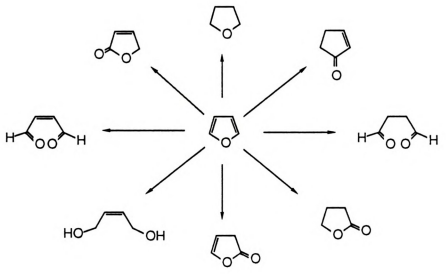


Figure 2: Furan Equivalencies

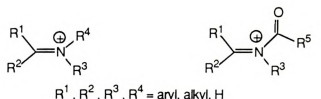


Figure 3: Iminium Ion and N-Acyl Iminium Ion

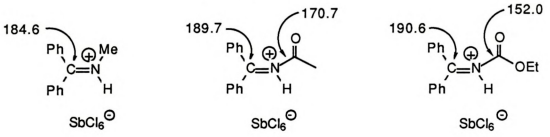


Figure 4: ^{13}C-NMR Data for Iminium Ions and N-Acyliminium Ions

trapped by a nucleophile. In the case of an iminium ion the product is an amine; in the case of an N-acyliminium ion the product is an amide. It is known that an amine is more reactive under a variety of reaction conditions.[7] Therefore, another advantage of N-acyliminium ions over iminium ions may be the production of a more stable product from the former over the latter. The efficacy of forming a more stable amide instead of an amine can be exploited while performing steps subsequent to the cyclization. An amine might be the ultimate target; however most workers choose to keep it masked as an amide, only exposing the free amine in the later stages of the synthesis.

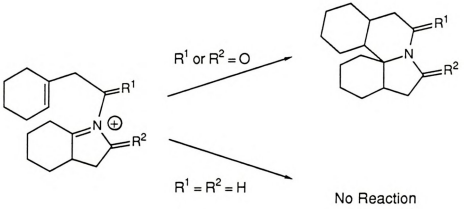
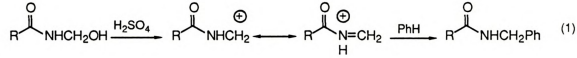


Figure 5: Cyclization of Acyliminium Ion vs N-Acyliminium ion

Upon evaluation of the points just discussed, the increased reactivity of an N-acyliminium ion, the milder conditions required for successful cyclization reactions, and procurement of a more stable product, it is not surprising that the N-acyliminium ion has become the initiator of choice in many syntheses. Since our terminator is relatively unreactive and is sensitive to Bronsted acidic conditions, we also chose to examine N-acyliminium ion in our furan terminated cyclizations.

N-acyliminium ions have been known since the early 1900's when the Tscherniac-Einhorn reaction (Eq. 1) was discovered.[8] They may be generated



(1)

in a number of ways as outlined in Figure 6.[2] The protonation of N-acylimines (Figure 6, path b) has seen limited use as the starting materials are not very stable.[9] N-acylation of imines [10] (Figure 6, path a) has some synthetic utility; the imine required can not often be isolated, but it can give rise to N-acyliminiun ion intermediates.[11] Enamides can in some instances be protonated to furnish N-acyliminiun ions (Figure 6, path c), however this reactions has limitations.[12] Amides will undergo electrochemical oxidation (Figure 6 path d), usually in the presence of methanol to give α-alkoxyamides.[13] As will be seen shortly, α-alkoxy amides are very efficient sources of N-acyliminiun ions.

Figure 6, path e describes the process most often used in synthetic sequences for generating N-acyliminium ions; the heterolysis of α-substituted amides. Usually the heteroatom to be solvolyzed is oxygen, but halogen,

nitrogen, sulfur or phosphorus have been used. When X=OH or)R, either Bronsted or Lewis acids can be employed to generate the N-acyliminium ion;[2] if R=OMs no acid catalysis is necessary.[14]

α-Alkoxy or α-hydroxy amides are, in turn, readily prepared from stable, often commercially available starting materials. The first method, the nucleophilic addition of amines to aldehydes or ketones (Eq. 2) requires use of very reactive carbonyl compounds or intramolecular addition.[2,15] The product hydroxy amide is often not isolated, but carried to an N-acyliminium ion intermediate directly. Equation 3 describes the reduction of N-acylimidates with $NaBH_4$ to provide α-alkoxy amides, which might suffer C-O bond heterolysis to generate the desired N-acyliminium ion.[16]

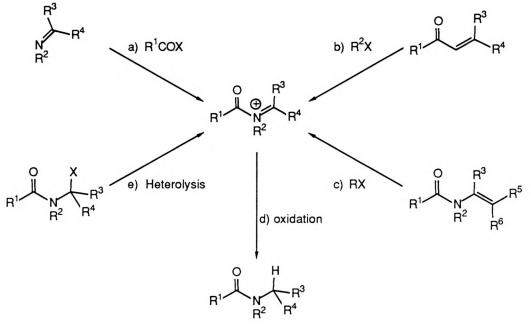
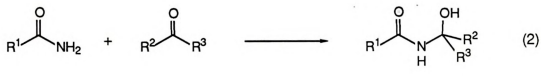


Figure 6: Precursors of N-Acyliminium Ions

Addition of some Grignard reagents to cyclic imides provides α-hydroxy amides in good yield (eq. 4, c,d).[17] If R'=H two equivalents of Grignard reagent are needed.



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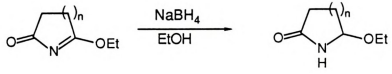
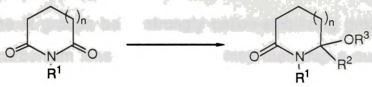


(3)

Possibly the most widely used route to α-alkoxy and α-hydroxy substituted amides is the partial reduction of cyclic imides. The pioneering work of Speckamp in the early seventies demonstrated that this was a viable method, and paved the way for the intense synthetic effort into N-acyliminium ion research over the last 15 years. Speckamp accomplished this feat by reducing either glutarimide or succinimide with $NaBH_4$ in ethanol in the presence of acid to provide α-ethoxylactams in good to excellent yields (Eq. 4b).[18] More recently Chamberlin has demonstrated that cyclic imides can successfully be reduced to α-hydroxy amides using $NaBH_4$ in methanol at low temperature (Eq. 4a).[14] He also reported that α-hydroxy lactams will form N-acyliminium ions, by solvolysis, in the presence of mesyl chloride and triethylamine, thus avoiding the use of acid catalysis. These last methods discussed, the heterolysis of α-substituted amides, account for an overwhelming majority of the approaches in which N-acyliminiun ions are in synthesis.



(4)

Entry	Conditions	R_1	R_2	R_3
a	$NaBH_4$, MeOH	alkyl	H	H
b	$NaBH_4$, ROH, H^+	alkyl	H	alkyl
c	R_2MgX	alkyl	alkyl	H
d	R_2MgX (2 eq.)	H	alkyl	H

We have described a number of routes for preparation of N-acyliminium ions but have not touched on some other facets of their use. Still to be discussed is the fate of an N-acyliminium ion: the types of terminators that have been employed in cyclizations and the types of ring systems available from this methodology. Specific issues to be considered are: 1) carbonolamides opening to ketoamides; 2) enamide formation/enamide dimerization; 3) regiochemical ambiguities in the termination step; 4) stereochemistry of the cyclization. A few examples highlighting these topics follow (vida supra).

Prior to Speckamp's discovery of the reduction of cyclic imides only a few stable terminators had been used in N-acyliminium ion cyclizations. Speckamp's methodology opened the door for experimentation with a variety of terminators, including olefins. Figure 7 outlines the proposed mechanism for an olefin terminated N-acylimnium ion initiated cyclization, proceeding from a carbinolamide ether, such as A. Treatment of α-alkoxy amide with acid leads to an N-acyliminium ion B which is in equilibrium with π complex D or C (D has also been depicted as a bridged carbenium ion D'). Complex C has a boat-like conformation and is consequently thought to be less favorable than the chair like conformation D. Attack of the terminating function on D will lead to either G or H depending of the ring size of the lactam and the nature of the R groups.

Should the R groups be a strongly cation-stabilizing group; B may provide discrete carbenium ions E or F which may then trap a nucleophile or lose a proton to form the products. If the terminator is aromatic, loss of a proton and rearomatization typically occurs.

The first problem Speckamp solved was inhibiting ring opening of the carbinol amide to a ketoamide which was susceptible to further reduction with $NaBH_4$ to yield an amide alcohol. He accomplished this by the careful addition of H_2SO_4 or HCl to the reaction medium during reduction to give the related α-alkoxyamides.[18] With a source of α-alkoxy-lactam assured, he then examined the crucial cyclization. Figure 8 outlines a few terminators and the ring systems first constructed.[19] Treatment of **1a** or **b** with formic acid for 72 hours provided, after capture with formate and hydrolysis, keto-amide **2a** in 97% (n=1) or **2b** in 88% (n=2). Compound **1c** under the same treatment for 18 hr provided formate **2c** (R=CHO) in nearly quantitative yield. This can be contrasted with the substituted olefin **1d** which cyclizes in formic acid (-5° C - RT)) immediately or under milder conditions (acetic acid) in 24 hr. The former conditions provide formate **2d** (R=COH); the latter condition acetate **2d** ($R=COCH_3$). It is interesting to note that with the exception of **2d**, extended periods of time in stronger acid (HCO_2H vs HOAc) were required to induce cyclization.

We see that six membered rings are generally favored, however there are examples in which either a mixture or mainly the 5-membered ring are obtained.[14,20] An elegant control method to avoid regiochemical ambiguities is to utilize the unique ability of either a silicon[21] or a sulfur[14,22] atom substituted terminator to direct the course of cyclization. Overman has used this methodology in the preparation of linearly fused systems;[21a] his results are outlined in equation 5. Reduction of imides **3a-c** with $NaBH_4$ and treatment of the carbinolamide with trifluoroacetic acid afforded cyclized products **4a-c**. By

using 1-bromo vinylsilane he is able to control the regiochemistry of the cyclization and also produce an olefin that is differentially substituted for further transformations.

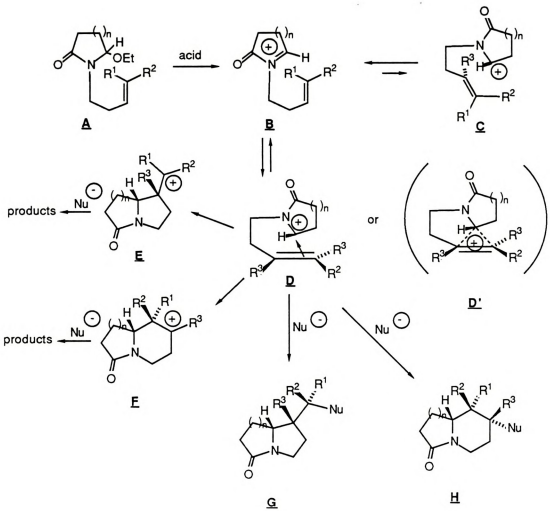
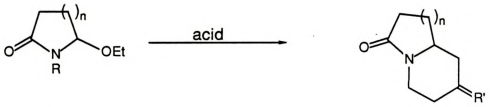


Figure 7: Cyclization of N-Substituted Cyclic Carbinol-Amides

N-acyliminium ion cyclizations can proceed not only with excellent regioselectivity, but, often with excellent stereoselectivity providing high yields

of single isomers[2c]. As shown in equation 6, the face of the lactam to be attacked can be determined by the size of the substituents on the lactam. Attack



1 **2**

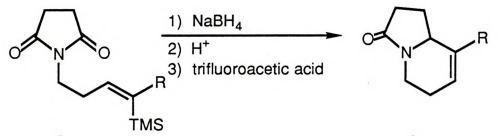
	n	R	R'	yield
2 a	1	$(CH_2)_2C{=}CH$	=O	97%
b	2	$(CH_2)_2C{=}CH$	=O	88%
c	1	$(CH_2)_2CH{=}CH_2$	H, OR	"100%"
d	1	$(CH_2)_2C(CH_3){=}CH_2$	CH_3, OR	"100%"

Figure 8: Some Preliminary Studies from the Laboratories of Speckamp

of formate from the equatorial position and cyclization gives a diasteroemeric mixture of **6** and **7** (2:1, ca. 100%) when R'=H (entry a), but only one isomer, **6**, (ca. 100%) when R'=Et (entry b).[23]

The final point to be discussed is enamide formation/dimerization. Enamides can be protonated to give N-acyliminium ions, which might cyclize; but if there are other problems with the cyclization such as unfavorable ring size or a terminator that is not sufficiently nucleophilic, enamides or enamide dimers may be the only products isolated. For example, in the cyclization of 8 if R=Me a 7-membered ring is formed in good yield however, if R= H then enamide formation and dimerization becomes competitive (Figure 9).[24] One might assume that the competitive dimerization process is sterically inhibited when

R=Me. Next, three synthesis which demonstrate the preparation of three 3 types of target ring systems will be presented. Only the critical N-acyliminium ion formation/termination steps will be outlined. These will be discussed individually with emphasis on the problems described above and on the relative merits of each terminator employed.



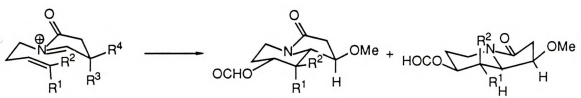
(5)

3 **4**

4 a n = 1, R = H, 92%

b n = 2, R = H, 91%

c n = 1, R= Br, 63%



5 **6** **7**

entry	R^1	R^2	6:7	% yield
a	H	H	2:1	ca. 100
b	Et	H	100:1	ca. 100

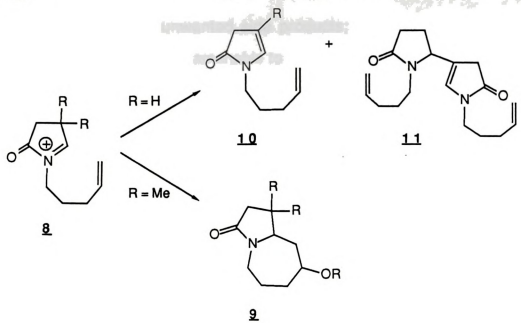
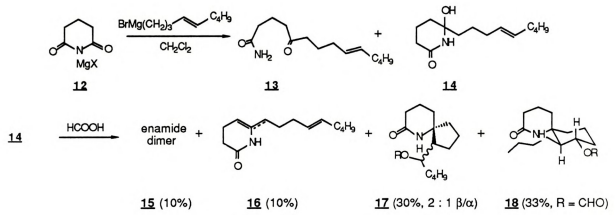


Figure 9: Cyclization vs. Enamide Dimerization

The first example is taken from the work of Evans who has used N-acyliminium ions to prepare spirocyclic alkaloids[25]. As described in Scheme 1 Evans utilized the addition of a Grignard reagent to a cyclic imide to generate his cyclization precursor. Thus, treatment of glutarimide in ether with MeMgI followed by addition of the Grignard reagent derived from 1-bromo-4-nonene provided both ketoamide **13** and carbinolamide **14** as a 1:1 mixture (61%). Evans later found that he could avoid ketoamide formation if the Grignard addition was performed in dichloromethane instead of ether. Having thus obtained mainly the carbinolamide **14**, it was subjected to HCO_2H (48 hr) to provide the desired spiro-cyclic compound **18** (33% yield from glutarimide) along with enamide dimer **15** (10%), enamide **16** (10%), 6,5-spirocycle **17** (20%) and epi-**17** (10%). As can be seen, this route is troubled by relatively low

yields, and formation of unwanted side products; however it does concisely construct a ring system that is amenable to transformation to

Scheme 1: Evans'[25] Approach to Spiropiperidine Preparation

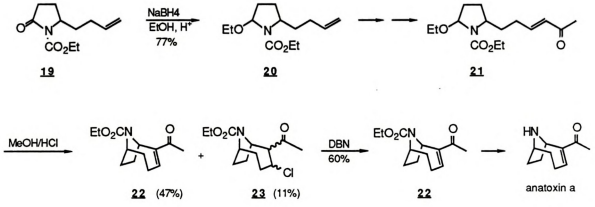


perhydrohistrionicotoxin. Another potential drawback is that the terminator is not very versatile, affording only a protected alcohol as residual functionality.

Speckamp's synthesis of anatoxin-a, published in 1986, will serve to demonstrate the preparation of a bridged ring system (Scheme 2).[26] Reduction of **19** ($NaBH_4$) in the presence of H_2SO_4 and EtOH provided **20** in 77% yield. Elaboration of the side chain to the required terminator afforded cyclization precursor **21** (83%). Treatment of **21** with HCl in MeOH at -50°C and gradual warming to room temperature over 18 hr resulted in a mixture of **22** and **23** in 47% and 11% yield respectively. The mixture was exposed to DBN to provide the enone **22** in 60% yield. This product was carried on to anatoxin-a. A unique feature of this synthesis is the directed closure to the α-carbon of an α,β−unsaturated carbonyl compound as the nucleophilic terminator.

It may be interesting to compare the synthesis anatoxin-a using acyliminium

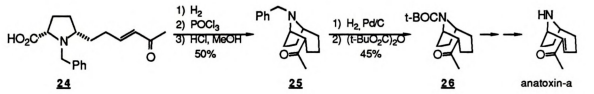
Scheme 2: Speckamp's[26] Synthesis of Anatoxin-a



ion technology to the Rapoport sequence described in Scheme 3.[27] Treatment of **24** with $POCl_3$ followed by HCl and MeOH did not produce the desired enone containing bridged product. However, treatment of ketone, derived from reduction of **24**, under the same conditions did result in closure, generating compound **25** in 50% yield. To facilitate completion of the synthesis the benzyl group was removed by hydrogenolysis and the amine was protected with di-t-butyl dicarbonate (45 %, 2 steps). In comparing the Rapoport and the Speckamp syntheses a few points deserve comment. Speckamp was able to use a terminator which incorporated the required double bond; and the N-acyliminium ion initiated cyclization resulted in a slightly better cyclization, and overall yield. Finally; this serves as an example of the utility of the N-acyl portion of the molecule serving as a protecting group both before and after a cyclization.

The final ring system to be considered is a linearly fused ring system drawn from the work of Chamberlin (Scheme 4).[14] Treatment of cyclic imides **27a-e** with $NaBH_4$ in MeOH at 0°C provided carbinolamides **28 a-e** which were not isolated but immediately treated with MsCl/TEA in CH_2Cl_2 to afford cyclized

Scheme 3: Rapoport's[27] Synthesis of Anatoxin-a



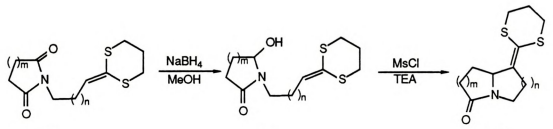
products, **29a-e**, in excellent yields. The advantages of using ketenedithioacetals as the terminating functions are: 1) a single regiochemistry was observed, and 2) the functionality remaining was useful for completing the desired synthesis.

It is known that a large variety of terminators, including olefins, alkynes, allenes, dienes, vinyl silanes, propargyl silanes, and allyl silanes, as well as aromatic, terminators such as phenyl, substituted phenyl, thiophene, indole,naphthalene, and imidazole can also be employed.[2] From these (vide supra) and other examples we can see that the requirements for a useful terminator are: 1) regiochemical predictability in the termination step; 2) that the terminator be sufficiently nucleophilic for the cyclization to take place under mild conditions, and 3) that the terminator residue provide useful functionality for completing the synthesis at hand.

Furans could complement the list of known terminators very nicely; provided they prove to be stable to the reaction conditions and are sufficiently nucleophilic. As a result of our experience with furans as terminators in cationic cyclizations we expect to observe the desired cyclization product without any regiochemical ambiguities. Secondly, the product furan, after certain well precedented manipulations (Figure 2), should provide a more highly

functionalized intermediate than many of the previously utilized terminators. Questions to be addressed in this study are: 1) can the required cyclization

Scheme 4: Chamberlin's[14] Construction of the Pyrrolizidine, Indolizidine, and Related Ring Systems



27 28 29

	m	n	%
a	1	1	86
b	1	2	70
c	2	1	71
d	2	2	79
e	1	3	48

precursors be readily prepared, 2) will these furan containing compounds withstand the conditions needed to generate N-acyliminium ions, 3) can we observe both the electronically preferred furan 3-2 closure as well as the 2-3 mode of closure, and 4) can the product furans be manipulated to form natural product targets.

Three modes of closure could conceivably be performed by using furan terminated N-acyliminium ion cyclizations. The proposed system consists of a cyclic initiator, a furan terminator, and a tethering unit to connect the two. Attachment of the tethering unit at different points on the initiating function will result in the three skeletal types described in Figure 10. Thus, attachment at the nitrogen of an imide derived N-acyliminium ion will provide a linearly fused system, such as in **A**. Likewise attachment at the carbon adjacent to the

nitrogen in a similar system, **B** will provide a spirocyclic system; and as in **C**, attachment at the α'-site of an N-acyl-lactam derived acyliminium ion will afford bridged systems as described in Figure 10, **C**. The length of the tethering unit will determine the size of the forming ring. Finally the furan may be appended to the tethering unit at either the indicated 2- or the 3-position.

Our previous work in the carbocyclic series can lend some insight as to how this endeavor may proceed. Six-membered rings have proven to be the easiest to prepare; five-membered rings have not been prepared under any conditions. We have constructed 7-membered rings via a furan terminated cyclization, but often in low yield. In terms of the skeletal types formed, linearly fused systems have generally been the easiest to form, followed by spiro-cycles and finally the bridged ring systems. A final critical observation is that the electronically more favorable 3 to 2 closure has been observed to be a more general mode of closure than the alternative furyl 2- to 3- cyclization.

The design of our substrates will be unique for each mode of closure (Figure 10). The preparation of linearly fused and spirocyclic ring type precursors, without the requisite furyl teminator, are precendented in the literature. A well established route to the systems needed for the linearly fused closure is found in addition of an electrophile containing the teminator to an imide, which later serves as the initiator (see Scheme 4). For the linearly fused systems we can envision employing this strategy by coupling a furyl containing tethering unit with the nucleophilic nitrogen of an imide. There is also a clear precendent for the preparation of a spirocyclic type precursor in the work of Evans (Scheme 1). Unlike the first two modes of closure there are several possible approaches to the design of the bridged ring forming precursors, these will be discused in more detail in later sections of this thesis.

