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This is to certify that the

dissertation entitled

PYRROLES AS TERMINATORS IN CATIONIC CYCLIZATIONS. THE PREPARATION OF 5,6,7,8-TETRAHYDRO-INDOLIZIDINES AND 6,7,8,9-TETRAHYDRO-[5H]-PYRROLO[1,2a]-AZEPINES. STUDIES DIRECTED TOWARDS THE SYNTHESIS OF SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS.

presented by

Jeffrey W. Raggon

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Major professor

Date April 21, 1986

PART I

PYRROLES AS TERMINATORS IN CATIONIC CYCLIZATIONS. THE PREPARATION OF 5,6,7,8-TETRAHYDRO-INDOLIZIDINES AND 6,7,8,9-TETRAHYDRO-[5H]-PYRROLO[1,2a]-AZEPINES.

PART II

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS.

By

Jeffrey William Raggon

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Submitted to
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ABSTRACT

PART I

PYRROLES AS TERMINATORS IN CATIONIC CYCLIZATIONS. THE PREPARATION OF 5,6,7,8-TETRAHYDRO-INDOLIZIDINES AND 6,7,8,9-TETRAHYDRO-[5H]-PYRROLO[1,2A]-AZEPINES.

PART II

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS.

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In Part I of this thesis, N-(epoxyalkyl) pyrroles **8**, **9**, **10**, **11**, **12** and **13** are readily prepared either by direct pyrrole N-alkylation with ω-iodo-1,2-epoxy alkanes or *via* alkylation with ω-iodo-1,2-alkanediol acetonides followed by conversion to the corresponding epoxides. The cyclization of these N-(epoxyalkyl) pyrroles were examined with five Lewis acids: $EtAlCl_2$; Et_2AlCl; $Ti(O\text{-}iPr)_3Cl$; ZnI_2; and $BF_3 \cdot OEt_2$, Et_3N providing cyclized products **14**, **16**, **17**, **18**, **19**, **20** and **21** in moderate to excellent yields. The cyclization products **14**, **16** and **20** are formally the products of "anti-Markovnikov" attack on the less-substituted epoxide terminus.

In Part II, carbinol amides **21**, **24**, **28**, **31**, **35**, **38**, **42** and **45**, derived from Mitsunobu coupling of either succinimide **17** or glutarimide **18** and the appropriate furyl alcohol followed by reduction, were employed as N-acyliminium ion precursors. Treatment of the precursors with a two-phase mixture of formic acid and cyclohexane resulted in facile cyclization to 5,6; 6,6; 5,7 and 6,7-membered, fused-ring systems in the electronically favored 3-to-2-furyl closure and 5,6- and 5,7-membered rings only in the 2-to-3-furyl closure. In similar fashion, carbinolamides **61** (n=1) and **64** (n=2) prepared by Mitsunobu coupling of succinimide **17** or glutinimide **18** and 2-(5-methyl-2-furyl) ethanol **58** followed by reduction, provided, under the standard cyclization conditions (HCO_2H, c-C_6H_2) 2 to 3 minutes, the diones **62** (n=1) and **65** (n=2), respectively. The chemical manipulations of the furyl residue necessary to transform indolizidine precursor **62** and quinolizidine precursor **65** into the bioactive alkaloids elaeokanine A **12** and lipinine **15** or epi-lupinine **16**, respectively, are described.

TO MY LOVING PARENTS,

JOHN AND NORMA RAGGON.

ACKNOWLEDGEMENTS

The author wishes to express his sincerest gratitude to Dr. Steven "Man with hair of fire" Tanis for his patience, support, guidance, friendship, and many excellent parties throughout this project.

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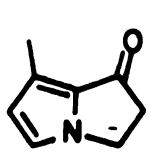
INTRODUCTION

The alkaloids present a multitude of skeletal and structural types providing a broad spectrum of potent and interesting biological activities.[1] A common skeletal arrangement displayed by a number of the bioactive alkaloids is a five-membered nitrogen-containing ring fused to a five-, six-, or seven-membered carbocycle. The N-containing heterocyclic moiety, in the pyrrole or pyrrolidine oxidation state, is an integral part of such molecules as the pyrrolizin-1-one 1[2], from the hairpencil secretion of the male Monarch butterfly *Lycorea ceres ceres*; the haepatotoxic pyrrolizidine alkaloid heliotridine 2[3]; the *Dendrobatid* alkaloid pumiliotoxin B 3[4]; the potent α-mannosidase inhibitor swainsonine 4[5]; and the insecticide, tuberostemonine 5.[6]