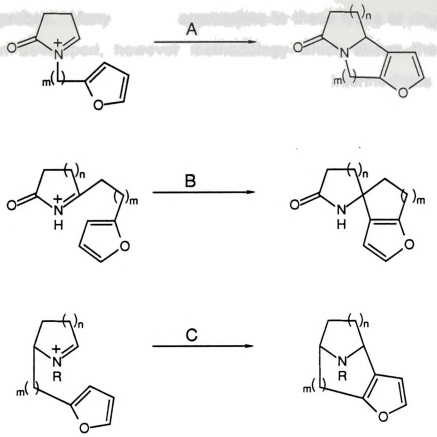


Figure 10: Basic Structural Possibilities for Furan Terminated N-Acyliminium Ion Initiated Cyclizations

Target Structures

The alkaloids present a large array of skeletal and structural types[28]. Among these are the linearly fused systems of lupinine (**31**)[14,29], and elaeokanine A[30] (**30**), the bridged alkaloids cocaine (**34**)[31] and anatoxin-a (**35**)[26,32], and the spirocyclic histrionicotoxin (**32**) and perhydrohistrionicotoxin (**33**) (Figure 11).[33] These alkaloids have been the target of intense synthetic interest because of their challenging structural features and because many of them display intense biological activities that has rendered them useful, among other things, as

biological probes. Many elegant approaches to these types of ring systems have been developed, however methodology which allows the concise preparation of a variety of ring systems from common intermediates is always desirable.

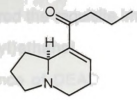
We have presented arguments which suggest the utility of furan terminated N-acyliminium ion cyclizations, for the construction of a variety of ring systems. We should have access to the linearly fused ring systems present in lupinine, the spiro-cyclic system of the histrionicotoxins, and the bridged ring systems of the type found in cocaine and anatoxin-a. Upon closer examination of these structures, it becomes clear that in order to obtain appropriately substituted, synthetically useful intermediates we will need to use the 2 to 3 closure mode. Assuming that we are able to observe these cyclizations, the furan will provide residues at positions in these alkaloids where functionality is needed. However these residues will need to be modified. Crucial to our synthetic strategy is that the furans be easily and selectively manipulated to form the desired natural products.

Linearly Fused Systems: Lupinine and Elaeokanine-A

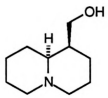
Initially we directed our efforts the relatively simple linearly fused indolizidine and quinolizidine alkaloid skeletal types. It was hoped that we could routinely access fused 5-6, 5-7, 6-6, and 6-7 membered ring systems using either the 2 to 3 cyclization mode or the relatively more reactive 3 to 2 closure mode. We anticipated preparing the required cyclization precursors by Mitsuobu coupling[34] of appropriately substituted furyl alcohols to either succinimide or glutarimide.[35] Subsequent $NaBH_4$ reduction should provide the desired N-acyliminium ion precursors.[14] The first sequence examined is outlined in Scheme 5. This study was designed to provide some insight on how readily the

furan precursors could be made, what cyclization conditions would be most ideal and how well the furyl moiety would survive the reaction conditions. Mitsunobu coupling of the readily available 3-(2-furyl)-1-propanol[36] to glutarimide provided **38d** in 53% yield. Reduction of the imide according to the procedure of Chamberlin ($NaBH_4$, MeOH, -4°C) afforded the corresponding carbinol amide in good yield (95%). Carbinol amide **39d** was then subjected to the cyclization conditions we had successfully employed in our sequences with allylic alcohols and enone initiators[1a,1c]. Exposure of **39d** to a two phase mixture of HCO_2H and cC_6H_{12} resulted only in the destruction of the starting material. This led to an extensive examination of alternative cyclization conditions to no avail. Submission of the carbinolamide to MsCl, TEA according to the procedure of Chamberlin[14] or to PPTs led to the corresponding enamide; THF/HOAc,THF or rexyn 300 led to destruction of starting material; with alumina as the acid catalyst some starting material was recovered but in overall poor mass balance. Derivitization of the carbinol amide as its acetate[36],and activation with ZnI_2[38] failed as well. We also attempted to cyclize the derived enamide, since some workers have reported success with this approach.[36e] We treated the enamide with HCO_2H-cC_6H_{12}, with $Hg(CO_2CF_3)_2$, and with NBS, and in each case observed destruction of the starting material with no trace of product detectible by NMR. Hart has accomplished cyclizations using N-acylimino radicals, derived from α-phenylthiolactams, as initiators.[35f] We were able to prepare the phenyl thio derivative corresponding to **39d**, but upon treatment with nBu_3SnH, and AIBN, we obtained only recovered starting material with overall poor mass balance.

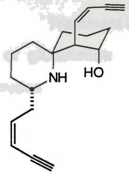
We had previously encountered such seven-membered, ring forming problems in the carbocylic series, and there have been reports of similar problems in the literature.[2] As discussed earlier, Speckamp has succeeded in



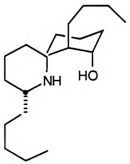
elaeokanine-A
30



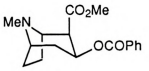
lupinine
31



histrionicotoxin
32



perhydrohistrionicotoxin
33



cocaine
34

anatoxin-a
35

Figure 11: Potential Alkaloid Targets

preparing seven membered rings only when the beta position of the carbinol amide is blocked with two alkyl substituents (Figure 9).[24] Based upon our previous experience, we did not expect to encounter such a bias in the electronically more favorable 3- to 2-furyl closure, or in the six membered ring forming reactions.[1] Investigation of this surmise was elegantly carried out by co-worker Jeffery Raggon.

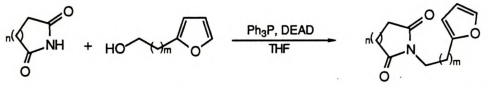
To examine the cyclization in the six membered ring forming sequences, we

prepared the requisite imides as described above (Scheme 5). Treatment of 2-(2-furyl)ethanol **37** (m=1)[38] with either succinimide or glutarimide in the presence of DEAD and Ph_3P provided N-substituted imides **38a** and **38b** in 31% and 51% yields, respectively, after chromatography. Reduction of 38a and 38b, according to the procedure of Chamberlin ($NaBH_4$, MeOH, -4°C)[14], provided the corresponding carbinolamides **39a** and **39b** in 88% and 95% yields, respectively. Exposure of **39a** to a two-phase mixture of anhydrous HCO_2H and c-C_6H_{12} for 2-3 minutes gave the desired indolizidine alkaloid precursor **40a** in 70% yield. The reaction time (2-3 min.) was found to be crucial as lengthening of this period (5-10min.) caused a substantial reduction in yield and a poor mass balance. The isolation of good yield of **40a** is noteworthy in that it is but our third example[1d,e] of the previously unknown and relatively disfavored 2-substituted -to-3-furyl cyclization. Similarly, carbinolamide **39b** afforded quinolizidine precursor **40b** in 71% yield after purification by chromatography. As might be expected, the remaining seven membered ring forming possibility represented by **40c** also failed to cyclize

We had yet to demonstrate that seven membered rings could be prepared. Therefore, we prepared the 3-substituted furan containing imides **42a** (100%), **42b** (100%), **42c** (41%), and **42d** (56%), from glutarimide or succinimide, and 2-(3-furyl)ethanol **41** (m=1)[39] or 3-(3-furyl)propanol **41** (m=2) and subjected these materials to the standard reduction and cyclization conditions (Scheme 6). The yields of product carbinolamides were uniformly high, and, to our delight, all of these substrates provided good yields (66%, 71%, 50%, 67%) of cyclized products **44a**, **b**, **c**,and **d** after brief treatment with HCO_2H/cC_6H_{12}.

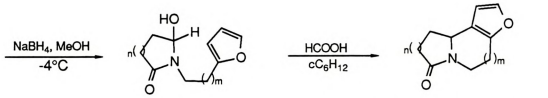
At this point we had answered the first two questions posed above (vide supra). We were able to prepare the required starting materials and show that the product furans were stable to the reaction conditions. Next we needed to

Scheme 5: An Approach to Linearly Fused Alkaloids



36 n	37 m
1,2	1,2

38	n	m	Yield (%)
a	1	1	31
b	2	1	69
c	1	2	51
d	2	2	53



39	n	m	Yield (%)
a	1	1	88
b	2	1	95
c	1	2	94
d	2	2	95

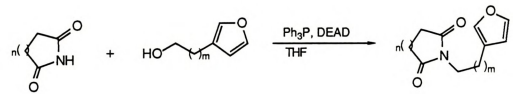
40	n	m	Yield (%)
a	1	1	70
b	2	1	71
c	1	2	0
d	2	2	0

demonstrate that the linearly fused ring systems prepared by this method provides intermediates that are useful in natural product synthesis. We chose the alkaloid lupinine as our first target.

Lupinine (**31**) is a quinolizidine alkaloid originally isolated from yellow lupine seeds (*Lupinus luteus.*) by Cassola in 1835.[41] It was obtained in pure form by Baumert in 1881[42], and posseses little biological activity.[28] Many routes to lupinine and and its more stable epimer epilupinine have been published.[29] It has been reported that if care is not taken to avoid epimerization epilupinine is the isomer that is most often isolated. One synthesis of epilupinine that has been mentioned previously is that of Chamberlin.[14] In this sequence (Scheme

7) the cyclized material **29** is deprotected with $HgCl_2$ in MeOH and aqueous $HClO_4$ to give the ester **46**. Treatment of **46** with LAH completes his synthesis

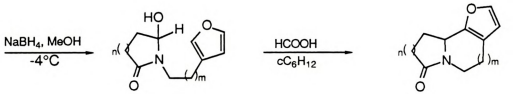
Scheme 6: Linearly Fused Furan 3- to 2- Closure



36 n
1, 2

41 m
1, 2

42	n	m	yield (%)
a	1	1	100
b	2	1	100
c	1	2	56
d	2	2	84



43	n	m
a	1	1
b	2	1
c	1	2
d	2	2

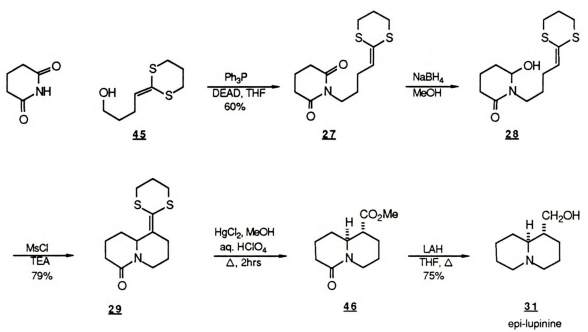
44	n	m	yield (%)
a	1	1	66
b	2	1	71
c	1	2	50
d	2	2	67

of epilupinine (epi-**31**, 75%, 2 steps).

A synthesis that employs an approach other than N-acyliminium ions is that of Tufariello described in Scheme 8.[29b] Tufariello utilizes a nitrone cycloaddition to prepare the 6-6 membered linearly fused ring system. When methanesulfonate **48** (prepared in 5 steps from 3-buten-1-ol) was exposed to 2,3,4,5-tetrahydropyridine-1-oxide in toluene at 0-5° C for 60 hrs., the salt **50**

was isolated in 74% yield. After reduction of **50** with Zn and acetic acid (80%) the product alcohol was dehydrated with $POCl_3$ in pyridine to give the unsaturated ester **52** in 75% yield. **52** has been carried on to lupinine (**31**) by reduction of the double bond with H_2/Pt_2O[40], then reduction of the lactam with LAH.[41] Alternatively ester **53** can be epimerized with NaOMe in MeOH and reduced with LAH to provide epilupinine (epi-**31**).

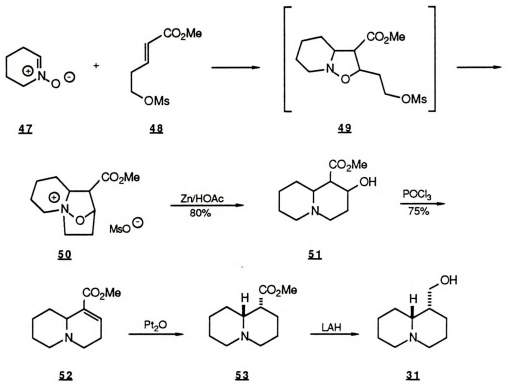
Scheme 7: Chamberlin's[14] Synthesis of (+/-)-epi-Lupinine



Having the methodology to form the 6-6-membered fused ring system, our next step toward a total synthesis is to transform the furan into the functional groups present in lupinine. Referring back to the structure of lupinine (**31**), we see that the furan provides an alkyl residue at an appropriate location on the 6-6 membered ring system and an oxygen residue that we need to remove; we

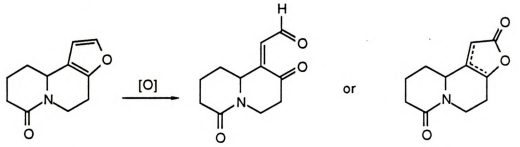
must also consider a C-C bond cleavage as furan **40b** possesses one more carbon than does our target.

Scheme 8: Tufariello's[29b] Synthesis of Lupinine



Towards this end the crucial oxidative cleavage of the 2,3-disubstituted furyl moiety was examined. Numerous methods for transforming a wide variety of variously substituted furans into their corresponding keto-enals (**54**) or butenolides (**55**) have been reported (eq. 7). Of these methods, we initially investigated oxidation with MCPBA in CH_2Cl_2 buffered with $NaHCO_3$[46] or unbuffered[42,43], the chromium VI-based reagents (PCC[44] and variants, such as 2-CNPCC[45]; and the more classical Clauson-Kaas oxidation, Br_2 in buffered

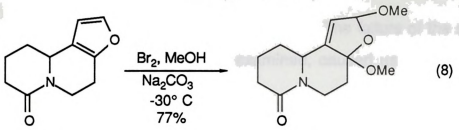
CH_3OH[46]), followed by **hydrolysis** of the intermediate α,α'-dimethoxy-dihydro **furan** derivative.[42,46c,47]



(7)

40b **54** **55**

In the event, the readily available quinolizidine precursor **40b** was subjected to the oxidation methods mentioned above. Thus, treatment of **40b** with MCPBA under a variety of reaction conditions (2.2 equiv., CH_2Cl_2, 0° C to reflux[42,43]; 2.2 equiv., $NaHCO_3$, 0° C to reflux[42]; 2.2 equiv,. NaOAc, HOAc) followed by reductive ($NaBH_4$) workup[48]; and finally, 2.2 equiv.MCPBA, CH_2Cl_2, 0° C to 25° C followed by trifluoroacetic acid (TFA) quench[42], led only to recovery of the starting material, or a number of unidentified products with overall poor mass-balance. Similarly ineffective in oxidizing the furyl residue of **40b** was PCC, CH_2Cl_2, 25° C to reflux and the more reactive 2-CNPCC, CH_2Cl_2, 25° C to reflux.[44] Clauson-Kaas oxidation (Br_2, Na_2CO_3, MeOH, -30° C) of the indolizidine precursor **40b** did provide the corresponding a,a"-dimethoxy-dihydro derivative in 77% yield[46] (eq. 8); however, we were unable to isolate the presumably formed keto-enal upon acid hydrolysis of the crude reaction mixture using a variety of known methods (i. 1% aqueous HOAc, Δ[47a]; or ii. 1N HCl, H_2O, 45° C[47a]; or iii. 2% aqueous H_2SO_4, 25° C).



(8)

40b **56**

Other methods that have been successfully employed in oxidizing related substituted furan systems, but which failed to oxidatively open the furyl residue in **40b**, were NBS, NaOAc, dioxane-H_2O, followed by $NaBH_4$ reduction[49] and $Ce^{IV}(NH_4)2(NO_3)_6$, H_2O-CH_3CN, 25° C[50]. We can safely conclude after this extensive examination of chemical oxidants that furan cleavages are non-standard operations which are extremely substrate dependent. Since all standard and even esoteric methods for oxidizing the furyl moiety of substrate **40b** proved fruitless, efforts were directed towards a photochemical means of achieving this necessary transformation. The use of photochemically generated singlet oxygen to oxidize variously mono- and di-substituted furans has received considerable attention over the years.[51] Treatment of **40b** with $^1O_2$, generated by bubbling oxygen through solution of substrate in CH_3OH or CH_2Cl_2 and either rose bengal[52], hematoporphrin[51] or tetrahydroporphrin[51,53], as sensitizers at 25° C using either a medium-pressure Hanovia lamp or a 500W Tungsten filament source, failed to provide any of the desired products and, in general, resulted in poor mass-recovery. Consequently, the temperature at which the photolysis mixtures were quenched with reducing agents, including $NaBH_4$ in MeOH or i-PrOH[54] and Ph_3P[52f,53b] was decreased. In these low-temperature photolyses, only recovered starting material was observed with no traces of oxidatively cleaved photoproducts,

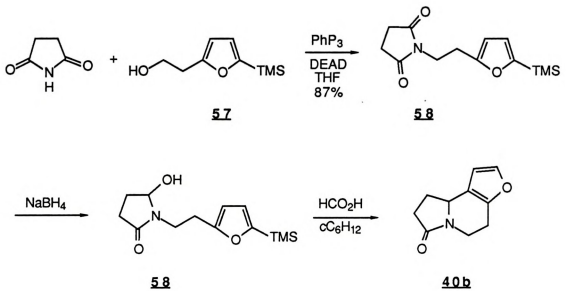
such as butenolides or keto-enals, detected (eq.7). The failure of the standard chemical and $^1O_2$ oxidations, thus far examined, caused us to consider the alternatives outlined below.

Based upon our previous experience in oxidizing furans[55] and the studies of others[53c,56], we elected to increase the nucleophilicity of the furyl moiety in the cyclized substrate **40b** by introducing a TMS group at the unsubstituted-α'-position. Following a procedure developed by German workers, who successfully silylated analogous pyrrole systems using Et_3N and TMSOTf at 5° C to 25° C[57], we exposed furan **40b** to TMSOTf and Et_3N. After a number of attempts, we failed to obtain any of the desired C-silylated furan. In fact, it appeared from a cursory examination of the EI-MS and ^{1}H-NMR (250MHz) spectra that the lactam moiety had been silylated; a surmise which was substantiated by treating the crude silylated mixtures with K_2CO_3 in MeOH leading to recovery of **40b**. Alternatively, the silyl group could be introduced intact on the furyl piece prior to the Mitsunobu coupling reaction as is outlined in Scheme 9.

The coupling of 2-(5-trimethylsilyl-2-furyl) ethanol **57**[58] with succinimide using the Mitsunobu procedure (DEAD, Ph_3P)[34] provided imide **58** in 87% yield after chromatography. Reduction ($NaBH_4$, MeOH, -4° C)[14] yielded cyclization precursor **59** in quantitative crude yield. Attempted cyclization of carbinolamide **59** using a variety of conditions (e.g., i. HCO_2H, cC_6H_{12}; ii. 1N HCl, CH_2Cl_2; MsCl, Et_3N, -23°C to 25°C) gave only desilylated cyclized material **40b**.

We had encountered similar difficulties in furan elaboration during our formal total synthesis of (+/-)-aphidicolin. That problem of furan oxidation was overcome by transforming the substrate 2,3-disubstituted furan to a 2,3,5-trisubstituted furan; oxidative cleavage of the substance was then smoothly

Scheme 9: The Examination of a Silyl Furan as a Terminator



57 **58** **58** **40b**

accomplished[1c]. Because of our concern for the survival of this system under the strongly basic conditions required to introduce a CH_3- onto the cyclized **40b**, we elected to employ the strategy depicted in Scheme 10 and utilize a furyl piece with the requisite group already in place.

Therefore, the required imides, **62a** (n=1, 83%) and **62b** (n=2, 55%), were prepared from succinimide (n=1) or glutarimide (n=2) and 2-(5-methyl-2-furyl) ethanol **60**.[59] Reduction provided crude carbinolamides **62a** and **62b** in quantitative yields. Subjecting these two substrates to the standard cyclization condition (HCO_2H, cC_6H_{12}, 2 to 3 min.) afforded diones **63a** (n=1) and **63b** (n=2) in 35% and 64% yields, respectively, as mixtures of epimers. This observation is unique in that the spontaneous hydrolysis of the putative furan intermediate is essentially unprecedented. Our experience in the parent systems and in a related perhydrohistrionicotoxin spirocyclization[1d,e], which will be discussed later, suggests that the serendipitious hydrolysis might result from the presence of an sp^2-hybridized nitrogen in the forming cycle and

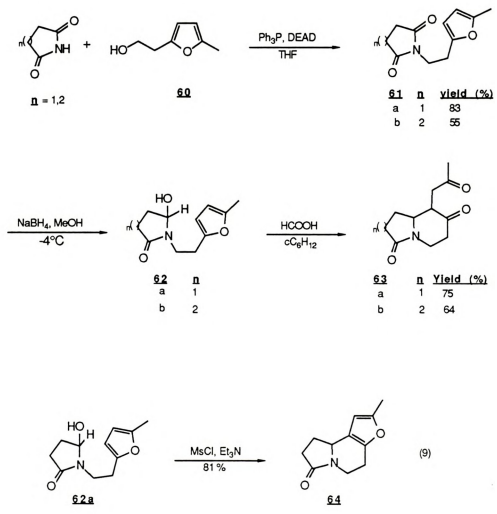
perhaps might be related to torsional[60] and or allylic strain[61]. We can demonstrate (eq. 9) that there is nothing intrisically wrong with the furan intermediate by submitting **62a** to Chamberlins' solvolytic conditions (MsCl, TEA) to give **64** in 81% yield. When **64** is dissolved in cC_6H_{12} and HCO_2H containing 1 eq. of water, we obtain the previously observed dione **63a** in 62% yield.