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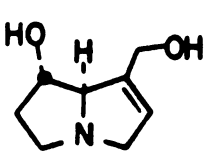

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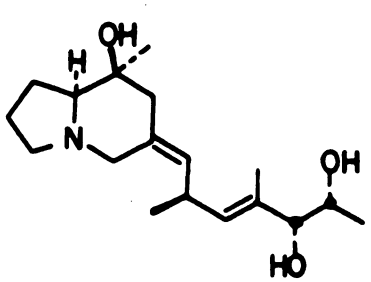

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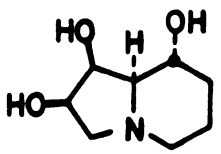

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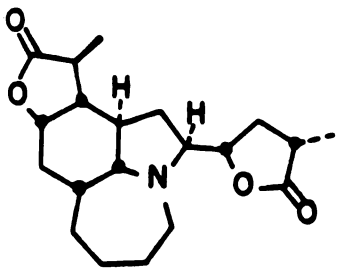

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Alkaloids 1-5 exhibit an N-α attachment of the fused ring system, as opposed to an α,β-fused array which is indicative of the indole class of alkaloids. As a result of our success in preparing fused-ring systems via furan-terminated cationic cyclizations[7], we became intrigued by the possibility of preparing the fused-ring systems of compounds 1-5 by a pyrrole-terminated cationic cyclization. In principle, the pyrrole nucleus should be a more effective terminator in cationic π-cyclizations than a furan, owing to pyrrole's greater nucleophilic character.[8] The general sequence (Eq. 1) for preparing the N-α fused system consists of cyclizing an N-alkyl substituted pyrrole 6, possessing a latent electrophilic site at a well-defined location in the alkyl chain. Compound 7 would result after activation of

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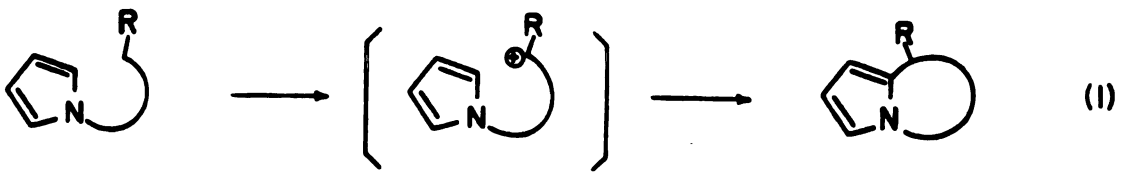
the benign electrophile, electrophilic attack at the more nucleophilic α-position, and rearomatization. The resulting N-α-dialkyl pyrrole 7, obtained from the cyclization of 6, establishes the pyrrole nucleus as the operational equivalent of the hypothetical pyrrolyl dianion illustrated in Equation 2. Variation of the distance between the active and latent electrophilic centers of the alkyl chain (Eq. 2) would provide compound 7 in which the size of the formed ring could be easily altered. In addition, the residual functionality resulting from the cyclization initiator might provide sufficient synthetic "handles" for the completion of a complex synthesis.



(1)

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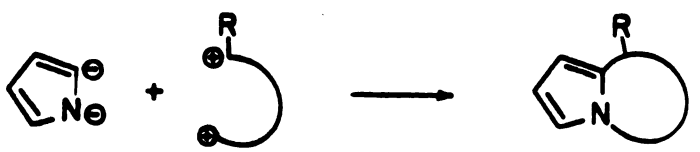

(2)

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Design and Synthesis of the Cyclization Substrates.

Cationic π-cyclization, in the construction of carbocyclic ring systems, has been the object of intense study since 1950.[7,9a-n] A classic example is the biomemetic

polyene cyclizations which have yielded a variety of naturally occurring steroids and other natural products with remarkable stereoselectivity at ring junctions and remote stereocenters in the polycyclic framework.[10,11]

For a polyene cyclization to succeed, a suitably electrophilic cyclization initiator and a sufficiently nucleophilic terminator-functionality are imperative. During the course of previous investigations of cationic cyclizations, a wide variety of initiator and terminator functions have been examined.

Some commonly utilized nucleophilic terminators include simple olefins[12], aromatic rings[13], acetylenes[14], allyl- and propargyl silanes[15] and allenes.[9a] Other terminator functions that are used with less regularity are vinyl ethers[16] or heteroaromatics, such as thiophene[17] and furan.[7] Conspicuously missing are numerous examples in which pyrrole has been used as a successful cyclization-terminator function.[2,9t,18] The lack of precedent in this area is undoubtedly due to the reactivity of the N-alkyl pyrrole starting materials and the enhanced sensitivity of the derived N-α-dialkyl pyrrole products. This is expected as pyrrole and simple alkyl substituted pyrroles have been reported to react readily with oxygen and acids, providing polymeric materials.[19]

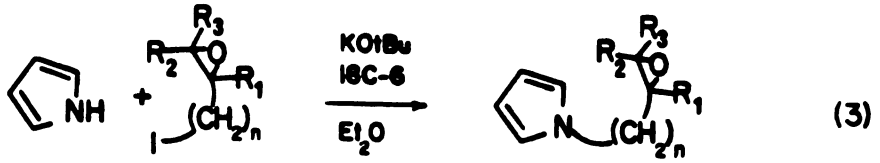
The range of electrophilic-initiator functions has been studied to a much greater extent. A wide variety of functional groups have been used to "trigger" cyclization

reactions. Some of the common initiators are simple olefins[20]; epoxides[9a,k;16;21]; allylic alcohols[7b,9a,14]; and their oxidation products, α,β-unsaturated ketones.[12a,b] Additionally, Johnson has shown that acetals can be used to initiate cationic cyclizations and that chiral acetals have the ability to transfer chirality to the resulting cyclization products.[22] Recently, attention has been directed towards the use of N-acyliminium ions as cationic cyclization initiators culminating in the syntheses of several alkaloid skeletal types.[9r-hh]

Our earlier work with furan-terminated cationic cyclizations[7] and the excellent studies of others[9a,k;16;21] has demonstrated the utility of the epoxide function as a cyclization initiator. A wide variety of Lewis acids were examined in that study and successful cyclization to acid labile 2,3-disubstituted furans was observed when the Brönsted acidity of the reaction medium was moderated. These relatively mild conditions, coupled with the ease of epoxide introduction, either insertion intact or as the corresponding diol acetonide, made the epoxide the initiator of choice. Another equally important aspect of this study was to assess the effectiveness of the sensitive pyrrole nucleus as a terminator function in cationic π-cyclizations.

The cyclization substrates examined were designed to permit entry into five-, six-, or seven-membered ring systems. In all of the cases examined, the substitution

about the oxirane was biased to favor one mode of C-O bond polarization over the alternative bond.[9b,13,16] Furthermore, we have examined placing the initiator function within the ring being formed (endocyclic) or outside the forming cycle (exocyclic).[23] The requisite N-epoxyalkyl pyrroles and possible reaction products are illustrated in Table I.

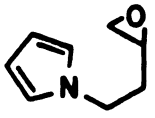
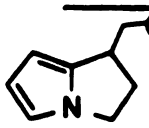
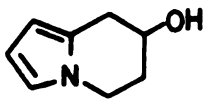
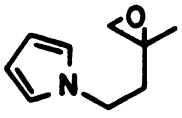
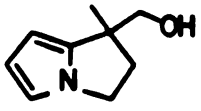
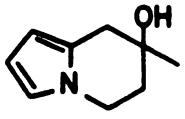
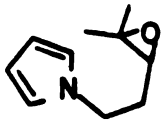
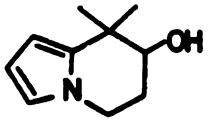
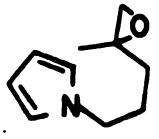
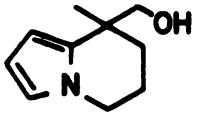
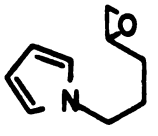
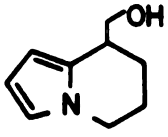
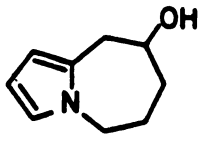
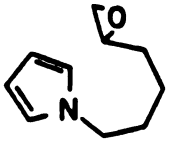
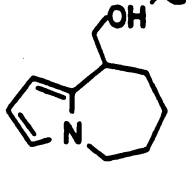