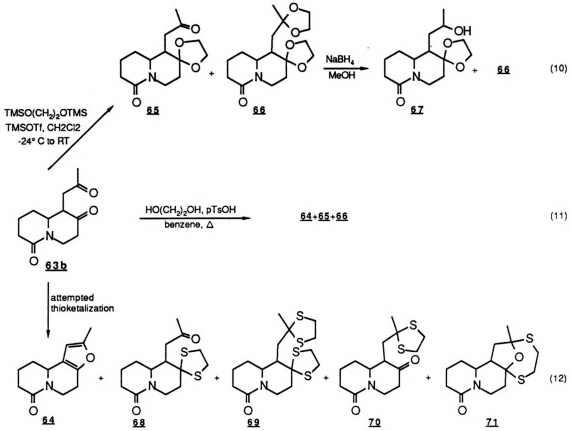
With quinolizidine **63b** in hand, we next examined its conversion to the relatively simple naturally occurring alkaloid lupinine **31** (or epi-lupinine). To complete a synthesis of lupinine we needed to reductively remove the lactam and the "ring" carbonyls, and transform the "side chain" into a methanol residue. We chose to leave the lactam carbonyl intact until the latest possible step to avoid exposing the amine to harsh reaction conditions. One problem that is immediately obvious is distinguishing between the two ketone functions. The ability to selectively protect one of the ketones and perform manipulations on the other unprotected ketone is crucial to the successful completion of the synthesis.

We began our investigation by examining various ketalization conditions. It was found that submission of **63b** to a modification of Noyori's kinetic ketalization conditions (excess $TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, -78° to RT)[62] provided a mixture of the ring ketal **65** and the bis-ketal **66** (10:1 to 1:1, 78-88%). The predominant formation of the ring ketalized material **65** was demonstrated when the reaction mixture was submitted to $NaBH_4$ reduction. Two products, that were easily separable by column chromatography, were obtained. The ^{1}H-NMR (250MHz) spectrum of the major product ketal-alcohol (lower R_f by tlc) revealed that the methyl singlet of the starting material, now appeared as a pair of doublets, indicating that the major product under these conditions was hydroxy ketal **67**, prepared as a mixture of stereochemistries at

the carbinol center. **Examination of** the ^{1}H-NMR (250MHz) spectrum of the minor product indicated that the singlet corresponding to the methyl group had migrated upfield relative to the starting dione, **63b**. This observation would be consistent with bis-ketal structure **66**. Our presumption was substantiated by EI-MS. We found that by carefully limiting the amount of $TMSOCH_2CH_2OTMS$ employed in the reaction (one equivalent) that we could prepare **65** almost exclusively (>98:<2, 93%)

Scheme 10: Second Generation Approach to Lupinine and Indolizidine Alkaloids





Exposure of **63b** to the "standard" ketalization conditions ($HOCH_2CH_2OH$, TsOH, PhH, Δ)[63] afforded a mixture of **64**, **65**, **66** (eq. 11). Knowing that the ring oxo-ketal was readily available we surmised that if we could prepare the ring thioketal (**68**) in an analogous manner, and if that thioketal could be reductively removed with Raney nickel[64] we would be in a position to complete the synthesis by Baeyer-Villager oxidation,[65] followed by treatment of the derived acetate with LAH[14].

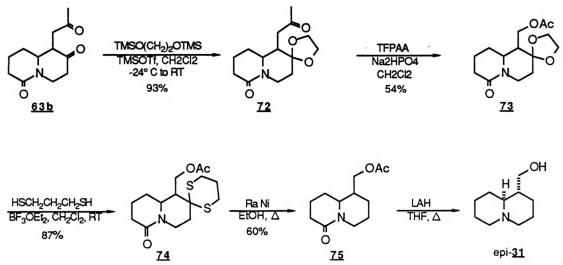
Treatment of dione **63b** under thermodynamic thioketalization conditions (i. $HSCH_2CH_2CH_2SH$, pTsOH, refluxing benzene ii. $HSCH_2CH_2SH$, pTsOH,

refluxing benzene)[66] led to furan **64**. Noyori's kinetic ketalization procedure ($TMSSCH_2CH_2STMS$, TMSOTf, CH_2Cl_2,)[62,67] provided an inseparable mixture of products. Elucidation of the structures was not possible by examination of the NMR. An examination of the ^{1}H-NMR (250MHz) spectra of both crude and chromatographed material indicated the presence of a methyl group adjacent to a carbonyl group and a methyl group adjacent to a ketal. Possible products include furan **64**, ring ketal **68**, bisketal **69**, side chain ketal **70** or bicyclic ketal **71**. We attempted to modify the reaction conditions to provide the desired ring thioketal **68** to no avail. Thus exposure of dione **63b** to various thioketalization conditions resulted in either the formation of furan **64** (i. $HSCH_2CH_2SH$, BF_3-OEt, CH_2Cl_2[29c]; ii. $TMSSCH_2CH_2STMS$, ZnI_2, CH_2Cl_2[67]; iii. $HSCH_2CH_2SH$, Nafion, benzene[68]), a mixture of products (i. $TMSSCH_2CH_2STMS$, TMSOTf, CH_2Cl_2[62]; ii. $TMSSCH_2CH_2CH_2STMS$, TMSOTf, CH_2Cl_2[66]; iii. $HSCH_2CH_2SH$, polystyryl catalyst, CH_3CN[69]; iv. $HSCH_2CH_2CH_2SH$, polystyryl catalyst, CH_3CN[69]; v. $TMSSCH_2CH_2STMS$, ZnOTf, CH_2Cl_2[70]; vi. $TMSSCH_2CH_2STMS$,$ZnCl_2$, CH_2Cl_2), or recovered starting material (i. t-BuSH, TMSCl, CH_2Cl_2[71]; ii. $TMSSCH_2CH_2STMS$, $MgBr_2$, CH_2Cl_2; iii. $TMSSCH_2CH_2STMS$, Mg-OEt_2, CH_2Cl_2, iv. 2-phenyl-1,3,2-dithiaborolane, $SHCH_2CH_2SH$, $CHCl_3$[72]).

In view of these problems, and our success with preparing oxo-ketal **65**, we elected to examine the route outlined in Scheme 11. Baeyer-Villager oxidation[65] of the ring oxoketal should provide acetate **73**, which might be transketalized to thioketal **74**. Raney nickel reduction, and treatment with LAH should provide either (+/-)-lupinine or (+/-)- epi-lupinine

In the event, Baeyer-Villager oxidation of **72**, using freshly prepared trifluoroperacetic acid in CH_2Cl_2 buffered with anhydrous Na_2HPO_4[65b], provided the acetate **73** in 54%

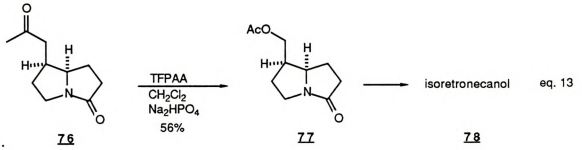
Scheme 11: Synthesis of (+/-)-epi-Lupinine



yield. In an attempt to improve the yield of this step, other oxidative conditions were examined. More mild conditions provided only recovered starting material (i. TMSOOTMS[65d]; ii. permaleic acid[65k]; iii. MCPBA), while more harsh conditions using Lewis acid catalysts (BF_3OEt, H_2O_2[65e]) resulted in deprotection of the ring ketal and a variety of products. This seems to be a problem inherent in the system, since conditions that will promote the Baeyer-Villager oxidation will also promote deprotection of the oxoketal. However, a recent report by Hart suggests that, even with a methylene unit in place of the oxoketal, the yield may not be significantly improved[73]. Equation 13 illustrates the Hart example.

Continuing the synthesis as outlined in Scheme 11, transketalization of the oxoketal **73** to the thioketal **74** ($HSCH_2CH_2CH_2SH$, BF_3OEt, CH_2Cl_2) proceeded in 87% yield.[74] Reductive removal of the thioketal (Raney nickel,

EtOH)[70] provided the acetate **75** in 60% yield. Treatment of **75** with LAH led to a compound (nearly quantitative crude) whose spectral data was similar to the published values for (+/-)-epilupinine.[14] Believing that we have successfully accomplished the preparation of a linearly fused alkaloid via furan terminated cyclization, we have demonstrated that the furyl residue left after cyclization provides a convenient "handle" for completing alkaloid syntheses.



76 **77** **78**

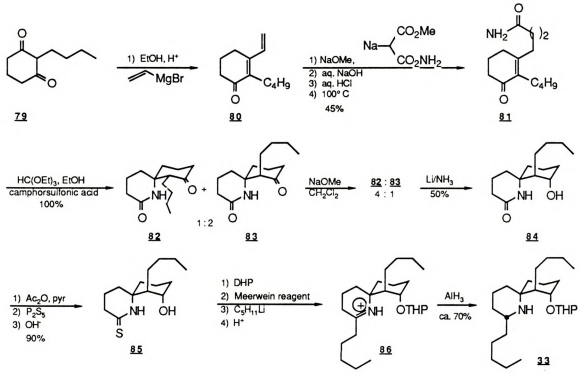
Spiro-Cyclic Alkaloids: A Formal Total Synthesis of (+/-)-Perhydrohistrionicotoxin

The tropical "arrow poison frogs" of the genera Dendrobates have yielded a host of structurally unique alkaloids.[75,76] The C-19 alkaloid histrionicotoxin **32** and its non-natural hydrogenation product perhydrohistrionicotoxin **33**, which possess a novel azaspiro[5.5]undecane ring system have been the target of intense synthetic interest for over ten years.[77,33] The attention directed toward **32** and **33** is due to their unusual structures, their potent biological activities, and their low natural abundance (ca. 200 μg HTX per frog); both alkaloids block post-synaptic membrane depolarization.[78] The realization that the structurally more simple perhydrohistrionicotoxin possesses nearly the same biological activity as histrionicotoxin has led to the former being a common target for synthesis.

Recently Kishi culminated nearly a decade of effort with the first total synthesis of (+/-)-histrionicotoxin itself[79]; however **34** remains a target of interest. Kishi's total synthesis of **33** has established that lactam **83** is a useful precursor to perhydrohistrionicotoxin (Scheme 12)[33c,d].

Kishi treated 2-butyl-1,3-cyclohexandione (**79**, available in 2 steps from methyl 4-(chloro-formyl)butyrate) with acidic ethanol followed by vinyl magnesium bromide to provide **80**. Compound **80** was subjected to i. NaOMe, $NH_2COCH_2CO_2Et$; ii. aqueous NaOH; iii. aqueous HCl; iv. 100° C, dioxane to afford **81** in 45% overall yield. Intramolecular Michael addition provided the two epimers (**82**:**83**) in a 1:2 ratio (100%).

Scheme 12: Kishi's Synthesis[33c,d] of (+/-)-Perhydrohistrionicotoxin



Epimerization of the mixture with NaOMe in MeOH afforded a 4:1 ratio of 82 and **83** which were reduced with Li/NH_3 to provide the desired orientation of the hydroxyl group (**84**, 50%). Formation of the thiolactam (1) Ac_2O, pyr; 2) P_2S_5; 3) ^-OH, 90%) **85** followed by preparation of the imine (1. Meerwein's reagent; 2. $CH_3(CH_2)_4Li$) afforded **86**. Reduction of the imine with AlH_3 (70%) completed the synthesis of perhydrohistrionicotoxin.

Evan's approach to perhydrohistrionicotoxin using an N-acyliminium ion cyclization was discussed previously (Scheme 1).[33e] We can see that the with the preparation of cyclized compound **18** all that remains to complete a synthesis of perhydrohistrionicotoxin is attachment of the 5-carbon side chain. Evans accomplished this in a manner analogous to Kishi's approach. While Evans cyclization product is functionalized very well for a synthesis of perhydrohistrionicotoxin, his approach would not be amenable to a synthesis of histrionicotoxin itself.

As is outlined in Figure 12, furan terminated N-acyliminium ion cyclization of **89** should provide the spiropiperidine **88**. Furan elaboration could conceivably furnish an intermediate which might be utilized in the synthesis of either histrionicotoxin or perhydrohistrionicotoxin. The aldehyde could provide a "handle" for attachment of the eneyne side chain of histrionicotoxin, while addition of a two carbon fragment at the position of the aldehyde should afford Kishi's perhydrohistrionicotoxin intermediate **83.**

Our first attempt to construct spirolactam **88** is described in Scheme 14. Reaction of glutarimide with CH_3MgI followed by the Grignard reagent prepared from 3-(2-furyl)-1-bromopropane[80], by the procedure of Evans[33e], afforded the carbinolamide **89** in quantitative crude yield. Without purification **89** was immediately exposed to the two-phase mixture HCO_2H-cC_6H_{12} (3 minutes) which provided spiropiperidine **88** in 55% chromatographed yield.

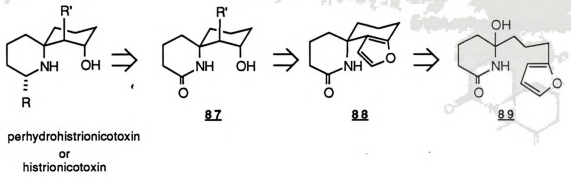
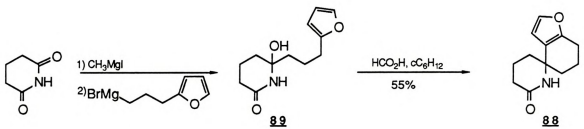


Figure 12: A Possible Approach to (+/-)-Perhydrohistrionicotoxin

Scheme 13: First Generation Spiropiperidine Construction



With the desired cyclization substrate in hand we initially turned our attention to the preparation of perhydrohistrionicotoxin. As outlined in Figure 13 we envisioned oxidative cleavage of the furan, followed by reduction of the unwanted double bond. Alternatively hydrolytic cleavage of **88** should provide keto-aldehyde **91** directly.

We subjected **88** to a variety of oxidative and hydrolytic conditions to no avail. We observed either no reaction or we obtained unacceptably low yields and mass balances. For example, MCPBA under a variety of conditions (0.9 - 2 equivalents in CH_2Cl_2 at 0°C to reflux[42,43]; 0.9 - 2 equivalents in a two phase mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$[42]; 2.7 equivalents, NaOAc and HOAc[48b]; 1 equivalent, followed by

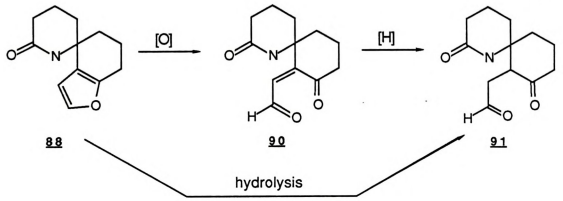
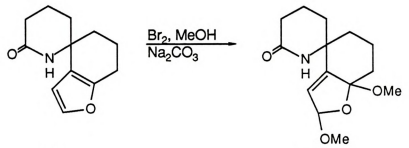


Figure 13: Possible Furan Elaboration Protocol

addition of $NaBH_4$[48]; 1 equivalent followed by addition of CF_2CO_2H) led only to recovery of starting material or a number of unidentifiable products with overall poor mass balance.

Similarly ineffective in oxidizing the furyl residue in **88** were a variety of oxidation conditions such as PCC[44], CNPCC[45] and CAN[50]; Br_2, pyridine, acetone, H_2O; NaOAc, AcOH, MCPBA, Me_2S[48b]; NBS in dioxane and H_2O provided a complex reaction mixture in which an aldehyde proton was observed by ^{1}H-NMR (250MHz), however it could not be recovered in good yield.[49] Clauson-Kaas oxidation of **88** (eq. 15) did provide the α,α'-dimethoxy-dihydro derivative in 86% yield; however, we were unable to cleanly hydrolyze this intermediate to the desired keto-enal under a variety of known methods (i. H_2O at reflux[81]; ii) dowex resin[82]; iii) 0.7N HCl in THF; iv) $HOCH_2CH_2OH$, benzene, pTsOH[83]; v) 0.005M H_2SO_4[84]; vi) THF, H_2O, CF_3CO_2H; vii) 1% HOAc in H_2O[47a]; viii) 2% H_2SO_4[47c,85]; iv) ppts, THF, H_2O). Attempted hydrolysis of **88** itself ($HOCH_2CH_2OH$, TsOH[83]; HCl, MeOH[86]) led only to recovered starting material. As had been described

during our adventures leading to lupinine, a furan unravelling sequence assisted by Si or a halogen might be considered. These substrates might obviate our oxidation problems; therefore, the 5-bromo derivative of **88** was prepared (NBS, DMF, 68%)[87], but it could not be oxidized with PCC[44d]. We attempted the preparation of the 5-silyl derivative of **88** by silylating the furan



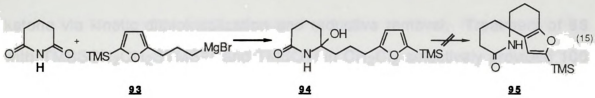
(14)

88 **92**

according to a published procedure which successfully silylated pyrroles with Et_3N and TMSOTf[57]. Unfortunately, as is the lupinine synthesis submission of **88** to these conditions did not result in silylation of the furan, but apparently silylation of the lactam.

The silyl furan could conceivably be brought in intact, by using 1-bromo-3-(2-furyl)-5-silylpropane[80] in the Grignard coupling, as outlined in equation 15. This proved to be the case as coupling of **93** to glutarimide according to the procedure of Evans provided **94** in nearly quantitative crude yield. Submission of **94** to the usual cyclization conditions led to loss of silicon and a variety of products.

We have already encountered numerous and described problems in oxidizing furans; alternatively we have also had difficulties in keeping the furan intact (*vide supra*). To summarize, we have observed that trisubstituted furans



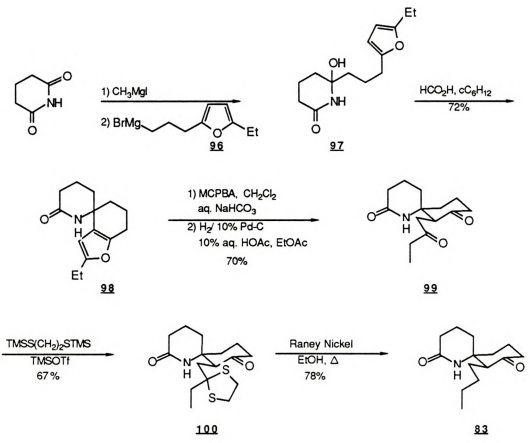
93 **94** **95**

are much more susceptible to either oxidative or hydrolytic cleavage. With these precedents in mind, we elected to incorporate the needed two carbon unit into the starting furyl organometallic compound; hopefully obviating the furan manipulation difficulties encountered previously. A successful formal total synthesis of (+/-)-**33** employing this modification is outlined in Scheme 14. In the event, treatment of the N-MgI salt of glutarimide with the Grignard reagent prepared form 1-bromo-3-(5-ethyl-2-furyl)propane[80] gave the corresponding carbinolamide **97** in excellent crude yield[33e]. Without purification **97** was cyclized as described above (HCO_2H, cC_6H_{12}) affording spiro-piperidine **98** (72%) with the furan intact. The furan contained in **98** did indeed suffer smooth oxidative cleavage (MCPBA, CH_2Cl_2, saturated aqueous $NaHCO_3$) yielding **99** (70%) after reduction (H_2-Pd/C; EtOAc-aqueous HOAc) of the rather unstable ene-dione. The side chain and ring ketone carbonyl moieties must now be differentiated, and the unwanted side chain oxygen removed.

Toward that end we exposed dione **99** to thermodynamic ethylene ketal forming conditions ($HOCH_2CH_2OH$, pTsOH, PhH, reflux) and to the kinetic ketalization conditions of Noyori ($TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, -78°C to RT)[63]. Under "thermodynamic" conditions **99** was cleanly converted to the starting furan **98** (90%); however the "kinetic conditions" of Noyori led almost exclusively to "side chain" ketal. (>95:<5, 55%). Having realized selectivity in carbonyl protection we investigated removing the "side chain"

ketone via kinetic dithioketalization and reductive removal. Treatment of **99** with $TMSSCH_2CH_2STMS$[67] and TMSOTf in CH_2Cl_2 selectively provided **100** (>98:<2) in 67% chromatographed yield. Attempts to improve this yield were unsuccessful, some conditions examined included (i. thionyl chloride, silica gel, $HSCH_2CH_2SH$, toluene[88]; ii. $HSCH_2CH_2SH$, pTsOH, refluxing benzene[66]; iii.

Scheme 14: A Formal Total Synthesis of (+/-)-Perhydrohistrionicotoxin



$HSCH_2CH_2CH_2SH$, BF_3-OEt_2, CH_2Cl_2[64c]; iv. $TMSSCH_2CH_2CH_2STMS$, ZnI_2, CH_3CN[68]) the majority of which resulted in formation of furan **98**.

Reductive cleavage (78%) was accomplished with Raney Nickel in refluxing ethanol to give a product which was identical in all respects to published data. A low ratio of catalyst to substrate was used to avoid the problem of over reduction of the ketone to a mixture of diastereomeric alcohols (the alcohols could be oxidized to **83** under either Swern[89] of Jones[90] oxidation conditions).

In summary we have described a concise (6 steps, 26%) preparation of lactam **83**, thus constituting a formal total synthesis of (+/-)-perhydrohistrionicotoxin **33**. The advantages of this annulative approach are brevity and the regiochemical integrity of the crucial furan terminated N-acyliminium ion initiated cyclization.

Bridged Alkaloids: An approach to (+/-)-Cocaine and (+/-)-Anatoxin-a

Cocaine (**34**) will be the first of two bridged ring containing alkaloids to be discussed. Cocaine is an aza[3.2.1]bicyclic ring containing alkaloid that is isolated from *Erythroxylan coca*. Historically it has figured prominently in the development of local anesthesia, but it is more notorious for its use as a psychoactive drug. More recently because of its toxic, highly addictive nature its medical use has been limited to topical application primarily in opthamology[91]. Numerous analogs of cocaine have been prepared and found to possess a wide variety of biological activities. Because of its challenging structural features, and the need for analogues, preparation of the tropane ring system still attracts considerable attention[92].