(3)

	n	R_1	R_2	R_3		
22	2	Me	H	H	9	40%
23	3	Me	H	H	11	34%

As previously mentioned, the propensity of pyrroles to readily react with oxidizing agents necessitates the introduction of the epoxide, or its synthetic equivalent, intact. Standard olefin epoxidation methodology[7a] would undoubtedly result in destruction of the sensitive pyrrole nucleus. Therefore, we envisioned the most direct route to the requisite epoxy pyrroles 8-13 to be that described in Equation 3. Treatment of pyrrole with KO<u>t</u>-Bu and 18-crown-6 ether followed by the addition of epoxy-iodide 22, which is prepared from the commercially available 3-methy-3-buten-1-ol[24], provided <u>N</u>-epoxyalkyl pyrrole 9 in a very modest 40% yield. Similarly, iodo-epoxide 23[25] led to epoxyalkyl pyrrole 11 in a disappointing 34% yield. The low yields of epoxy-pyrroles 9 and 11 forced us to consider introducing the epoxide function in a protected form, as the

TABLE I: Cyclization Substrates and Possible Products

Designation	Epoxyalkyl-Pyrrole	Possible Products
5-exo/6-endo	 8	 13  14
5-exo/6-endo	 9	 15  16
6-endo	 10	 17
6-exo	 11	 18
6-exo/7-endo	 12	 19  20
7-exo	 13	 21

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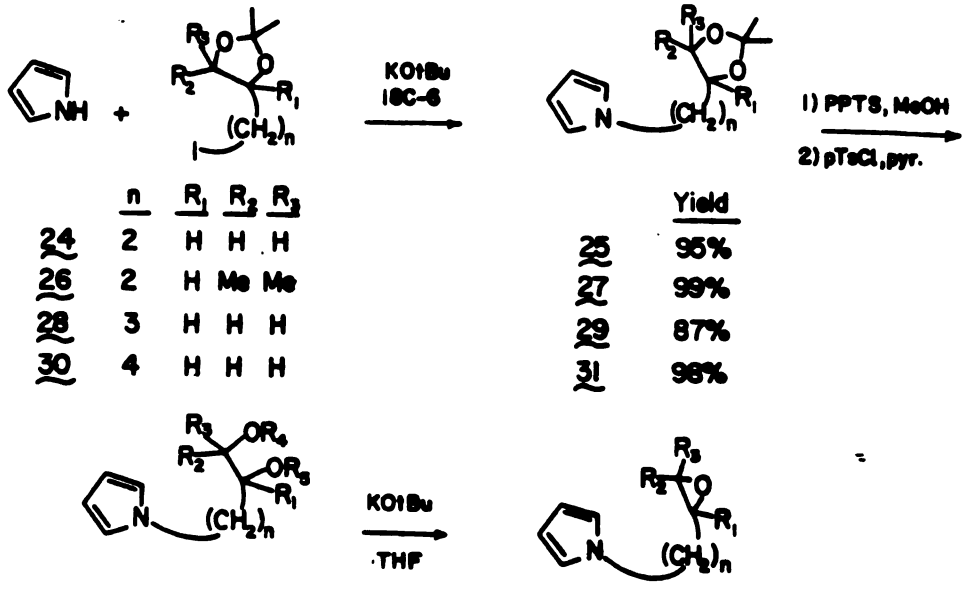
corresponding diol-acetonide, in order to complete the synthesis of 8, 10, 12, and 13 (See Figure 1).



	n	R_1	R_2	R_3	Yield
24 → 25	2	H	H	H	95%
26 → 27	2	H	Me	Me	99%
28 → 29	3	H	H	H	87%
30 → 31	4	H	H	H	98%

	n	R_1	R_2	R_3	R_4	R_5	Yield
32	2	H	H	H	H	H	89%
	2				pTs	H	91%
33	2	H	Me	Me	H	H	78%
	2				H	pTs	40%
34	3	H	H	H	H	H	91%
	3				pTs	H	83%
35	4	H	H	H	H	H	90%
					pTs	H	93%

	n	R_1	R_2	R_3	Yield
8	2	H	H	H	90%
10	2	H	Me	Me	86%
12	3	H	H	H	86%
13	4	H	H	H	88%

Figure 1 : The Synthesis of N-(Epoxyalkyl)-Pyrroles 8, 10, 12, and 13.