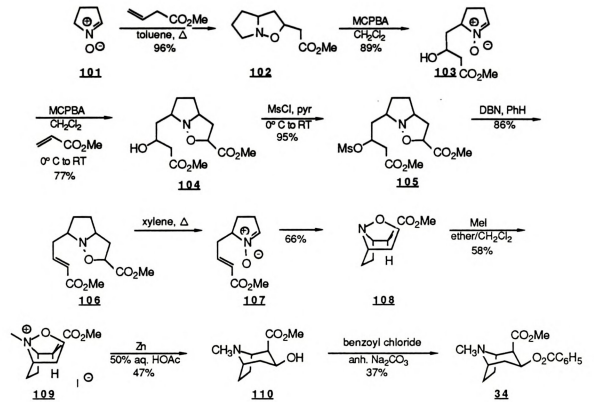
Willstatter initiated work in the synthesis of tropane alkaloids by accomplishing a synthesis of tropinone starting from cycloheptanone[31c]. This was soon followed by Robinson's efficient preparation of tropinone involving the condensation of succindialdehyde, methylamine, and the calcium salt of 1,3-acetonedicarboxylic acid[93]. Attempts to adjust this approach to a synthesis of

cocaine encountered stereochemical difficulties. More recently there have been several synthetic entries into the tropane ring skeleton[94]. However, like Robinson's synthesis, most fail to address the stereochemical aspects of cocaine itself. Examination of the structure of cocaine reveals two stereocenters that need to be controlled in any successful synthesis. The oxygen functionality at C-3 has been controlled by reduction of the corresponding ketone. The axial C-2 carbomethoxy residue has proven to be more difficult; it is readily epimerized in basic medium to the more stable equatorial position. Tufariello has published a total synthesis of cocaine that successfully addresses these problems.[31a]

Scheme 15 outlines Tufariello's[31a] approach to cocaine. 1-Pyrroline-1-oxide **101** reacts with methyl-3-butenoate to provided adduct **102** in 96% yield. Oxidation (MCPBA) to **102** (89%), followed by further oxidation with MCPBA and subsequent addition of methyl acrylate affords **104** in 77% yield. Formation of **105** (MsCl, pyridine,95%), followed by treatment with DBN, to effect dehydration, provided **106** (86%). Refluxing in xylene results in spontaneous nitrone cycloadditon of **107** to provide **108** (66%) directly. Addition of MeI (**109**, 58%), and treatment of **109** with Zn and 50% aqueous HOAc afforded ecgonine methyl ester in 47% yield. Benzoylation as described by de Jong[95] completed the synthesis of (d,l)-cocaine (37%).

Our retrosynthetic approach to (+/-)-cocaine is outlined in Figure 14. Cocaine may be available from furan **111**, which could be derived from N-acyliminium ion **112**. Acetal **113**, which might serve as the cyclization precursor, could be available by reduction of nitro-olefin **114** and protection of the product amine. Compound **114** could in turn be available by a condensation between furfural and 4-nitrobutanaldimethylacetal **115**. One major drawback of the illustrated approach is that we might be unable to

Scheme 15: Tufariello's[31a] Synthesis of (+/-)-Cocaine



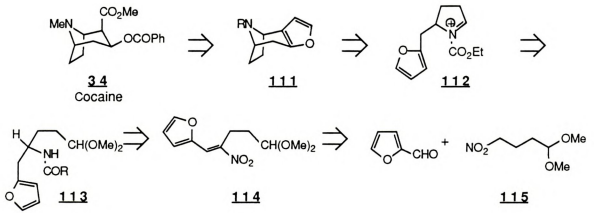
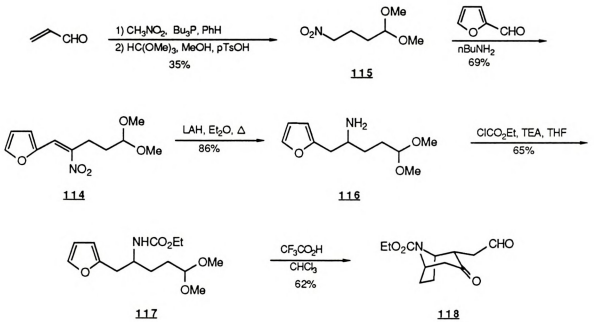


Figure 14: A Retrosynthetic Analysis for a Cocaine Synthesis

pinpoint our exact problem should the acyclic furan containing amido-aldehyde fail to provide the desired bridged furan. Finally, if the oxidation/hydrolysis step fails we could adjust our retrosynthetic plan to include a disubstituted furan synthon from the outset.

In the forward sense, Michael addition of nitromethane to acrolein catalyzed by Bu_3P followed by in situ dimethyl acetal formation ($HC(OMe)_3$, MeOH, pTsOH[96]) provided 4-nitrobutanaldimethylacetal in 35% yield (Scheme 16). The nitroaldol reaction between **115** and furfural, catalyzed by $nBuNH_2$[97], gave nitroolefin **114** (69%), which was reduced with LAH to afford an amine (86%), which was not purified but immediately treated with $ClCO_2Et$ and TEA in THF[98] to provide cyclization precursor **117** in 65% yield.

Scheme 16: The Construction of the Cocaine Ring System



With the successful preparation of the cyclization precursor we next examined several cyclization conditions. Treatment of **117** under a variety of acidic conditions provided a plethora of products[99]; however we found that trifluoroacetic acid/H_2O (1:1) added to a solution of **117** in $CHCl_3$[99a] provided a 62% yield of cyclized product **118**; a compound in which the furan was *not* intact. Based upon our previous results we were surprised to observe the furan hydrolysis under the reaction conditions. Recall that we had, in several cases, failed to oxidize or hydrolyze a disubstituted furan. One might guess that the added strain which would accompany rearomatization, in this bridged system, drives the intermediate toward trifluoroacetate capture, and ultimately to keto-aldehyde **118** after hydrolysis upon workup

To complete a synthesis of cocaine we need to consider several factors. First the stereocenters at C-2 and C-3, need to be controlled, and we need to remove a one carbon fragment from the C-2 side chain. The correct orientation of C-2 carbomethoxy residue in cocaine (Figure 15) could conceivably result from exocyclic protonation of the dianion **120**. For this to occur we would need access to hydroxy ester **120** with the C-3 OH oriented in an equatorial position. Having the OH equatorially oriented, and in the form of an anion should reduce the possibility of β-elimination during the enolization step. This surmise is further supported by the driving force for the hydrolysis of the initial cyclization product. We could envision obtaining **121** from alkene **122** by some oxidative process such as ozonolytic cleavage. Alkene **122** could in turn be prepared by selective dehydration of a primary alcohol which should be available by reduction of the cyclization product **123**. Since this retrosynthetic plan hinges on being able to selectively reduce the C-3 ketone to an equatorial alcohol, we began by examining this reaction.

Our first attempt at selective reduction utilized $NaBH_4$ as the reducing agent. Treatment of **118** with $NaBH_4$ in MeOH provided a 4:1 ratio of two diols **124a** and **124b** in excellent yield (84%). Since we had two carbinol centers present

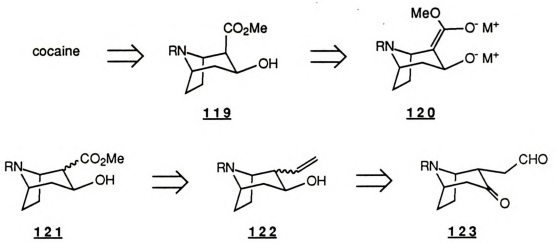


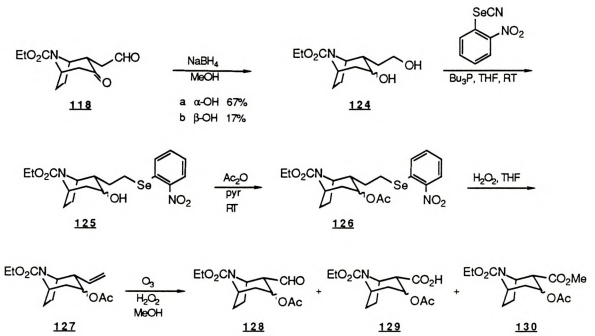
Figure 15: A Possible Route to (+/-)-Cocaine

in the molecule, it was difficult to determine the stereochemistry at the C-3 hydroxyl. In order to prepare a compound whose stereochemistry could be unequivocally assigned and investigate the rest of the sequence we chose to carry this diol through the dehydration step.

It is well known that primary and secondary alcohols may be conveniently eliminated by first transforming them into a selenide, and then treating the selenide with H_2O_2 to induce elimination[100]. A survey of the literature suggested that the selenide formation was selective for primary alcohols[101]. Upon treatment of the mixture of **124a** and **124b** with o-nitrophenylselenylcyanate[100a,102] and Bu_3P in THF, two primary selenides were isolated, **125a** 64.8% and **125b** in 24% yield. In order to protect the

secondary alcohol during the oxidation steps the corresponding acetates were formed. Selenide **124a** was stirred with pyridine, DMAP, and acetic anhydride for 2 days to furnish acetate **126a** (97.5%) Selenide **125b** was stirred with pyridine, and acetic anhydride overnight to furnish acetate **126b** (100%). Both **126a** and **126b**, after being dissolved in THF and treated with 30% H_2O_2, underwent smooth oxidation and elimination to provide olefins **127a** and **127b**

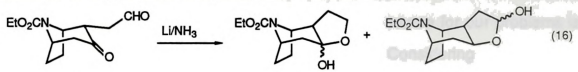
Scheme 17: Cocaine Side Chain and Carbinol Manipulation



in 99% and 88% yields respectively. At this point it was clear, by comparison of the ^{1}H-nmr's of **127a** and **127b** to published spectra of the epimers of cocaine, that our major product was the undesired axial alcohol.[103]

Anticipating that we would be able to adjust the hydroxyl orientation, perhaps by a more judicious choice of reducing agents, we continued with the synthesis. We were concerned that **127** might not withstand harsh C=C cleavage conditions; therefore we sought the mildest cleavage conditions possible. Toward this end, we submitted a solution of **127b** in MeOH at -78° C to ozone[104], followed by oxidative work up with H_2O_2. We obtained a good yield of a mixture of compounds that appeared to consist of aldehyde **128**, acid **129**, and ester **130**. In the final route we will need to cleanly obtain one of these oxidation products, preferably the methyl ester since that is our final goal. It has been reported that ozonolysis of alkenes in a solution of anhydrous HCl in MeOH allows clean isolation of methyl esters.[104e] Knowing that our compound will withstand ozonolytic cleavage we returned to the problem of hydroxyl stereochemistry.

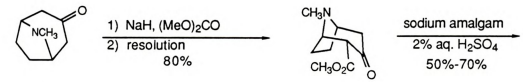
Extensive studies on the reduction of tropinone have been reported. With tropinone or 2-(carbomethoxy)-3-tropinone the most efficient reduction to date has been accomplished using sodium metal or sodium amalgam in alcoholic solvents[31b,105]. We attempted to apply this protocol to our keto-aldehyde system. Treatment of the keto-aldehyde with Na in EtOH or Na in s-BuOH failed to provide any trace of alcoholic products. A more modern method, that, like the Na/EtOH reduction, results in formation of the more stable equatorial alcohol (in the absence of severe steric hinderance) is reduction by Li/NH_3.[106] When we treated a solution of keto-aldehyde **118** in THF with Li/NH_3 we isolated instead of the desired alcohols, two isomeric lactols **131** and **132** . We could imagine the major product resulting from the reduction of the aldehyde to an alcohol and attack of the alcohol on the ketone. Likewise, reduction of the ketone and attack of the alcohol on the aldehyde would result in lactol **132**.



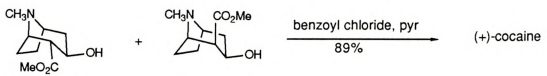
118 **131** **132**

Lewin and coworkers have recently examined the reduction of 2-(carbomethoxy)-3-tropinone (**134**) extensively (Scheme 18).[31b] In an attempt to improve the ratio obtained with the standard sodium amalgam reduction, they examined $NaBH_4$ in MeOH at -30° C; H_2, Pd/C; K, HMPA; lithium tri-sec-butylborohydride; and potassium graphite. They conclude that the sodium amalgam reduction is still the most viable synthetic route from 2-(carbomethoxy)-3-tropinone **134** to ecgonine methyl ester **110b**.

Scheme 18: Lewin's[31b] Synthesis of (+)-Cocaine



133 **134**



110a **110b**

1:2 to 2:3

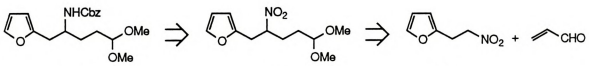
There is no reason to believe that a 2-substituted system such as ours should behave much differently than tropinone. A possible source for our problems is the fact that the 2-substituted group is an aldehyde. Considering the difficulties inherent in this system we decided to attempt a formal total synthesis by preparing the Lewin intermediate 134. Having 2-(carbomethoxy)-tropinone as our ultimate goal, another factor we now had to consider is how to prepare the N-methyl group present in this molecule. The carboethoxy group that we were presently using as a protecting group can be transformed into an N-methyl group by reduction with LAH[107], however LAH is a very strong reducing agent that will attack many other functional groups. Removal of such a group requires either strong acid, strong base, or TMSI, all of which are harsh conditions and probably not compatible with the present system[98]. We decided to switch to a protecting group that should be stable to oxidative conditions, but will be easier to remove. The carbobenzyloxy group most closely meets these requirements.

Another potential problem with the synthesis is the low yields in preparing the cyclization precursor. This is usually most troublesome when the starting materials are difficult to obtain or when the sequence is not amenable to large scale synthesis. Neither of these cases are true, since our starting materials, nitromethane, acrolein, and furfural are very inexpensive and all of the reactions can be easily performed on a large scale. Nevertheless it is aesthetically more pleasing to see a reaction sequence where as many reactions as possible proceed in high yield.

With this in mind we considered the retrosynthetic plan, incorporating the Cbz protecting group, as outlined in Figure 16. The requisite cyclization precursor should be available from protection of the amine, produced by the reduction of a nitrocompound **136**. The nitro compound could arise from

Michael addition of 2-(2-furyl)-ethanol with acrolein and subsequent acetal formation.

In the forward direction (Scheme 19) treatment of 2-(2-furyl)-1-nitroethane[108] and acrolein in MeOH with NaOMe then addition of $HC(OMe)_3$ and HCl provided 5-(2-furyl)-4-nitropentanaldimethylacetal in 57% yield. Reduction of the nitro-compound (NiB_2, $NaBH_4$, MeOH) provided amine **138** in 48%



135 **136** **137**

Figure 16: Second Generation Approach to (+/-)-Cocaine

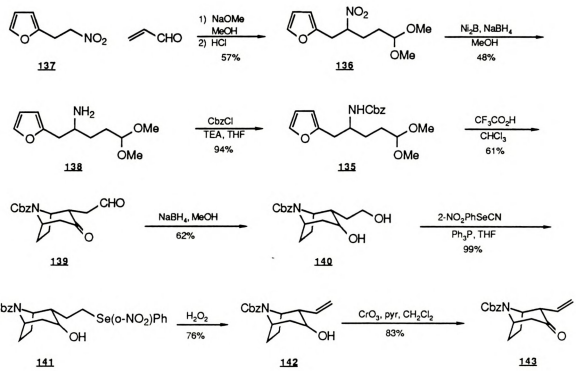
yield[109], which was treated was treated with CbzCl and TEA in THF to supply the Cbz protected cyclization precursor (**135**) in 94% yield.

Submission of **135** to the usual reaction conditions ($CHCl_3$, trifluoroacetic acid H_2O 1;1) resulted in formation of the cyclized product (61%) accompanied by several unidentified compounds. After purification by column chromatography, **139** in MeOH was treated with $NaBH_4$ to provide a mixture of diols (**140**,71%). Treatment of the epimeric mixture of diols in THF with o-nitrophenylselenylcyanate furnished two selenides (**141**) in 99% combined yield[100], which were oxidized and eliminated to afford the terminal alkenes **142** in 76% combined yield. Oxidation of the epimeric alcohols (Collins reagent) provided the ketone **143** in 83.3% yield[110]. In order to obtained the desired methyl ester directly the alkene was taken up in a solution of HCl in MeOH and submitted to ozonolysis[104e]. Two products were obtained in good overall mass

balance, however ^{1}H-NMR,EI-MS, and ir spectral data indicated that neither corresponded to the desired compound. It is possible, either before or after ozonolytic cleavage, that there is elimination of the nitrogen functionality. This would provide a compound that would be susceptible to further attack by ozone. Alternatively, under the acidic conditions, **143** may be enolizing during the ozonolysis. It is well known that ozone can attack enol derivatives.

In view of these problems a different approach seems necessary. Ozonolysis

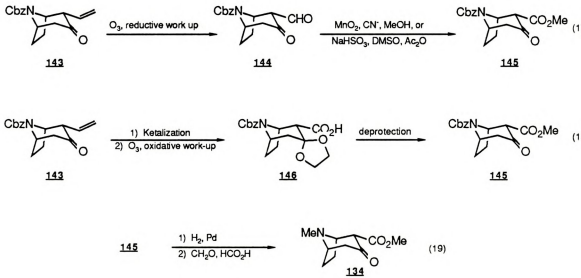
Scheme 19: Second Generation Preparation of the Tropane Ring System



of alkene **143** in CH_2Cl_2 with an acidic work up may provide the corresponding acid, but as a β-ketoacid it may be susceptible to decarboxylation. Ozonolysis of alkene **143** in CH_2Cl_2, and workup with dimethyl sulfide could provide

aldehyde **144** which may be oxidized, according to Corey's (MnO_2, CN^-, MeOH)[111] or Wuts' conditions ($NaHSO_3$, DMSO, $(Ac)_2O$, MeOH)[112], to the desired methyl ester. Another approach may be to protect the ketone as an oxoketal and then perform the cleavage to a methyl ester or a carboxylic acid. Also to be examined are other oxidizing agents such as OsO_4, RuO_4, and $KMnO_4$. These oxidations could be performed on either the ketone or the ketal (see eq. 17, 18, and 19).

After obtaining the desired keto-ester **145** all that remains to complete a



formal total synthesis of cocaine is the deprotection of the Cbz protected amine and methylation of the free amine. The deprotection could be accomplished by treatment of **145** with H_2 in the presence of Pd catalyst. Methylation of the amine could be accomplished by a method such as the Eschweiler-Clarke procedure (CH_2O, HCO_2H).[113]

A few comments about the desirability of the two approaches to the cyclization precursor should be made. The low yield on both of the Michael

additions (Scheme 16 and Scheme 19) might be improved by examining some alternate conditions. The nitro group reduction in the second approach might be more efficiently accomplished with LAH. Putting the yields of each reaction sequence aside, the first approach stands out as being more efficient because all of the starting materials are commercially available. In addition, this furan terminated N-acyliminium ion cyclization constructs the bridged ring system of the tropane alkaloids very quickly. We will continue to examine the synthesis of (+/-)-cocaine by the procedures outlined in equations 17-19.

The final alkaloid to be discussed is anatoxin-a. Anatoxin-a was isolated by Edwards, Gorham and coworkers from the fresh water blue-green alga *Anabaena flos-aquae*.[114] It was originally called "very fast death factor" (VFDF) after it was deemed responsible for numerous incidence of livestock and waterfowl poisoning[115]. As one of the most potent nicotinic acetylcholine receptor agonists known, it has proven very useful in neuropharmacological studies[116]. Abnormalities in acetylcholine mediated neurotransmission has been linked to myasthenia gravis, Parkinson's disease and Alzheimer's disease. Because of its low natural abundance and the need for convenient sources for both anatoxin-a and anatoxin-a analogues, this bridged alkaloid has generated considerable synthetic interest.

There have been relatively few approaches to anatoxin-a. Two of the most efficient routes to this molecule are the Speckamp[26] and Rapoport[27] syntheses presented earlier. The Speckamp route is described in detail in Scheme 20.

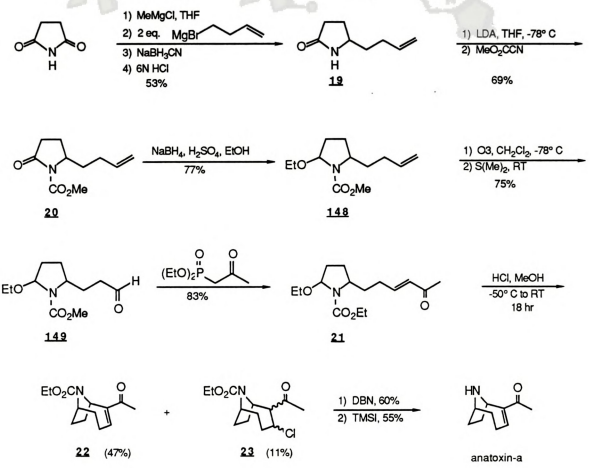
Formation of the Mg-salt of succinimide, addition of 2 eq of the Grignard reagent derived from 4-bromo-1-butene, reduction with $NaBH_3CN$ and acidification afforded butenylpyrrolidone **19** (53%) Protection of the lactam (LDA, THF,EtO_2CCN, 69%) followed by reduction and in situ ethanolysis provided **148** (77%). The olefin was then converted into the requisite

terminator by cleavage (i. O_3, CH_2Cl_2, -78° C; ii. $S(Me)_2$, RT) and Wittig addition of dimethyl (2-oxopropyl)phosphonate(83%) under the Masamune-Roush conditions. Submission of cyclization precursor **21** to HCl in MeOH (-50° C to RT) afforded the desired cyclization product **22** (47%) and chloride **23** (11%). The mixture could be treated with DBN to provide **22** (60%). Deprotection (TMSI, 55%) completed the synthesis of anatoxin-a.

Our retrosynthetic plan for anatoxin-a is analogous to the initial plan for cocaine (Scheme 16). Figure 17 shows how the side chain in anatoxin-a could be derived from the alkyl group residue of a furan while the double bond could be obtained from the ketone residue. The bicyclic furan (**50**) could be available from an acyclic precursor (**152**) which was obtained from a one carbon analogue of the nitroolefin used in the cocaine synthesis. The extra carbon atom could be obtained by using furanacetaldehyde (**153**) rather than furfural in the initial Michael addition.

Unlike furfural, furanacetaldehyde (**153**) is not a commercially available compound. This meant that our first task in the anatoxin-a synthesis was to devise a convenient method for obtaining large quantities of furanacetaldehyde. At the time, the only reported literature preparation was by the Darzens condensation[117]. We were able to prepare small amounts of furanacetaldehyde by this route, but it was always accompanied by side products. During our search search for a more convenient route, we examined the oxidation 2-(2-furyl)-ethanol to furanacetaldehyde under a variety of conditions (Swern[89]; PDC[118]; PCC[44c]; PCC/pyridine; PCC/NaOAc; BH_3-SMe_2/PCC[119]; pyr-SO_3[120]; CrO_3-pyr[109]; DEAD[121], Ph_3P, $NO_2CH_2CO_2Et$[122]; $BaMnO_4$[123]; $K_2Cr_2O_7$, 9M H_2SO_4, CH_2Cl_2, Bu_4NHSO_4[124]; DEAD; 5%NaOCl, Bu_4NHSO_4[125]). The best yield (33%) was obtained from the DEAD, Ph_3P, $NO_2CH_2CO_2Et$ method, but the product was difficult to separate from the excess

Scheme 20: Speckamp's [26]Synthesis of Anatoxin-a



reagents. With several of the other reagents mentioned, we were able to observe small amounts of aldehyde formation, but the reaction never proceeded in high enough mass balance to be considered synthetically useful. We attempted to condense furfural with methoxytriphenylphosphorane[126], then hydrolyze the intermediate enol ether by refluxing in acetone, H_2O and PPTs.[127] The only product observed was the product of aldol condensation between two molecules of furanacetaldehyde.

During an attempted Michael addition employing 2-(2-furyl)-1-nitroethane as the Michael donor we observed furanacetaldehyde dimethylacetal as a bi-

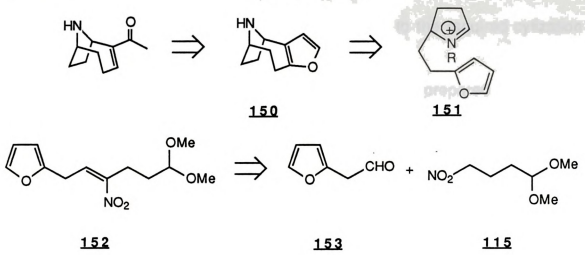


Figure 17: First Retrosynthetic Plan Leading to Anatoxin-a

product.[128] By treating 2-(2-furyl)-1-nitroethane with NaOMe in MeOH followed by HCl we were able to obtain **156** exclusively in a 74% yield (eq. 20). This led us to examine some modifications of the Nef reaction as routes to furanacetaldehyde.[129] Treatment of 2-(2-furyl)-1-nitroethane under a variety of conditions failed to give satisfactory results (i. 1) THF, 2N NaOH[130]; 2) 10N H_2SO_4; ii. 1) KOH/MeOH 2) $KMnO_4/MgSO_4$[131]; iii. 1) t-BuONa 2) $KMnO_4$[132]; iv. $TiCl_3$[133]; v. H_2O_2; vi. 1) aq. NaOH 2) aq. H_2SO_4[134]; vii. 1) 30% H_2O_2, K_2CO_3, H2O[135]; viii. 1) TEA, CTAP[136]). We finally found that if the lithium salt of 2-(2-furyl)-1-nitroethane was oxidized, in an aqueous solution of $Na_2B_4O_7$, with $KMnO_4$, furanacetaldehyde[137] was produced (50% mass balance) cleanly (eq. 21).[138] The aldehyde was then subjected without purification to nitroaldol condensation with nitrobutanaldimethyl acetal (eq. 22). Under a variety of base catalysis (i. LDA[139]; ii. NaOH, EtOH[139,140]; iii. KF[141]; iv. Amberlyst[142]), the alcohol was obtained in only 20% yield (from furanacetaldehyde). As a result of

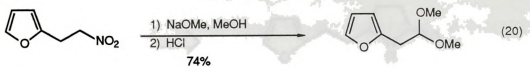
the low yield we investigated an alternate approach to the required cylization precursor.

We surmized that the cyclization precursor could be prepared in a fashion similar to the second sequence of the cocaine synthesis (Figue 19). Thus, the required lactam could be derived from a nitro compund, which in turn is prepared from the condensation between acrolein and an appropriate furan compound

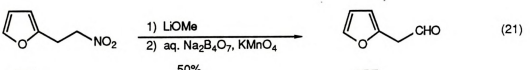
Condensation of 3-(2-furyl)-1-nitropropane (**159**)[143] with acrolein in MeOH with catalytic NaOMe, then addition of HCl provided acetal **160** in 47% yield[31a]. Reduction to the corresponding amine (Ni_2B, $NaBH_4$)[109] and immediate protection provided **161** in 72% yield. Unfortunately submission of this acetal to the usual cyclization conditions ($CHCl_3$, trifluoroacetic acid H_2O, 1:1) did not provide cyclized material. Instead, a single, high molecular weight compound was isolated. At this point we did not attempt further identification. We decided that we should approach the cyclization in a more stepwise manner, since in the current one pot cyclization protocol it is difficult to ascertain which step in the multi-step process is problematic.

With this in mind we designed an N-acyliminium ion precursor in which the lactam ring is preformed. The requisite N-acyliminium ion should be available from lactam **163** by one of the reductive methods described above, and the lactam should be readily available from a nitro ester (**164**), which in turn could be prepared by a Michael addition.

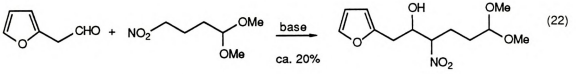
In the forward direction Triton B catalyzed condensation of 3-(2-furyl)-1-nitroethane[143] with freshly distilled ethyl acrylate in EtOH[144] provided ethyl-7-(2-furyl)-5-nitroheptanoate **164** in 94% yield (Scheme 22). Ni_2B reduction and in situ cyclization afforded lactam **165** (86%).[109] Protection of the nitrogen by



137 156

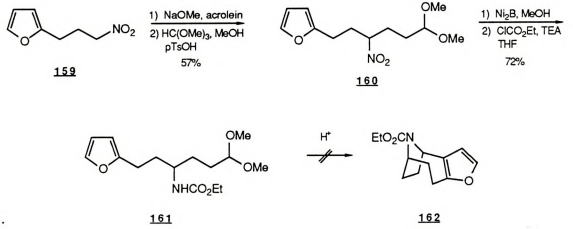


137 157



156 115 158

Scheme 21: Second Generation Construction of the Anatoxin-a Ring System



159 160 161 162

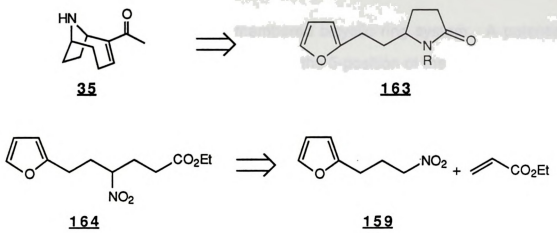


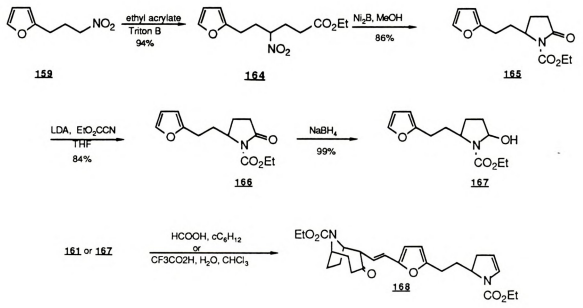
Figure 18: Third Retrosynthetic Plan Leading to Anatoxin-a

treatment of **165** in THF with LDA (-78° C) followed by ethyl cyanoformate gave **166** (84%)[26]. Reduction of the lactam according to Chamberlin's procedure provided carbinolamide **167** in 90% crude yield.[14] Alternatively, reduction of **166** according to Speckamp's procedure provided the corresponding ethoxy-carbamate (nearly quantitaive crude yield).[18] With both N-acyliminium ion precursors in hand we submitted them both to various cyclization conditions. In each case, the only product obtained was the same high molecular weight compound observed previously. Closer examination of the ^{1}H-NMR spectra provided some insight into the structure of this unknown compound. There were no resonances in either the aldehydic or the α-furyl regions. There were several signals in the β-furyl and olefinic regions. One very characteristic signal, a doublet of triplets, was observed at 4.9ppm A similar signal was observed at 5.1ppm in the spectra of the enamide formed from **39d**. All this data pointed towards a compound such as **168**. This could result from attack of starting material at the 5-position of the furan onto the aldehyde of a cyclized, hydrolyzed furan. If this is the case it suggests that there in nothing inherently

wrong with formation of a seven membered bicyclic ring system. A potential way around this "dimer" problem is to block the 5-position of the furan with some group. We decided that the easiest, most reliable group to utilize would be a methyl group.

Preparation of the needed cyclization precursor proceeded exactly as before with the unsubstituted furan (Scheme 23). Thus, Triton B catalyzed addition of 3-(5-methyl-(2-furyl))-nitropropane[143] to freshly distilled ethyl acrylate provided ethyl-7-(5-methyl-(2-furyl))-5-nitroheptanoate **169** in 88% yield. Reduction (Ni_2B, $NaBH_4$) and in situ cyclization provided lactam **170** in 98% yield.[108] Protection as before (LDA, $CNCO_2Et$) afforded lactam **171** (58%).[26] Submission of **171** to Speckamp's reduction conditions provided **172** in 74%

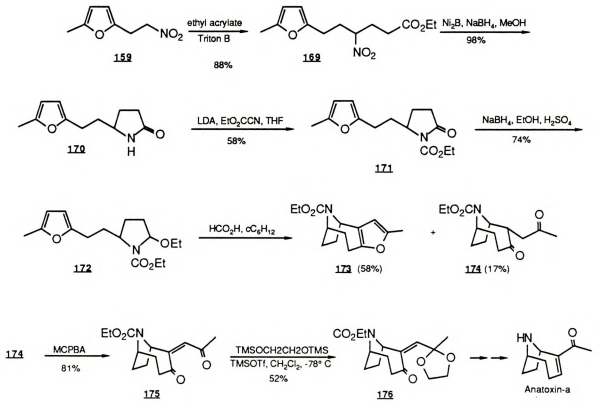
Scheme 22: Third Generation Construction of the Anatoxin-a Ring System



yield.[18] As predicted blocking the 5-position of the furan allowed smooth cyclization. Submission of **172** to cC_6H_{12}/HCO_2H afforded a mixture of furan **173** in 58% yield and dione **174** in 17% yield. Furan **173** was readily oxidized to ene-dione **175** (83%) by treatment with MCPBA in a two phase mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$.

With both dione and enedione in hand we had to consider their transformation to anatoxin-a. The first question to answer is how to select between the two carbonyl groups of **174** or **175**. We had previously encountered problems with furan formation during ketalization attempts. If the ene-dione could be selectively protected we could avoid the furan formation

Scheme 23: Fourth Generation Construction of the Anatoxin-a Ring System

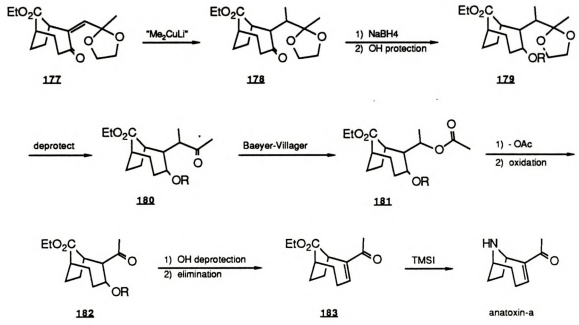


problem since **175** is not in the same oxidation state as a furan. Toward this end we submitted dione **174** to both thermodynamic ($HOCH_2CH_2OH$, p-TsOH, refluxing benzene)[63] and modified kinetic ketalization conditions (CH_2Cl_2, $TMSOCH_2CH_2OTMS$, TMSOTf, -78° C to RT).[62] In both cases we observed significant furan formation. Submission of enedione **175** to Noyori's kinetic ketalization conditions (-78° C, $TMSOCH_2CH_2OTMS$, TMSOTf)[62] provided the side chain ketal selectively in 52% yield. The low yield may be a result of the low stability of ene-dione **175**. If this is the case, modification of the ketalization conditions may result in higher yields. Work toward this end will continue.

To complete a synthesis of anatoxin-a we need to modify the side chain and insert a double bond into the ring. One way we envisioned accomplishing this is outlined in Scheme 24. Conjugate addition of a cuprate reagent should provide **178** with the required methyl group in place. Reduction of the ring ketone and protection with an appropriate group should afford **179**. Deprotection of the side chain ketal and Baeyer-Villager oxidation should yield acetate **181**. Hydrolysis of the acetate and oxidation of the derived alcohol would complete the synthesis of the side chain. Deprotection of the alcohol and elimination to an alkene would provide **183**, with the anatoxin-a ring skeleton in place. All that would need to be done to complete the synthesis of anatoxin-a is deprotection of the amine with TMSI.

In summary, we have demostrated the 2- and 3-furyl moieties are sufficiently nucleophilic and stable to serve as terminator functions for N-acyliminium ion-initiated cyclizations. These processes provide access to 5,6; 5,7; 6,6; and 6,7-membered, fused-ring systems with both the electronically favored 3-to2-furyl closure (all) and the regioisomeric 2- to-3-furyl closure (5,6- and 6,6-membered rings only) being realized. In addition a 6-6 spiro-cyclic

Scheme 24: **Proposed Conclusion** to the Anatoxin-a Synthesis



ring, an 8-aza-bicyclo[3.2.1] and an aza-bicyclo[4.2.1] ring have been prepared. By accomplishing this we have shown that furans meet two of the requirements for terminators to be deemed useful: they cyclize under mild conditions, and they proceed with regiochemical predictability. We have completed a total synthesis of lupinine, a formal total synthesis of perhydrohistrionicotoxin, and have prepared the functionalized ring systems present in cocaine and anatoxin-a. In summary, we have shown that a furan is a highly functional and versatile teminator for the N-acyliminium ion cyclization.

During the course of these studies we have repeatedly encountered an extreme substrate dependent furan hydrolysis/oxidation relationship. The pattern that seems to be emerging is that the more strained the system the more susceptible to cleavage it becomes.

EXPERIMENTAL

EXPERIMENTAL SECTION

General. Tetrahydrofuran (THF), benzene, and diethyl ether were dried by distillation under argon from sodium benzophenone ketyl; methylene chloride, triethylamine (TEA), pyridine, n-butylamine, acetic anhydride, and diisopropylamine were dried by distillation under argon from calcium hydride. Acrolein was distilled from hydroquinone and copper sulfate and used immediately. Ethyl acrylate was distilled and used immediately. Trimethylsilyl trifluoromethanesulfonate (TMSOTf), 1,2-bis(trimehtylsilyloxy)ethane, tributylphosphine, and furfural were distilled at reduced pressures prior to use. Cyclohexane was dried over molecular sieves, and nitromethane was filtered through basic alumina prior to use. MeMgI was prepared from dried Mg and MeI that was used as received. Formic acid (98%) was purchased from Fluka and was used as received. Diethyl azodicarboxylate and Ph_3P were purchased from Aldrich Chemical Comnpany, Miwaukee, Wisconsin and were used as received. All other reagents were used as received unless otherwise stated; all reactions were performed under argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 167 spectrometer. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian T-60 at 60MHz or a Bruker WM-250 spectrometer at 250MHz as mentioned in deuteriochloroform unless otherwise indicated.

Chemical shifts are reported in parts per million (δ scale) from internal standard tetramethylsilane. Data are reported as follows: chemical shifts (muliplicity: s = singlet, bs = broad singlet, d = doublet, t= triplet, m = multiplet, coupling constant (Hz), integration). Electon impact (EI/MS, 70eV) 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.[145] by using the Whatman silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (o. d.) is listed in millimeters.

Kinetic ketalization of **63b**.

To a solution of **63b** (188.8mg, 0.84mmol) in CH_2Cl_2 (3ml) cooled to -24° C in a dry ice-CCl_4 bath, was added $TMSOCH_2CH_2OTMS$ (174.4mg, 0.845mmol) followed by TMSOTf (31 drops). The cooling bath was maintained at -24° C for 3 hours, then stirring was continued overnight while allowing the yellowish solution to warm to room temperature. Pyridine (15 drops) was added and the solution was cast into saturated aqueous $NaHCO_3$ (5ml) and the aqueous layer was extracted with CH_2Cl_2 (4 x 5ml). The combined organic layers were washed with 1N HCl (10ml), saturated aqueous $NaHCO_3$ (10ml), brine (10ml), dried (Na_2SO_4), and concentrated *in vacuo* to provide 85.3mg of a yellow oil. The crude product was purified on a column of silica (230-400 mesh, 20g silica, 20mm o. d., ethyl acetate-methylene chloride-methanol, 8:1:1, 4.5ml fractions) using the flash technique. Fractions 13-23 provided 210.8mg, 93 %, of **72** as a water white amorphous solid.

^{1}H-NMR ($CDCl_3$): δ = 4.77 (ddd, J=14.4, 6.4, 3.4Hz, 1), 3.98 (m, 4), 3.3 (m, 1), 2.7-2.16 (m, 5), 2.15 (s, 3), 1.9-1.75 (m, 4), 1.6-1.4 (m, 3); ^{13}C-NMR: 207, 169, 108, 64.6, 65.0, 58.7, 44.2, 40.3, 39.7, 33.7, 32.9, 29.6, 27.5, 18.9; IR (CCl_4): 2945, 2780, 1715, 1640, 1440, 1350, 1250, 1150, 1050, 940, 900, 650.; EI-MS

(70 eV): 268 (M+·+1, 3.43), 224 (10.24), 209 (53.16), 179 (19.37), 150 (15.39), 137 (31.02), 99 (base), 87 (64.12), 69 (23.19), 55(79.63), 43 (68.21).

Baeyer-Villager oxidation of **72**.

To a solution of **72** (34.9mg, 0.013mmol) in dry CH_2Cl_2 (2ml) was added anhydrous Na_2HPO_4 (720mg, 5mmol), then freshly prepared triflouroperacetic acid (0.6ml). The mixture was warmed to reflux for 4 hours. After cooling to room temperature, saturated aqueous $Na_2S_2O_4$ was added until the reaction mixture tested negative to peroxides by the starch iodide test. The aqueous layer was concentrated *in vacuo*, taken up in CH_2Cl_2 (10ml), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give 38.8mg of an amorphous solid which was purified on a column of silica gel (230-400 mesh, 4g, 20mm o.d., ethyl acetate-methanol-methylene chloride 8:1:1, 1.5ml fractions) using the flash technique. Fractions 5-8 provided 18.8mg, 54 %, of **73** as water white oil.

^{1}H-NMR (250MHz): δ = 4.7 (ddd, J=14.4, 6.4, 3.4Hz, 1), 4.25-4.09 (m, 2), 4.0 (m,4) 3.58 (m, 1), 2.7 (dt J=13.1, 3.4Hz, 1), 2.45 (m, 2), 2.06 (s, 3), 2.0 - 1.65 (m, 6), 1.56 (dt, J=14.4, 4.7Hz, 1); IR ($CHCl_3$): 2980, 1735, 1625, 1470, 1450, 1420, 1350, 1250, 1205, 1165, 1050, 950; EI-MS (70eV): 284 (M+·+1, 6.83), 293 (M+·, 2.79), 224 (10.70), 210 (20.66), 192 (2.93), 178 (2.72), 166 (3.01), 150 (180), 138 (9.74), 125 (10.51), 110 (7.10), 99 (base), 69 (28.41), 55 (78.82), 43 (77.06).

Exchange ketalization of **73**.

To a solution of **73** (26.4mg, 0.093mmole) in dry CH_2Cl_2 (2ml) was added 1,3-propanedithiol (20.2mg, 0.186mmol) followed by BF_3-OEt_2 (13.2mg, 0.093mmol). After stirring overnight, 10% aqueous NaOH was added (8ml) and

the aqeous layer was extracted with CH_2Cl_2 (4 x 8ml). The combined organic layers were washed with brine (20ml), dried over Na_2SO_4 and concenetrated *in vacuo* to give 30 mg of an oil which was purified on a column of silica gel (230-400 mesh, 3g, 20mm o. d., EtOAc-MeOH-CH_2Cl_2, 40:1:1, 2ml fractions) using the flash technique. Fraction 8-13 provided 26.7mg, 87%, of **74** as a colorless oil.

^{1}H-NMR (250 MHz): δ = 4.68 (m, 2), 4.2 (dd, J=11.9, J=5.5Hz, 1), 3.62 (m, 1), 3.19-2.8 (m, 4), 2.7-2.2 (m, 6), 2.03 (s, 3), 1.9-1.5 (m, 6); IR ($CHCl_3$): 3010, 2960, 1730, 1620, 1440, 1420, 1230, 1210, 730; EI-MS (70eV): 330 (M^++1, 10.34), 329 (M^+. 81.03), 222 (60.34), 55 (65.52), 43 (base).

Raney Nickel Reduction of **74**.

To a solution of **74** in absolute EtOH (1ml) was added Raney nickel (0.25ml) as a slurry in EtOH (commercial Raney Nickel was rinsed with 8x5 ml EtOH). After 1h at room temperature followed by 6 hours at reflux, the catalyst was quenched by adding 1N HCl (50ml) then a few drops of 6N HCl. The green solution was extracted with CH_2Cl_2 (4 x 50ml), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 9.1 mg of a brownish green oil which was purified on a column of silica gel (230-400 mesh, 0.5g, pipet, EtOAc-CH_2Cl_2-MeOH 40:1:1, 0.5 ml fractions) using the flash technique. Fractions 7-15 provided 5.4mg, 60%, of **75** as a water white oil.

^{1}H-NMR (250Mz): δ = 4.81 (m, 1), 4.06 (dd, J=11.01, 4.2Hz), 4.0 (dd, J=11.01, 4.2Hz), 3.15 (m, 1), 2.5-2.1 (m, 4), 2.04 (s, 3), 1.9-1.3 (m, 8); IR ($CHCl_3$): 3040, 3005, 2960, 1730, 1620, 1440, 1200, 1145, 700, EI-MS (70eV): 227 (M^++2, 4.41), 226 (M^++1, 34.96), 251 (M^+, 43.9), 197 (17.48), 182 (25.54), 166 (64.83),

151 (56.32), 138 (62.09), 124 (20.78), 112 (84.08), 96 (46.85), 84 (38.13), 69 (89.73), 55 (base).

Reduction of **75**.

To a suspension of lithium aluminum hydride (3.5mg, 0.091mmole) in THF (1ml) was added a solution of **75** (4.1mg, 0.0182mmole) in THF (2ml). The mixture was heated to reflux overnight, then cooled to room temperature, and quenched with 15% aq. NaOH (5 drops) and H_2O (5 drops). The mixture was dried over Na_2SO_4 and concentrated *in vacuo* to give 19mg of **31** as an orange-yellow amorphous solid.

1H-NMR (250MHz): δ = 3.8 (m,2), 3.0 (m, 2), 2.2-1.6 (m, 10), 1.5-1.0 (m, 5); IR ($CHCl_3$): 3360, 2940, 1400, 1240, 1060, 1000, 750; EI-MS (70eV): 169 (M^+, 40.99), 168 (52.50), 152 (59.24), 138 (60.78); 111 (48.76), 97 (34.98).

Preparation of 6-(3-(2-furyl)-propyl)-6-hydroxy-2-piperidinone **89**.

Methyl magnesium iodide (20ml, 1.2M in Et_2O) was added dropwise to a solution of glutarimide (3.44g, 26.2mmol) in methylene chloride (500ml). The mixture was heated to reflux for 30 minutes, then cooled to room temperature and 3-(2-furyl)-propyl magnesium bromide (35ml, 0.98mmole) was added over 20 min. The mixture was refluxed overnight (18 hours), cooled to 0° and quenched with saturated aqueous ammonium chloride (170ml). The precipitate was removed by filtering through a pad of celite and the layers separated. The aqueous layer was extracted with methylene chloride (4x80 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford 5.3g, 90.5%, of the crude carbinolamide **89** as a slightly yellow amorphous solid, which was used without further purification.

^{1}H-NMR (250MHz): δ = 8.16 (bm, 1), 7.22 (m, 1), 6.93 (bs,1), 6.21 (m, 1), 5.93 (m, 1), 4.77 (b,2) 2.7-1.6(m, 10); IR ($CHCl_3$): 3685, 3620, 3380, 3200, 2980, 2400, 1710, 1660, 1220, 760, 670 cm-1; EI-MS (70eV): 205(M^+-18, 5.78), 124 (22.82), 111(8.86), 94(base), 82 (1872), 55 (30.24), 41 (23.71).

Preparation of **88**.

To a vigoursly stirred solution of **89** (5.3g, 23.7mmol) in cyclohexane (290ml) was added HCO_2H (29ml). The two phase mixture was stirred for 3 min then immediately cast into CH_2Cl_2 (350ml) and H_2O (500ml). The aqueous layer was separated and extracted with CH_2Cl_2 (3x300ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (500ml), brine (200ml), dried ($MgSO_4$), and concentrated *in vacuo* to give 4 g of an off white solid. The crude product was purified on a column of silica gel (230-400 mesh, 300g. 60mm o.d., ethyl acetate, 100ml fractions) using the flash technique. Fractions 11-21 yielded 2.96 g, 55%, of **88** as a white solid. mp 193-194

^{1}H-NMR (250MHz): δ = 7.19 (d, J=2.1Hz, 1), 6.28 (d, J=2.1Hz, 1), 6.74 (bs, 1), 2.52 (m, 2), 2.36 (m. 2), 1.76 (m, 8); IR (CCl_4): 3065, 2920, 1662, 1540, 1450, 1395, 1125, 752, 732cm^{-1}; EI-MS (70 eV): 205 (M^+, 60.6), 190, (10.65), 177 (b), 162 (28.29), 149 (37.11), 134 (34.60), 118 (11.01), 107 (29.16), 91 (21.66), 77 (20.11), 55 (40.45)

Preparation and cyclization of 6-(3-(5-ethyl-(2-furyl))-propyl)-5-hydroxy-2-piperidinone **97**.

Methyl magnesium iodide (4.9ml, 2.4M in Et_2O) was added over 15 min. to a solution of glutarimide (1.45g, 12.8mmol) in CH_2Cl_2 (210ml). The reaction mixture was heated to reflux for 30min, cooled to room temperature and 3-(5-ethyl-2-furyl)-propyl magnesium bromide (14ml, 1.1M) was added over 15min.

The mixture was refluxed overnight (18hr), cooled to 0° and quenched with saturated aqueous NH_4Cl (700ml). The precipitate was removed by filtering through a pad of celite and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 300ml), the combined organic layers dried over $MgSO_4$, and concentrated *in vacuo* to afford 5.07g, (ca.100%) of the crude carbinol amide as a slightly yellow amorphous solid, which was used without further purification.

To a vigorously stirred solution of **96** (5.07g, 22.7mmol) in cyclohexane (275ml) was added HCO_2H (27ml). The two phase mixture was stirred for 3 min, then cast into CH_2Cl_2 (500ml) and H_2O (500ml). The aqueous layer was separated, saturated with NaCl and extracted with CH_2Cl_2 (4 x 500ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (750ml), brine (75 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give 5.2g of an amorphous solid which was purified on a column of silica gel (230-400 mesh, 200g, 50mm o. d., ethyl acetate-methylene chloride-methanol, 40:1:1, 75ml fractions) using the flash technique. Fractions 13-21 provided 2.17g, 72.7%, of **98** as a white solid mp. 128-130° C

^{1}H-NMR (250 MHz): δ = 5.91 (s,1), 5.83 (bs, 1), 2.59 (m, 4), 2.41 (bt, J=5.9Hz, 2), 1.88 (m, 8), 1.2 (t, J=7.6Hz, 3); IR ($CHCl_3$): 3000, 2960, 1700, 1580, 1450, 1385, 1205, 980, 760. EI-MS: 233 (M^+, 3.37), 205 (5.49), 195 (4.81), 176 (3.876), 149 (8.98), 124(32.43), 96 (20.77), 84 (b), 51 (15.74), 49 (53.78), 41 (54.28);

MCPBA Oxidation and Reduction of **98**.

To a solution of **98** (81.3mg, 0.35mmol) in CH_2Cl_2 (3ml) cooled in an ice-water bath was added saturated aqueous $NaHCO_3$ (3ml) followed by MCPBA (80-85%, 81.7mg, 0.40mmol) in one portion. Stirring was continued at 0° C for

2h then at room temperature for 3 h. After separating the two phase mixture, the organic layer was dried (Na_2SO_4) and the aqueous layer was concentrate *in vacuo*. The residue was taken up in CH_2Cl_2 and dried over Na_2SO_4. The two oganic phases were combined and concentrated *in vacuo* to give 82.6mg of a clear oil which was immediately dissolved in 20ml of 20 % aqueous EtOH to which had been added 4 drops of HOAc. The solution was hydrogenated (1atm) over 10% Pd/C (20mg) for 45 min. The mixture was immediately filtered through a pad of celite, and the celite was rinsed with CH_2Cl_2. To the combined filtrates was added saturated aqueous $NaHCO_3$ (10 drops) , and the mixture was concentrated *in vacuo* to near dryness. The residue was taken up in CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to give 78mg of a yellow oil, which was purified on a column of silica gel (230-400 mesh, 10g, 20mm o.d., ethyl acetate-methylene chloride-methanol-triethylamine 40:1:0.5: 0.5, 2ml fractions) using the flash technique. Fractions 9-16 provided 61.1mg, 70%, of 99 as a water-white oil.

^{1}H-NMR (250MHz): δ= 6.01 (bs, 1), 3.12 (m), 3.09 (dd, J=8.9, 2.5Hz, 3), 2.6-2.15 (m, 8), 1.85-1.5 (m, 6), 1.07 (t, J=7.6Hz, 3); IR (CHCl3): 3000, 2950, 1705, 1655, 1450, 1375, 1215, 715; EI-MS (70eV): 251 (M^+, 7.98), 222 (4.3), 194 (41.2), 176 (293), 166 (6.83), 152 (5.73), 134 (6.55), 124 (b), 112 (33.67), 96 (31.86), 84 (45.07), 55 (84.91), 41 (36.72).

Preparation of thioketal **100**.

A solution of **99** (13.9mg, 0.0554mmol) and $TMSSCH_2CH_2STMS$ (14.5mg, 0.0609mmol) in CH_2Cl_2 (0.5ml) was cooled to -24° in a dry ice-CCl_4 bath, and 3 drops of TMSOTf was added. The solution was stirred at -24° C for 1.5h, then allowed to warm to room temperature and stirred overnight. To the solution was added 10 drops of pyridine and the solution was cast into saturated aqueous

$NaHCO_3$ (5ml). The aqueous layer was extracted with CH_2Cl_2 (4 x 4ml), and the combined organic layers washed with 1N HCl (7ml), saturated aqueous $NaHCO_3$ (7ml), and brine (7ml), dried over Na_2SO_4, and concentrated *in vacuo* to provide 14mg of an amorphous solid. The crude product was purified on a column of silica gel (230-400 mesh, 15g, 20mm o. d., ethyl acetate-methylene chloride-methanol-triethylamine 25:1:0.5:0.5, 3ml fractions) using the flash technique. Fractions 20-29 yielded 12mg, 67% of **100** as a white solid. mp=168.5-170.0° C

^{1}H-NMR (250 MHz): δ = 6.05 (bs, 1), 3.21 (m, 4), 2.73 (m,2), 2.4(m, 3), 2.2 (m, 2), 1.9-1.6 (m, 10), 1.09 (t, J=7.6Hz, 3);13C-NMR: 207, 172, 73, 62, 59, 41, 39, 39.2, 38, 37.5, 32, 31, 24, 22, 17, 11; IR: ($CHCl_3$): 3350, 3000, 2960, 1715, 1650, 1450, 1380, 1210, 720, 660; EI-MS: 327 (M , 3.07), 298 (7.15), 280 (5.88), 268 (b), 250 (17.36), 234 (28.24), 194 (40.74), 176 (19.56), 133 (92.09), 124 (62.86), 112 (25.49), 96 (15.42), 55 (25.63).

Raney nickel reduction of **100**.

To a solution of **100** in absolute EtOH (5ml) was added 1/8 teaspoon Raney Nickel. The mixture was refluxed for 2 hours, cooled to room temperature and quenched with 1 N HCl. The green solution was extracted with CH_2Cl_2 (4 x 25ml). The combined organic extracts were washed with saturated aqeous $NaHCO_3$ (25ml), brine (25ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil which was purified on a column of silica gel (230-400, 7g, 20 mm o.d., ethyl acetate-methylene chloride-methanol-triethylamine 30:1:.5:.5, 1.5 ml fraction) using the flash technique. Fraction 16-21 provided 45.6 mg, 78.5%, of **83** as a water white oil.

^{1}H-NMR (250MHz): δ = 6.56 (bs, 1), 2.32 (m, 5), 2.2-1.0 (m, 14), 0.86 (bt, 3); IR ($CHCl_3$): 3020, 2950, 1710, 1650, 1440, 1390, 1210, 720; EI-MS (70 eV): 237

(10.33), 194 (7.42), 175 (3.67), 138 (9.94), 124 (base). 112 (34.08), 96 (50.88), 82 (18.99), 55 (71.26).

4-Nitrobutanaldimethylacetal **115**.

To acrolein (11.2g, 0.2mol) and nitromethane (97.6g, 1.6mol) in benzene (200 ml) in a water bath at room temperature, was added a solution of Bu_3P (0.08g, 0.0004mol) in benzene (2ml) over 5 min. After 45 min MeOH (20.2ml, 0.5mol), $HC(OMe)_3$ (24.1ml, .22mol) and pTsOH (0.4gm, 0.002mol) were added and the solution was heated to 35° for 45 min. The organic phase was washed with 5% aqueous $NaHCO_3$ (75ml), brine (75ml), dried over Na_2SO_4, concentrated *in vacuo*, and the orange viscous liquid was purified by distillation under reduced pressure bp (3.5mm) 110-113° to give 11.4g of **115**, 35%, as a water white liquid.

^{1}H-NMR (60 MHz): δ = 4.42-4.22 (m, 3H), 3.25 (s, 6H), 2.3-1.4 (m, 4H); IR ($CHCl_3$): 300, 2940, 2840, 1555, 1440, 1380, 1200, 1130. 1060, 950, 715, 670; EI-MS (70 eV): 163 (M^+, 0.17), 162 (1.81), 161 (8.55), 132 (58.83), 100 (11.25), 85 (67.73), 75 (base), 71 (39.11).

5-(2-furyl)-4-nitro-4-pentenaldimethylacetal **114**.

To a solution of 4-nitrobutanaldimethylacetal **115** (2.45g, 15mmol) in absolute EtOH (1.5ml) was added furfural (1.44g, 15mmol) and n-$BuNH_2$ (52mg, 0.71mmol). The solution was heated to reflux for 8 hr, cooled to room temperature, and the dark reaction mixture was then cast into brine (200ml). The aqueous phase was extracted with Et_2O (2 x 200ml), and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give 4.1g of a dark viscous liquid which was purified on a column of silica gel (230-400

mesh, 200g, 50mm o. d., ether-hexane 1:1, 100ml fractions) using the flash technique. Fractions 12-19 provided 2.5g, 69%, of **114** as a yellow liquid. ^{1}H-NMR (250MHz, $CDCl_3$): δ = 7.7 (s, 1), 7.6 (m, 1), 6.8 (m, 1), 6.5 (m, 1), 4.4 (t, J = 5.65Hz, 1), 3.22 (s, 6), 3-1.6 (m, 4); IR ($CHCl_3$): 3010, 2950, 1650, 1550, 1510, 1440, 1310, 1130, 1070, 730; EI-MS (70 eV): 210 (M+-31, 11.65), 179 (9.03), 163 (12.95), 152 (16.42), 137 (18.37), 119 (21.03), 106 (33.75), 91 (28.50), 75 (base), 71 (78.50).

4-amino-5-(2-furyl)-pentanaldimethylacetal **116**.

To a suspension of LAH (2.67g, 70.1mmol) in Et_2O (300ml) cooled in an ice-water bath was added 5-(2-furyl)-4-nitro-4-pentenedimethylacetal, **114**, (6.7g, 28mmol) in Et_2O (300ml) over 1 hr. After the addition was complete, the mixture was heated to reflux for 2 hours, cooled to 0° and quenched with 20% NaOH (35ml). The precipitate was filtered through a pad of celite and the celite rinsed well with Et_2O. The combined organic filtrates were dried over Na_2SO_4,and concentrated in vacuo to give 5.11g, 86%, of **116** as dark yellow liquid, which was used without further purification.

^{1}H-NMR (250MHz): δ = 7.3 (m, 1), 6.26 (m, 1), 6.02 (m, 1), 4.33 (t, J= 5.61Hz, 1), 3.28 (s, 6), 3.0 (m, 1), 2.75 (dd, J=4.46, 14.75Hz, 1), 2.5 (dd, J=8.16, 14.75, 1), 1.8-1.2 (m, 6); IR (CCl_4): 3400, 2940, 2825, 1600, 1510, 1450, 1390, 1365, 1190, 1130, 1070, 1115, 965, 730; EI-MS (70eV): 214 (M^++1, 10.07), 182 (3.30), 150 (12.72), 132 (20.55), 100(base), 81 (90.22), 75 (44.38), 68 (48.69).

Preparation of **117**.

To a solution of **116** (5.11g, 24.0mmol) in THF (80ml), cooled in an ice-water bath, was added Et_3N (3.15g, 31.2mmol), and ethylchloroformate (2.6g, 24.0mmol). After stirring at room temperature overnight, the mixture was filtered

through celite and the filtrate washed with brine (50ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 0.66g of a dark yellow oil which was purified on a column of silica gel (230-400 mesh, 60g, 40mm o. d., ethyl acetate-hexane 1:2, 30ml fractions) using the flash technique. Fractions 10-18 provided 4.4g, 65%, of **117** as a yellow solid. mp 53-55° C

^{1}H-NMR (250MHz): δ = 7.3 (m, 1), 6.25 (m, 1), 6.05 (m, 1), 4.7 (bm, 1), 4.3 (t, J=5.8Hz, 1), 4.07 (q, 7.1, 2), 3.88 (bm, 1), 3.27 (s, 3), 3.28 (s, 3), 2.8 (m, 2), 1.7-1.3 (m, 4), 1.15 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3440, 3005, 2950, 1710, 1510, 1450, 1220, 1130, 1080, 1055, 750; EI-MS (70eV): 222 (M+-63, 7.57), 204 (5.54), 172 (69.95), 132 (15.93), 81 (41.16), 75 (34.30), 68 (base), 53 (15.84), 43 (15.23).

Cyclization of **117**.

The acetal **117** (0.2g, 0.70mmol) was dissolved in $CHCl_3$ (22ml), cooled in an ice-water bath and trifluoroacetic acid-H_2O (1:1, 11.6ml) was added. The mixture was stirred for 1.5 h at 0°, then 1.5 h at room temperature. The mixture was cautiously cast into CH_2Cl_2 (50ml), and saturated aqueous $NaHCO_3$ (50ml). The organic layers were extracted with CH_2Cl_2 (3 x 25ml) and the combined layers washed with brine (50ml), dried over Na_2SO_4 and concentrated *in vacuo* to provide a dark yellow oil, which was purified on a column of silica gel (230-400 mesh, 8g, 20mm o. d., ethyl acetate-hexane 1:1, 2ml fractions) using the flash technique. Fractions 9-17 provided 101.3mg, 60%, of **118** a light yellow oil.

^{1}H-NMR (250MHz): δ = 9.78 (bs, 1), 4.5 (bm, 1), 4.3 (bm, 1), 4.2 (q, J=7.1 Hz, 2), 3.26 (m, 1), 2.9 (m, 1), 2.7 (m, 1), 2.33 (dd, J=1.95, 15.1Hz, 1), 2.15 (dd, J=4.68, 17.7Hz, 1), 1.55 (d, J=7.45Hz, 2), 1.28 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3020, 3005, 2980, 1690, 1420, 1380, 1335, 1320, 1205, 1110, 750; EI-MS (70eV): 239

(M+•+1, 3.79), 210 (8.43), 194 (2.49), 168 (2.59), 149 (5.40), 140 (base), 96 (14.63), 82 (10.21), 68 (93.18), 55 (31.43).

Reduction of **118**.

To a solution of the dione (59.2mg, 0.247mmol) in MeOH (3ml), cooled to 0°C in an ice water bath, was added $NaBH_4$ (28mg, 0.741mmol) in one portion. The solution was allowed to warm to room temperature over 4.5hr, then the excess $NaBH_4$ was quenched with H_2O (0.15ml). The solution was concentrated *in vacuo*, the residue taken up in CH_2Cl_2, dried over Na_2SO_4, and concentrated *in vacuo*, to provide a yellow oil which was purified on a column of silica gel (230-400 mesh, 13g, 20mm o. d., ethyl acetate (30ml), then ethyl acetate-methylene chloride-methanol 8:1:1 (50ml), 2ml fractions) using the flash technique. Fractions 10-16 provided 40.5mg, 67% of **124a**, and fractions 21-35, 10.2mg, 17% of **124b**.

Data for **124a**:

^{1}H-NMR (250MHz): δ = 4.2 (bm, 1), 4.1 (q, J=7.1Hz, 2), 4.06 (bt, 1), 3.9 (m, 1), 3.82 (m, 1), 3.7 (m, 1), 3.0 (bs, 2), 2.2 (m, 1), 2.1-1.5 (m, 7), 1.2 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3620, 3430, 2950, 1670, 1435, 1325, 1230, 1110, 1045, 740; EI-MS (70eV): 243 (M+•, 2.11), 212 (1.82), 198 (2.91), 1961 (238), 180 (1.68), 170 (9.34), 158 (52.94), 139 (34.79), 126 (4.38), 82 (31.71), 68 (base), 55 (36.87).

Data for **124b**:

^{1}H-NMR (250MHz): δ = 4.3 (bm, 1), 4.11 (q, J=7.1Hz, 2), 4.03 (bm, 1), 3.8 (bm, 1), 3.66 (bm, 2), 3.41 (bs, 2), 1.98-1.5 (m, 9), 1.22 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3380, 2980, 1675, 1430, 1385, 1330, 1215, 1115, 750; EI-MS (70eV): 244 (M+•+1, 3.36), 243, (M+•, 2.62), 212 (1.44), 196 (2.50), 180 (1.34), 170 (10.25), 158 (52.28), 139 (35.84), 126 (5.50), 108 (6.71), 96 (13.29), 84 (72.62), 68 (base), 55 (30.07).

Preparation of selenide **125**.

To **124** (153.0mg, 0.63mmol) as a mixture of diasteriomers, and o-nitrophenylselenylcyanate (172.3mg, 0.76mmol) in THF (2ml) was added Bu_3P (153mg, 0.76mmol) dropwise. After stirring at room temperature overnight, the solvent was removed and the crude product purified on a column of silica gel (230-400 mesh, 30g, 20mm o. d., ethyl acetate-hexane 4:3 for 28 fractions then ethyl acetate for 45 fractions, 9ml fractions) using the flash technique. Fraction 15-26 provided 174.6mg, 64.8%, of an amorphous solid **125a**, and 29-45 provided 63.9mg, 24%, of a yellow oil **125b**.

Data for **125a**:

1H-NMR (250MHz): δ = 8.22 (m, 1), 7.5 (m, 2), 7.26 (m, 1), 4.2 (bm, 1), 4.1 (q, J=7.1Hz, 2), 4.05 (m, 2), 2.95 (m, 2), 2.2-1.6 (m, 10), 1.2 (t, J=7.1Hz, 3); IR ($CHCl_3$): 33610, 2990, 1665, 1575, 1480, 1410, 1305, 1275, 1170, 1080, 670; EI-MS (70eV): 428 (M+·+1, 1.79), 355 (9.80), 254 (3.54), 295 (2.08), 242 (61.07), 224 (50.00), 196 (48.27), 158 (base), 152 (25.67), 140 (57.14), 106 (16.64), 82 (17.23), 68 (41.29).

Data for **125b**:

1H-NMR (250 MHz): δ = 8.82 (m, 1), 7.5 (m, 2), 7.3 (m, 1), 4.3 (bm, 1), 4.2 (m, 1), 4.1 (q, J-7.1 Hz, 2), 3.6 (dt, J=11.5, 5.77Hz, 1), 3.02 (m, 2), 2.2 (m, 1), 1.95-1.5 (m, 9), 1.22 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3420, 3000, 2915, 1675, 1590, 1425, 1335, 1310, 1210, 1115, 700; EI-MS (70 eV): 428 (M+·+1, 4.25), 426 (M+·, 1.24), 355 (4.78), 254 (3.77), 242 (3.47), 224 (base), 196 (1.52), 158(24.20), 152 (21.17), 140 (33.38), 106 (11.91), 82 (11.85), 68 (21.72).

Preparation of Acetate **126b**.

To a solution of equatorial alcohol **125b** (62.4mg, 0.146mmol) in pyridine (0.23ml) was added acetic anhydride (149.1mg, 1.46mmol) and the solution

was stirred overnight. The solvent was removed *in vacuo*, and the dark oil was taken up in CH_2Cl_2 (5ml) and washed with saturated aqeous NH_4Cl (5ml). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to provide a dark oil that was purified on a column of silica gel (230-400 mesh, 9.0g, 20mm o. d., ethyl acetate-hexane 1:1, 2ml fractions) using the flash technique. Fractions 7-18 provided 66.8mg, 97.5% of a yellow oil.

^{1}H-NMR (250MHz): δ = 8.18 (m, 1), 7.4 (m, 2), 7.2 (m, 1), 4.7 (dt, J=11.5, 5.77Hz, 1), 4.2 (bm,1) 4.1 (bm, 1), 4.09 (q, J=7.1Hz, 2), 2.84 (m, 2), 1.9 (s,3), 2-1.4 (m, 12), 1.13 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3020, 2980, 1730, 1680, 1510, 1430, 1330, 1250, 1200, 1110, 1030, 700; EI-MS (70eV): 470 (M+•+1, 3.95), 411 (7.72), 3.39 (7.58), 284 (12.36), 268 (35.80), 224 (79.87), 208 (25.05), 186 (28.17), 152 (26.24), 140 (88.51), 106 (36.81), 82 (26.06), 68 (87.59), 43 (base).

Preparation of Acetate **126a**.

To a solution of axial alcohol **125a** (72.5mg, 0.17mmol) in pyridine (0.32ml) was added acetic anhydride (173.1mg, 0.17mmol), then a catalytic amount of DMAP, and the solution was stirred at room temperature overnight. The solvent was removed and the residue purified on a column of silica gel (230-400 mesh, 10g, 20mm o. d., ethyl acetate-hexane 1:1, 2ml fractions) using the flash technique. Fractions 9-18 provided 79.6 mg, 100%, of a yellow oil.

^{1}H-NMR (250MHz): δ = 8.22 (m, 1),7.46 (m, 2), 7.28 (m, 1), 5.16 (bt, J=3.21Hz, 1), 4.21 (bm, 1), 4.1 (bm, 1), 4.1 (q, J=7.1Hz, 2), 2.86 (t, J=8.97, 2), 2.1-1.6 (m, 9), 2.03 (s, 3), 1.21 (t, J=7.05, 3); IR ($CHCl_3$): 3020, 2980, 1730, 1680, 1510, 1430, 1330, 1250, 1200, 1170, 1110, 1030, 700; EI-MS (70eV): 470 (M+•, 2.88), 411 (2.66), 284 (14.85), 268 (8.65), 238 (28.46), 224 (26.38), 208 (4.96), 198 (base), 186 (6.8), 178 (7.41), 152 (6.45), 140 (17.67), 106 (4.35), 82 (1.09), 68 (1.23).

Elimination of selenide **126b**.

To **126b** (53.9mg, 0.115mmol) in THF (0.5ml) was added 30% H_2O_2 (0.1ml). After stirring overnight, the solution was cast into CH_2Cl_2 (5ml) and 10% $Na_2S_2O_3$ (5ml). The aqueous solution was extracted with CH_2Cl_2 (2x5ml), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10ml), brine (10ml), dried over Na_2SO_4, and concentrated i*n vacuo* to give a yellow oil that was purified on a column of silica gel (230-400 mesh, 4.5g, 20mm o. d., ethyl acetate-hexane 1:2, 2ml fractions), using the flash technique. Fractions 4-8 provided 30.8mg, 100%, of **127b** as a water-white oil.

^{1}H-NMR (250MHz): δ = 5.6 (m, 1), 5.12 (m, 1), 5.0 (m, 2), 4.3 (bm, 1), 4.12 (bm, 1), 4.1 (q, J=7.1Hz, 2), 2.43 (bm,1), 2.2-1.5 (m, 6), 1.95 (s, 3), 1.22 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3020, 1725, 1685, 1520, 1425, 1210, 1110, 1030, 720; EI-MS (15eV): 267 (M^+, 1.91), 208 (10.94), 180 (2.66), 7.14 (base), 118 (4.80), 68 (60.06), 43 (34.31).

Elimination of selenide **126a**.

To **126a** (79.6mg, 0.17mmol) in THF (0.7ml) was added 30% H_2O_2 (0.15ml). After stirring overnight, the solution was cast into CH_2Cl_2 (5ml), and 10% $Na_2S_2O_3$ (5ml). The aqueous solution was extracted with CH_2Cl_2 (2x5ml), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10ml), brine (10ml), dried over Na_2SO_4, and concentrated to give a yellow oil that was purified on a column of silica gel (230-400 mesh, 5g, 20mm o. d., ethyl acetate-hexane 1:2, 2ml fractions) using the flash technique. Fractions 5-8 provided 40.0mg, 88%, of **127a** as a water white oil.

^{1}H-NMR (250MHz): δ = 1.7 (m, 1), 5.12 (m,2), 5.09 (m, 1), 4.22 (bm, 1), 4.14 (bm, 1). 4.1 (q, J=7.1Hz, 2), 2.68 (bm, 1), 2.2 (m, 1), 2.0 (s, 3), 1.9 (m, 4), 1,7 (m, 1), 1.2 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3005, 2960, 1770, 1720, 1680, 1770, 1520,

1420, 1380, 1320, 1225, 1170, 1120, 1040, 1000, 730; EI-MS: 267 (M+, 0.27), 208 (13.35), 179 (1.49), 152 (3.93), 140 (base), 68 (46.96)..

5-(2-furyl)-4-nitropentanaldimethylacetal **136**.

To a solution of freshly prepared NaOMe (7.58mmol) in MeOH (125ml), cooled to -30° C (CH_3CN-dry ice) was added a solution of freshly distilled acrolein (3.69g, 65.9mmol) and 2-(2-furyl)-1-nitroethane (**137**) (6.24g, 44.2mmol) in MeOH (500ml) drowise over 2.5 h. After stirring at -40° to -30° C overnight, concentrated HCl (7.6ml) was added dropwise and the solution was allowed to warm to room temperature. Saturated $NaHCO_3$ was added to neutralize the reaction mixture, the solvent was removed. Water (350ml) was added to the residue, and the aqueous layer was extrated with CH_2Cl_2 (4 x 300ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow liqiud which was purified on a column of silica gel (230-400 mesh, 500g, 60mm o.d., ethyl acetate-hexane 1:8 for 8 fractions, 1:7 for 16 fractions, 1:2 for 50 fractions, 50ml fractions. Fractions 12-43 provided 6.14g, 57.1%, of **136** as a yellow liquid.

^{1}H-NMR (250MHz): δ = 7.3 (m, 1), 6.25 (m, 1), 6.08 (m, 1), 4.78 (m, 1), 4.3 (t, J=5.61Hz, 1), 3.29 (m, 1), 3.28 (s, 3), 3.27 (s, 3), 3.06 (, 1), 2.0 (m, 1), 1.88 (m, 1), 1.65 (m, 2); IR (CCl_4): 3120, 2950, 2830, 1600, 1510, 1450, 1370, 1200, 1130, 1175, 1120, 925, 860, 730; EI-MS (70eV): 212 (M+-31, 4.23), 196 (1.36), 181 (11.72), 164 (11.78), 133 (22.22), 107 (41.96), 101 (28.66), 81 (57.15), 75 (base), 71 (53.49)

4-amino-5-(2-furyl)-pentanaldimethylacetal **138**.

To a solution of $NiCl_2$-$6H_2O$ (0.49, 2.05) in MeOH (40ml) was added $NaBH_4$ portionwise (0.23g, 6.15mmol) and the black suspension was sonicated for 1h.

5-(2-furyl)-4-nitropentanaldimethylacetal, **136**, (1g, 4.1mmol) in MeOH (5ml), then $NaBH_4$ (0.54g, 14.4mmol) was added and the mixture was stirred for 6 h. The mixture was filtered through a pad of celite, and rinsed with MeOH. The solvent was removed *in vacuo* to provide a green liquid and white solid (1.6g), which was purified on a column of silica gel (230-400 mesh, 80g, 40mm o. d., ethyl acetate-hexane 1:2 for 10 fractions, ethyl acetate-methylene chloride-methanol-triethylamine 20:2:1:1 for 21, 50ml fractions) using the flash technique. Fractions 16-21 provided 0.62g, 71%, **138** as a yellow viscous liqiud.

^{1}H-NMR (250MHz): δ = 7.3 (m, 1), 6.26 (m, 1), 6.02 (m, 1), 4.33 (t, J=5.61Hz, 1), 3.28 (s, 6), 3.0 (m, 1), 2.75 (dd, J=14.75, 4.46Hz, 1), 2.5 (dd, J=14.75, 8.16Hz, 1), 1.8-1.2 (m, 6); IR (CCl_4): 3400, 2940, 2825, 1600, 1510, 1450, 1390, 1365, 1190, 11309, 1070, 1115, 965, 730; EI-MS (70eV): 214 (M+·+1, 1.07), 182 (3.30), 150 (12.72), 132 (20.55), 100 (base), 81 (90.22), 75 (44.38), 68 (48.69).

Preparation of **135**.

To **138** (320mg, 1.5mmol) and TEA (198.1mg, 1.95mmol) in CH_2Cl_2 (15ml), cooled to 0°C in an ice-water bath, was added benzylchloroformate (281.5mg, 1.65mmol). A precipitate formed immediately. The mixture was stirred at room temperature overnight, the precipitate removed by filtration through a pad of celite, rinsed with CH_2Cl_2, and the filtrates concentrated *in vacuo* to provide 0.52g of a yellow solid, which was purified on a column of silica gel (230-400 mesh, 40g, 30mm o. d., ethyl acetate-hexane 1:2, 20ml fractions). Fraction 22-34 provided 0.49g, 94%, of **135** as a yellow solid. m. p. 68-69° C

^{1}H-NMR (250MHz): δ = 7.3 (m, 6), 6.25 (m, 1), 6.08 (m, 1), 5.1 (s, 2), 4.82 (bm, 1), 4.31 (t, J=5.7Hz, 1), 3.9 (bm, 1), 3.3 (s, 3), 3.29 (s, 3), 2.82 (bt, 2), 1.72-1.3 (m, 4); IR ($CHCl_3$): 3440, 3005, 2960, 1715, 1550, 1220, 1125, 1020, 775, 700; EI-

MS (70 eV): 284 (M^+-63, 0.1), 266 (0.24), 234 (4.89), 190 (4.87), 158 (1.72), **312 (1.64), 108 (4.05), 98 (2.31), 91 (base), 75 (20.63).**

Cyclization of **135**.

To a solution of **135** (255.2mg. 0.734mmol) in $CHCl_3$ (23ml), cooled to 0°C, in an ice-H_2O bath, was added trifluoroacetic acid-H_2O (1:1,12ml). The mixture was allowed to warm to room temperature and stirred overnight, then cautiously cast into CH_2Cl_2 (50ml) and saturated aqueous $NaHCO_3$ (50ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 25ml), the combined organic layers were washed with brine (50ml), dried over Na_2SO_4 and concentrated *in vacuo* to give a dark oil, which was purified on a column of silica gel (230-400 mesh, 25g, 30mm o. d., ethyl acetate-hexane 1:2 for 20 fractions, 1:1 for 51, 7ml fractions) using the flash technique. Fractions 39-51 provided 135.6mg, 61%,**139** as a yellow oil.

^{1}H-NMR (250MHz): δ = 9.33 (bs, 1), 7.38 (m, 5), 5.22 (s, 2), 4.6 (bm, 1), 4.39 (bm, 1), 3.29 (m, 1), 2.95 (m, 1), 2.72 (m, 1), 2.33 (dd, J=15.1, 1.95Hz), 2.15 (dd, J=17.7, 4.68Hz, 1), 1.57 (d, J=7.45Hz, 2). 2.0-1.7 (m, 2); IR ($CHCl_3$): 3020, 1700, 1410, 1340, 1210, 1105, 700; EI-MS (25eV): 305 (M^+, 6.19), 220 (5.20), 176 (5.12), 170 (5.74), 158 (3.10), 152 (11.44), 68 (23.72).

Reduction of **139**.

To a solution of **139** (310mg, 1.03mmol) in MeOH (10ml) cooled to 0°C in an ice-water bath, was added $NaBH_4$ (117mg, 3.09mmol) in one portion. After stirring overnight at room temperature, saturated aqueous NH_4Cl was added (1ml) and the solution was stirred for 30min. The solvent was removed, the residue taken up in CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to provide a yellow oil, which was purified on a column of silica gel (230-400

mesh, 10g, 30mm o. d., ethyl acetate-hexane 1:2, 12 fractions, ethyl acetate, 38 fractions, 10ml fractions) using the flash technique. Fractions 22-38 provided 220mg, 71%, **140** of 2 alcohols.

^{1}H-NMR (250MHz): δ = 7.38, (m, 5), 5.12 (s, 2), 4.3 (bm, 1), 4.03 (bt, 1), 3.95 (bm, 1), 3.8 (m, 1), 3.65 (bm, 2), 2,9 (bm, 2), 2.29-1 (m, 8); IR ($CHCl_3$): 3610, 3400, 3005, 2975, 1680, 1420, 1325, 1210, 1100, 1045, 720; EI-MS (25 eV): 305 (M^+, 0.19), 220 (5.20), 176 (5.12), 170 (5.74), 158 (3.10), 152 (11.44), 91 (base), 68 (23.72).

Preparation of selenide **141**.

To **140** (220mg) and o-nitrophhenylselenylcyanate (200mg) in THF (3ml) was added Bu_3P (175mg, 0.86mmol) dropwise. After stirring at room temperature overnight the solvent was removed *in vacuo* and the crude product purified on a column of silica gel (230-400 mesh, 30g, 30mm o. d.,ethyl acetate-hexane 1:4 for 4 fractions, ethyl acetate-hexane 1:1 for 16, ethyl acetate for 28, 7 ml fractions) using the flash technique. Fractions 12-28 provided 350mg, 99%, of **141** as a orange oil.

^{1}H-NMR (250MHz): δ = 8.2 (m, 1), 7.4-7.15 (m, 8), 5.02 (m, 1), 5.01 (s, 2), 4.2 (bm, 1), 3.99 (bm, 1), 2.85 (bm, 2), 2.2-1.6 (m, 10); IR ($CHCl_3$): 3610, 3400, 3000, 2940, 1680, 1585, 1520, 1460, 1230, 1115, 1030, 720; EI-MS (25eV): 243 (M^+-246, 10.44), 224 (1.60), 210 (4.31), 197 (22.75), 184 (base), 149 (6.67), 130 (13.11), 93 (16.58), 71 (91.10).

Elimination of **141**.

To **141** (350mg, 0.715mmol) in THF (3ml) was added 30% H_2O_2 (0.62ml). After stirring overnight, the solution was cast into CH_2Cl_2 (10ml) and 10% $Na_2S_2O_3$ (10ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 5ml), and

the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10ml), brine (10ml), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil that was purified on a column of silica gel (230-400 mesh, 19g, 30mm o. d., ethyl acetate-hexane 1:8 for 4 fractions, 1:1 for 25 fractions, 20 ml fractions) using the flash technique. Fractions 6-8 provided 115.0 mg, 56%, 19-25 45.4mg, 22.1%, of **142**.

^{1}H-NMR (250MHz): δ = 7.3 (m, 5), 5.9 (m, 1), 5.28 (m, 2), 5.12 (s, 2), 4.3 (bm, 1), 4.22 (bm, 1), 4.05 (t, J=5.77Hz, 1), 2.6 (bm, 1), 2.3-1.7 (m, 7); IR ($CHCl_3$): 3450, 3010, 1690, 1425, 1325, 1220, 1105, 1040, 930; EI-MS (25 eV): 288 (M^++1, 0.12), 287 (M^+, 0.11), 220 (9.63), 176 (7.74), 152 (6.63), 91 (base), 68 (32.92).

Oxidation of **142**.

To a solution of pyridine (149.0mg, 1.88) in CH_2Cl_2 (2.5ml) was added CrO_3 (93.9, 0.94mmol). After stirring 15 min, a solution of **142** (45.0mg, 0.157mmol) in CH_2Cl_2 (4ml) was added and the dark mixture was stirred for 20 min. The solvent was decanted and the residue rinsed with CH_2Cl_2 (8 x 2ml). The combined organic phases were washed with 5% NaOH (5ml), 1N HCl (5ml), saturated aqeous $NaHCO_3$ (5ml), brine (5ml) dried over Na_2SO_4 and concentrated to give a dark yellow oil which was purified on a column of silica gel (230-400 mesh, 3.5g, 10mm o. d., ethyl acetate-hexane 1:3, 1.5ml fractions) using the flash technique. Fractions 2-8 provided 28.5mg, 64%, of **143** as a yellow oil.

^{1}H-NMR (250 MHz): δ = 7.3 (m, 5), 5.9 (m, 1), 5.28 (m, 2), 5.18 (s, 2), 5.12 (m, 1), 4.58 (bm, 1), 4.5 (bm, 1), 2.7 (bm, 1). 2.35 (m, 1), 2.0-1.5 (m, 4); IR ($CHCl_3$): 3005, 2960, 1680, 1410, 1315, 1260, 1210, 1095, 1015; EI-MS (70eV): 285 (M^+, 3.46), 257 (1.73), 229 (0.29), 202 (1.35), 166 (2.33)., 158 (8.60), 150 (5.42), 91 (base), 65 (12.14)

6-(2-furyl)-4-nitrohexanaldimethylacetal **160**.

To a freshly prepared solution of NaOMe (0.58mmol) cooled to -30°C in a xylenes-liquid N_2 bath was added slowly a solution of acrolein (0.283g, 5.05mmol) and 3-(2-furyl)-1-nitropropane **159** (0.53g, 3.4mmol) in MeOH (48ml) over 45 min. After stirring for 45 min at -30° the solution was allowed to warm to room temperature overnight, then cooled to -30° and conc. HCl (0.58ml) was added. The solution was allowed to warm to room temperature over 6h, solid $NaHCO_3$ was added and the solvent was removed. Water (75ml) was added to the residue and the aqueous layer was extracted with CH_2Cl_2 (4 x 50ml), brine (100ml), dried over Na_2SO_4 and concentrated *in vacuo* to provide 0.77g of a dark red oil which was purified on a column of silica gel (230-400 mesh, 77g, 40mm o. d., ethyl acetate-hexane 1:4, 25ml fractions) using the flash technique. Fractions 35-62 provided 411mg, 47%, of **160** as a yellow oil. ^{1}H-NMR (250MHz): δ = 7.3 (m, 1), 6.28 (m, 1), 6.01 (m, 1), 4.48 (m, 1), 4.29 (t, J=5.61Hz, 1), 3.28 (s, 6), 2.65 (m, 2), 2.29 (m, 1), 2.03 (m, 2), 1.8 (m, 1), 1.6 (m, 2); IR ($CHCl_3$): 3010, 2940, 1550, 1440, 1370, 1200, 1130, 1070, 740; EI-MS (25 eV): 228 (M^+-15, 4.94), 210 (1.62), 201 (2.60), 182 (1.21), 166 (8.30), 158 (5.52), 138 (2.17), 91 (base), 68 (7.39)

4-amino-6-(2-furyl)-hexanaldimethylacetal.

To a solution of $NiCl_2$-$6H_2O$ (68.9mg, 0.29mmol), in MeOH (5.6ml) was added $NaBH_4$ (32.9mg, 0.87mmol) portionwise. The black suspension was sonicated for 30min, then a solution of **160** (150mg, 0.58mmol) in MeOH (1ml) was added, followed by more $NaBH_4$ (77.1mg, 2.0mmol). After stirring overnight the mixture was filtered through a pad of celite, the celite rinsed with MeOH, and the organic filtrate concentrated *in vacuo* to give 120mg, 91%, of a yellow-green oil which was used without further purification.

^{1}H-NMR (250MHz): δ = 7.3 (m, 1), 6.28 (m,1), 6.12 (m, 1), 5.9 (bm, 2), 4.33 (t, J=5.6, 1), 3.32 (s, 6), 3.1 (bt, 1), 2.81 (t, J=7.7, 2), 2.0 (m, 2), 1.73 (m, 4).; EI-MS (70eV): 228 (M+1, 2.27), 227(M$^+$, 0.84), 164 (13.22), 124 (20.92), 100 (27.40), 94 (7.52), 81 (base), 75 (38.78), 68 (56.97), 53 (25.63), 43 (26.93)

Preparation of **161**.

To a solution of the crude amine (120mg, 0.53mmol) in THF (4ml) was added TEA (70mg, 0.689mmol) and $ClCO_2Et$ (63mg, 0.583mmol). After stirring overnight the mixture was filtered through a pad of celite and the celite rinsed with CH_2Cl_2. The organic filtrates were concentrated *in vacuo* to provide 280mg of a yellow oil which was purified on a column of silica gel (230-400 mesh, 17g, 30mm o. d., ethyl acetate-hexane 3:4, 10ml fractions) using the flash technique. Fractions 13-21 provided 125.1mg, 78.8%, of **161** as yellow solid. ^{1}H-NMR (250MHZ): δ = 7.3 (m,1), 6.22 (m, 1), 5.94 (m,1)4.31 (t, J=6Hz, 1), 4.1 (bm, 1), 4.08 (q, J=7.1Hz, 2), 3.29 (s, 6), 2.6 (m, 3), 1.8, 1.4 (m, 6), 1.1 (t, J=7.1Hz, 3); IR ($CHCl_3$): 3440, 3000, 2950, 1700, 1510, 1450, 1415, 1385, 1225, 1120, 1070, 740; EI-MS (70eV): 268 (M$^+$-31, 0.25), 235 (7.96), 196 (12.56), 146 (8.74), 107 (21.58), 97 (11.93), 81 (base), 75 (39.61), 71 (12.91), 68 (19.68), 53 (10.88)

Cyclization of **161**.

To **161** (52.7mg, 0.176mmol) in $CHCl_3$ (6ml), cooled to 0°C in an ice-H_2O bath, was added trifluoroacetic acid-H_2O (1:1, 2.9ml). After stirring overnight the two phase mixture was cast into H_2O (5ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x5ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10ml), brine (10ml), dried over Na_2SO_4, concentrated *in vacuo* to provide 59.8mg of a dark oil which was purified on a

column of silica gel (230-400 mesh, 5g, 20mm o. d., ethyl acetate hexane 3:4, 2ml fractions) using the flash technique. Fraction 7-9 provided 14.8 mg, 35%, of **168** as an amorphous solid.

^{1}H-NMR (250MHz): δ = 6.14-5.74 (m, 4), 4.84 (bdt, 2), 4.04 (m, 8),2.74-1.64 (m, 14), 1.19 (m, 6); IR ($CHCl_3$): 3005, 2980, 1780, 1560, 1420, 1380, 1345, 1120, 1010; EI-MS (70eV): 470 (M^+, 0.93), 397 (1.06), 381 (5.18), 292 (2.02), 266 (3.04), 266 (3.04), 234 (3.62), 222 (4.80), 196 (3.46), 172 (6.64), 159 (8.44), 120 (57.84), 107 (base), 81 (44.88), 68 (35.56).

Ethyl-6-(2-furyl)-4-nitrohexanoate **164**.

To a solution of 3-(2-furyl)-1-nitropropane **159** (2g, 12.89mmol) and dioxane (0.6ml) was added Triton-B (0.05ml) and the solution was warmed to 70°C (internal temperature). Ethyl acrylate (0.65g, 6.45mol) was added dropwise, maintaining the temperature at 90° or below. After stirring at 70-75°C for 8h, and cooling to room temperature, the solution was acidified with 1N HCl, cast into CH_2Cl_2 (35ml). The aqueous phase was separated, extracted with CH_2Cl_2 (2x5ml), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (10ml), H_2O (10ml), dried over Na_2SO_4 and concentrated *in vacuo* to provide a yellow liquid which was purified on a column of silica gel (230-400 mesh, 220g, 50mm o. d., ethyl acetate-hexane 1:6 for 20 fractions, ethyl acetate-hexane 1:4 for 48 fractions, 40ml fractions) using the flash technique. Fraction 27-48 provided 1.55g, 94%, of **164** as a yellow liquid.

^{1}H-NMR (250MHz): δ = 7.28 (m, 1), 6.24 (m, 1), 6.0 (m, 1), 4.55 (m, 1), 4.1 (q, J=7.2Hz, 2), 2.65 (m, 2), 2.35-1.95 (m, 6), 1.2 (t, J=7.2Hz, 3); IR (neat): 2980, 2940, 1720, 1550, 1440, 1380, 1200, 1100, 1020, 800, 740; EI-MS (25 eV): 225 (M^+-30, 1.22), 207 (15.13), 163 (12.34), 135 (14.20), 133 (31.70), 126

(12.15), **121** (17.06), 120 (52.61), 119 (16.27), 107 (11.09), 97 (43.02), 94 (7.91), 81 (base).

5-(2-(2-furyl)-ethyl)-2-pyrrolidinone **165**.

To a solution of $NiCl_2$-$6H_2O$ (74.6mg, 0.314mmol) in MeOH (6ml) was added $NaBH_4$ (35.6mg, 0.94mmol) and the black suspension was sonicated for 1.5h. Ethyl-5-(2-furyl)hexanoate **160** in MeOH (1ml) was added followed by $NaBH_4$ (83mg, 2.19mmol). After stirring for 2 days the catalyst was removed by filtration through a pad of celite, the celite rinsed with MeOH, concentrated *in vacuo* to provide **165** as a greenish oil which was purified on a column of silica gel (230-400 mesh, 10g, 20mm o. d., ethyl acetate, 5ml fractions) using the flash technique. Fractions 6-30 provided 96.2mg, 85.6% of **165** as a white solid. mp=72.0-73.5 ° C

^{1}H-NMR (250MHz): δ = 7.32 (m,1), 6.29 (m,1), 6.02 (m, 1), 5.0 (b, 1), 3.7 (m, 1), 2.7 (t, J=7.5Hz, 1), 2.3 (m, 3), 1.85 (m, 3); IR ($CHCl_3$): 3440, 3020, 1695, 1220, 1130, 930, 1775, 710, 670; EI-MS (70 eV): 179 (M^+, 22.77), 162 (6.11), 161 (2.75), 120 (10.16), 98 (11.25), 97 (32.31), 94 (9.72), 84 (base), 81 (36.43), 69 (10.33), 56 (16.11), 55 (11.25), 53 (18.96), 41 (28.62).

5-(2-(2-furyl)-ethyl)-1-carboethoxy-2-pyrrolidinone.**166**.

To a solution of diisopropylamine (0.84g, 8.26mmol) in THF (17ml), cooled to -28°C in a dry ice-CCl_4 bath was added nBuLi (3.4ml, 2.4M, 8.26mmol) after 30min, the solution was cooled to -78°C (i-PrOH-dry ice) and **165** (1.48, 8.26mmol) in THF (10ml) was added dropwise over 10min. Stirring was continued for 25min, then ethylcyanoformate (0.82g, 8.26mmmol) was added, and the resulting mixture was allowed to stir at -78°C for 15min, then was warmed to room temperature, and cast into CH_2Cl_2 (50ml), and H_2O(50ml).

The aqueous layer was extracted CH_2Cl_2 (3 x 30ml) and the combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* to provide 2.21g of a yellow liqiud which was purified on a column of silica gel (230-400 mesh, 210g silica, 50mm o. d. ethyl acetate-hexane 9:16 for 8 fractions, ethyl acetate hexane 1:1 for 16 fractions) using the flash technique. Fractions 11-16 provided 1.76g, 84%, of **166** as a yellow oil.

^{1}H-NMR (250MHz): δ = 7.28 (m, 1), 6.25 (m, 1), 6.03 (m, 1), 4.26 (q, J=7.2Hz); IR (neat): 3120, 1785, 1750, 1715, 1600, 1510, 1450, 1375, 1280, 1150, 1050, 1010, 930, 750; EI-MS (70eV): 251 (M^+, 32.83), 206(5.76), 162 (36.78), 157 (36.85), 120 (61.31), 95 (21.83), 94 (18.77), 85 (28.61), 84 (base), 81 (59.67), 56 (19.89), 55 (18.29), 53 (32.46), 41 (43.39).

Reduction of **166**.

To the lactam **166** (99.4mg, 0.40mmol) in MeOH (4.0ml), cooled to -5° C in an ice-water-NaCl bath, was added $NaBH_4$ in one portion (153.0mg, 4.0mmol). After stirring for 1h, the mixture was cast into saturated $NaHCO_3$ (4ml), CH_2Cl_2 (4ml) cooled to 0° and stirred rapidly for 15min. The aqueous layer was extracted with CH_2Cl_2 (4 x 4ml), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide 100mg, 98.8%, of **167** as a water-white oil which was used without further purification.

^{1}H-NMR (250MHz): δ = 7.26 (m, 1), 6.22 (m, 1), 6.01 (m, 1), 5.48 (m, 1), 4.14 (m, 2), 3.8 (bm, 1), 2.6 (m, 2), 2.2-1.5 (m, 7) 1.22 (t, J=7.2Hz, 3); IR (CCl_4): 3600, 3440, 1685, 1420, 1380, 1340, 1265, 1190, 1115, 1110, 730; EI-MS (70eV): 253 (M^+, 1.52), 235 (37.97), 158 (17.05), 146 (19.51), 141 (57.65), 140 (20.98), 120 (23.70), 107 (12.68), 96 (12.68), 94 (15.44), 86 (17.79), 82 (12.25), 81 (57.45), 80 (15.66), 69 (48.74), 68 (base), 56 (10.84), 53 (25.23), 41 (34.97)

Preparation of 1-carboethoxy-2-ethoxy-5-(2-(2-furyl)-ethyl)-pyyrolidine.

To a solution of **166** (50.3mg, 0.2mmol) in EtOH (1.5ml) cooled to -20°C in a dry ice-CCl_4 bath was added $NaBH_4$ (53.2mg, 1.4mmol). Every 15 min 2N H_2SO_4 (2-3drops) was added. After stirring for 4h at -20°C , the solution was acidified to pH2 with 2N H_2SO_4, warmed to room temperature, cast into CH_2Cl_2 (5ml), brine (5ml). The aqueous layer was extracted with CH_2Cl_2 (4 x 5ml), dried over Na_2SO_4, and concentrated to give 61.6mg of a water white oil. ^{1}H-NMR (250MHz): δ = 7.26 (m, 1), 6.22 (m, 1), 6.0 (m, 1), 5.3 (bs, 1), 4.12 (bm, 2), 3.83 (bm, 1), 3.52 (bm, 2), 2.61 (m, 2), 2.24 (b, 1), 2.04 (m, 1), 1.9-1.6 (m, 4), 1.22 (t, J=7.2Hz, 3), 1.13 (t, J=7.2Hz, 3); IR ($CHCl_3$): 2990, 1685, 1415, 1380, 1350, 1320, 1200, 1115, 1010, 930, 730; EI-MS (70eV): 235 (M^+-46, 12.46), 196 (1.46), 152 (3.60), 141 (29.83), 140 (25.59), 120 (1.74), 107 (5.46), 94 (9.26), 91 (2.53), 81 (40.82), 68 (base), 53 (21.91).

Ethyl-6-(5-methyl-(2-furyl))-4-nitrohexanoate **169**.

To a solution of 3-(2-furyl)-1-nitropropane (7.6g, 4.9mmol) and dioxane (2.2ml) was added Triton-B (0.45ml) and the solution was warmed to 70°C (internal temperature). Ethyl acrylate (2.25g, 22.46mmol) was added dropwise, maintaining the temperature at 90° or below. After stirring at 70-75°C for 6h, and cooling to room temperature, the solution was acidified with 1N HCl, cast into CH_2Cl_2 (50ml). The organic layer was washed with saturated aqueous $NaHCO_3$ (20ml), H_2O (20ml), dried over Na_2SO_4 and concentrated *in vacuo* to provide 10.7g of a yellow liquid which was purified on a column of silica gel (230-400 mesh, 400g, 60mm o. d., ethyl acetate-hexane 1:10 for 10 fractions, ethyl acetate-hexane 1:6 for 18 fractions, 60ml fractions) using the flash technique. Fraction 11-18 provided 5.3g, 87.6%, of **169** as a yellow liquid.

^{1}H-NMR (250MHz): δ = 5.9 (m, 1), 5.82 (m, 1), 4.58 (m, 1), 4.12 (q, J=7.2Hz, 2), 2.6 (m, 2), 2.3-2.0 (, 6), 2.21 (s, 3), 1.22 (t, J=7.2Hz, 3); IR (CCl_4): 2980, 2940, 1735, 1555, 1450, 1380, 1180, 1025, 740; EI-MS (70eV): 270 (M^++1, 1.20), 269 (0.44), 252 (0.48), 239 (0.52), 221 (2.77), 193 (1.11), 177 (2.13), 147 (2.72), 108 (21.62), 95 (base).

5-(2-(5-methyl-(2-furyl))-ethyl)-2-pyrrolidinone **170**.

To a solution of $NiCl_2$-$6H_2O$ (5.1g, 18.9mmol) in MeOH (18ml) was added $NaBH_4$ (1.07g, 28.4mmol) and the black suspension was sonicated for 40min. Ethyl-5-(2-furyl)hexanoate **169** in MeOH (12ml) was added followed by $NaBH_4$ (2.5g, 66.2mmol). After stirring for 2 days the catalyst was removed by filtration through a pad of celite, the celite rinsed with MeOH, concentrated *in vacuo* to provide **170** as a greenish oil which was purified on a column of silica gel (230-400 mesh, 220g, 50mm o. d., ethyl acetate-methylene chloride-methanol 20:1:1, 40ml fractions) using the flash technique. Fractions 2-6 provided 3.57g, 97.8% of **170** as a white solid. mp=69.5-70.0° C

^{1}H-NMR (250MHz): δ = 5.85 (m, 2), 3.62 (m, 1), 2.6 (t, J=7.0Hz, 2), 2.3 (m, 2), 2.21 (s, 3), 1.8-1.5 (m, 5); IR ($CHCl_3$): 3320, 3060, 2990, 1700, 1420, 1260, 1130, 900, 680; EI-MS (70eV): 193 (1.39), 134 (1.04), 105 (2.77), 95 (13.83), 84 (20.88), 69 (12.74), 56 (53.38), 43 (base).

1-carboethoxy-5-(2-(5-methyl-(2-furyl))ethyl)-2-pyrrolidinone **171**.

To a solution of diisopropylamine (1.86g, 18.4mmol) in THF (38ml), cooled to -24°C in a dry ice-CCl_4 bath was added nBuLi (7.7ml, 2.4M, 18.4mmol) after 30min, the solution was cooled to -78°C (i-PrOH-dry ice) and **170** (3.56g, 18.4mmol) in THF (18ml) was added dropswise over 10 min. Stirring was continued for 25 min and ethylcyanoformate (1.8g, 18.4mmmol) was added

dropwise over 10 min. The solution was stirred at -78°C for 15 min, allowed to warm to room temperature, and cast into CH_2Cl_2 (75ml), and H_2O(75ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 40ml) and the combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo* to provide 5.26g of a yellow liqiud which was purified on a column of silica gel (230-400 mesh, 220g silica, 50mm o. d. ethyl acetate-hexane 9:16 for 8 fractions, ethyl acetate hexane 1:1 for 16 fractions 50ml fractions) using the flash technique. Fractions 6-12 provided 2.85g, 58%, of **171** as a yellow oil.

^{1}H-NMR (250MHz): δ = 5.86 (m, 1), 5.8 (m, 1), 4.26 (q, J=7.2Hz, 2), 4.18 (m, 1), 2.6-2.3 (m, 4), 2.19 (s, 3), 2.1 (m, 2), 1.78 (m, 2 (1.28 (t, J=7.2Hz, 3); IR (CCl_4): 2980, 2940, 1735, 1555, 1450, 1380, 1180, 1025, 740; EI-MS (70eV): 265 (M+, 21.80), 249 (1.72), 192 (3.69), 176 (34.24), 157 (15.55), 148 (12.07), 134 (35.41), 121 (12.68), 109 (29.80), 95 (98.77), 84 (base), 55 (27.83), 43 (77.09).

Preparation of **172**.

To a solution of **171** (777mg, 2.93mmol) in EtOH (22ml) cooled to -20°C in a dry ice-CCl_4 bath was added $NaBH_4$ (779mg, 20.5mmol). Every 15 min 2N H_2SO_4 (2-3 drops) were added. After stirring for 4h at -20°C , the solution was acidified to pH2 with 2N H_2SO_4, warmed to room temperature, cast into CH_2Cl_2 (40ml), brine (30ml). The aqueous layer was extracted with CH_2Cl_2 (4 x 30ml), dried over Na_2SO_4, and concentrated *in vacuo* to give 0.84g of a yellow oil which was purified on a column of silica gel (230-400mesh, 40g silica, 30mm o. d., ethyl acetate-hexane 1:8, 20ml fractions) using the flash technique. Fractions 9-18 provided 640mg, 74%, of **172** as a yellow oil.

^{1}H-NMR (250 MHz): δ = 5.86 (m, 1), 5.8 (m, 1), 5.3 (bm, 1), 4.12 (bq, 2), 3.82 (bm, 1), 3.55 (bm, 2), 2.56 (m, 2), 2.2 (s, 3), 2.1-1.6 (m, 6), 1.25 (t, J=7.2Hz, 3), 1.16 (t, J=7.2Hz, 3); IR ($CHCl_3$): 3010, 2980, 1700, 1420, 1385, 1200, 1125,

700; EI-MS (70eV): 295 (M^+, 1.02), 266 (2.35), 249 (24.76), 191 (13.49), 160 (10.62), 141 (33.62), 95 (base), 68 (65.84).

Cyclization of **172**.

To a vigorously stirred solution of **172** (0.61g, 2.07mmol) in cyclohexane (33ml), was added rapidly HCO_2H (7.5ml). After stirring for 3 min. the two phase mixture was immediately cast into H_2O (50ml), and CH_2Cl_2 (50ml). The aqueous layer was separated, extracted with CH_2Cl_2 (3 x 50ml) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (100ml), brine (100ml), dried over Na_2SO_4, and concentrated *in vacuo* to provide a yellow oil which was purified on a column of silica gel (230-400 mesh, 45g, 30mm o. d., ethyl acetate-hexane 1:6 for 16 fractions ethyl acetate-hexane 1:1 for 12 fractions) using the flash technique. Fractions 7-12 provided 0.26g, 51%, of **173** as a yellow oil, and fractions 19-25 provided 0.12g, 22%, of **174** as a yellow oil.

Data for **172**:

^{1}H-NMR (250MHz): δ = 5.79 (m,1), 4.8 (m, 1), 4.45 (bm, 1), 4.08 (q, 2), 2.8 (m, 2), 2.2 (s, 3), 2.2-2.0 (m, 3), 1.23 (m, 30, 1.2 (t, J=7.2Hz, 3); IR ($CHCl_3$): 3005, 2980, 1685, 1470, 1430, 1425, 1335, 1305, 1210, 1115, 1030; EI-MS (70eV): 249 (M^+, 33.46), 221 (4.65), 193 (4.49), 176 (12.78), 160 (45.64), 148 (27.80), 134 (69.01), 117 (12.00), 105 (12.83), 91 (26.95), 77 (18.59), 68 (13.72), 55 (16.57), 43 (base).

Data for **174**:

^{1}H-NMR (250MHz): δ = 4.42 (bm, 1), 4.4 (bm, 1), 4.1 (q, J=7.2Hz, 2), 3.2-2.35 (m, 5), 2.18 (s, 3), 2.1-1.4 (m, 4), 1.22 (t, J=7.2Hz, 3); IR ($CHCl_3$): 3000, 2980, 1680, 1695, 1425, 1385, 1425, 1385, 1330, 11170, 1120, 1020; EI-MS (70eV): 267 (M^+, 2.94), 224 (25.89), 206 (1.04), 191 (21.9), 178 (10.99), 168 (3.55), 153

(20.78), 135 (10.88), 110 (6.58), 96 (9.00), 82 (31.84), 68 (25.59), 55 (42.76), 43 **(base).**

Oxidation of **173**.

To **173** (105.7mg), 0.424mmol) in CH_2Cl_2 (3ml) and saturated aqueous $NaHCO_3$ (3.5ml) cooled to 0°C in an ice-water bath was added MCPBA (84mg) in one portion. After stirring for 2h at 0°C the layers were separated, the organic layer washed with 10% $Na_2S_2O_3$ (5ml), dried over Na_2SO_4, and concentrated *in vacuo* to provide a yellow oil which was purified on a column of silica gel (230-400 mesh, 7g, 20mm o.d., ethyl acetate hexane 1:1, 2ml fractions) using the flash technique. Fractions 9-15 provided 89.4mg, 79.5% of **175** as a yellow oil.

^{1}H-NMR (250MHz, benzene): $\delta = 5.4$ (bs, 0.5), 5.38 (bs, 0.5), 4.6 (m, 1), 4.3 (m, 1), 4.0 (bm, 2), 2.35 (m, 4), 1.8 (s, 30, 1.6-1.3 (m, 4), 1.03 (t, J=7.2Hz, 3); IR ($CHCl_3$): 3020, 2980, 1685, 1420, 1380, 1330, 1220, 1200, 1125, 925, 720; EI-MS (70eV): 265 (M^+, 18.16), 237 (3.44), 22 (6.28), 208 (5.47) 176 (12.95), 150 (30.32), 122 (16.93), 94 (20.28), 68, (22.23), 55 (24.60), 43 (base).

Kinetic ketalization of **175**.

To a solution of **175** (195.6mg, 0.74mmol) in CH_2Cl_2 (2ml) cooled to -78° C in a i-PrOH-dry ice bath was added bis-trimethylsilylethyleneglycol (149.6mg, 0.74mmol), and TMSOTf as a solution in CH_2Cl_2 (0.0987M, 0.15ml) After stirring at -78°C for 8h, pyridine (5 drops) was added and the solution was cast into CH_2Cl_2 (5ml) and saturated aqueous $NaHCO_3$ (5ml). The aqueous layer was extracted with CH_2Cl_2 (3 x 5ml), the combined organic layers dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil which was purified on a column of silica gel (230-400 mesh, 20g, 30mm o. d., ethyl acetate-hexane 1:2,

7ml fractions) using the flash technique. Fractions 12-20 provided 107.1mg, 52% of **176** as an amorphous solid.

^{1}H-NMR (250MHz): δ = 5.3-5.14 (bs, 1), 4.9-4.7 (m, 1), 4.1 (m, 7), 2.2-1.7 (m, 6), 1.56 (s, 3), 1.3 (m, 2), 1.03 (t, J=7.2Hz, 3); IR ($CHCl_3$): 3005, 2980, 1780, 1430, 1385, 1335, 1205, 1120, 950, 720; EI-MS (70eV): 309 (M^+, 3.18), 291 (4.67), 266 (9.51), 249 (8.38), 220 (5.00), 160 (41.77) 134, (39.78), 43 (base).

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