As is illustrated in Figure 1, the alkylation (KOt-Bu, 18C-6, Et_2O) of pyrrole with ω-iodo diol acetonide 24[26] yielded the corresponding pyrrole-N-alkyl diol acetonide 25 in a much improved 95% yield after chromatography. Careful hydrolysis with pyridinium p-toluenesulfonate[27] in methanol provided diol 32 (R_4=R_5=H, 89%) which was converted to the

glycol monotosylate (pTsCl, pyridine) **32** (R_4=*p*-Ts, R_5=H) in 91% yield. Closure to the oxirane, with carefully chosen reaction conditions, (KO*t*-Bu, THF, -78°C) gave the desired *N*-(epoxyalkyl) pyrrole **8** (90%) in 69% overall yield from pyrrole. In similar fashion, alkylation of pyrrole with ω-iodo diol acetonides **26**[28], **28**[29], and **30**[30] provided the requisite *N*-(epoxyalkyl) pyrroles **10**, **12** and **13** in 25%, 57% and 72% overall yields, respectively. With the exception of the mono-tosylation of the highly hindered diol **33** (R_4=R_5=H), all yields were ≥ 78% per step. Although initially disappointed with the low yield for the tosylation of diol **33** (R_4=R_5=H), the remainder of the reaction mixture consisted of unreacted starting material (55%) which could be readily recovered and resubmitted to the reaction conditions, thus providing an acceptable yield of **33** (R_4=H, R_5=*p*-Ts).

Cyclization Studies

With the desired cyclization substrates available, the ring closing sequence was then examined. Given the acid lability of the pyrrole terminator-function and the enhanced sensitivity of the resulting product, *N*,α-dialkyl pyrroles, careful consideration of the reaction conditions are of primary concern. The choice of Lewis acid should have a profound effect in determining the preferred reaction pathway of the cyclization substrates. It was our hope that correct conditions could be found which would maximize the

pathway leading to fruitful cyclization and minimize the formation of unwanted side products.

In addition to the standard $BF_3 \cdot OEt_2$, which has seen considerable use in inducing cationic π-cyclizations[9a,b;16], four other Lewis acids were selected (See Table II) after considering two factors: (i) the ability to readily modify the potency of a group of Lewis acids with a common metal center and (ii) the possibility of moderating the Brönsted acidity of the medium through choice of Lewis acid. Extraneous protic acid might be scavenged by Lewis acids, such as the alkyl aluminum halides[31] which possess a protonolyzable carbon-metal bond, forming an alkane. Alternatively, with the proper choice of metal, the product metal-alcohol complex should be a much weaker Brönsted acid compared to a BF_3-alcohol complex.

Snider has reported the successful application of alkyl aluminum halides as Lewis acids in acid-sensitive cyclizations. The alkyl aluminum halides cover a wide range of Lewis acidity[31], from the very potent $AlCl_3$, to the barely acidic Me_3Al. It is this range in Lewis acidity, together with their ability to scavenge protic acids, which might make these Lewis acids appropriate choices for initiating epoxy-pyrrole cyclizations. Further modification of aluminum-centered Lewis acids is possible, as demonstrated by Boeckman in his use of activated alumina as

TABLE II Cyclization Results

N-(Epoxyalkyl)-Pyrrole	Lewis Acid				
	$BF_3 \cdot OEt_2$(1 eq.)	$EtAlCl_2$(2 eq.)	Et_2AlCl(2 eq.)	$Ti(OiPr)_3Cl$(3 eq.)	ZnI_2(3 eq.)
8	14(70%)	14(23%)	14(32%)	14(45%)	14(33%)
9	16(32%)	16(42%)	16(44%)	-------	16(67%)
10	17(91%)	17(60%)	17(61%)	17(74%)	17(70%)
11	18(73%)	18(81%)	18(81%)	18(80%)	18(72%)
12	19(20%)	19(35%) 20(45%)	19(37%) 20(48%)	19(64%)	19(21%) 20(30%)
13	21(21%)	21(56%)	21(56%)	21(85%)	21(48%, φH) +21% iodohydrin 21(26%, Et_2O) +49% iodohydrin

a catalyst for epoxide-initiated vinyl ether-terminated cationic cyclizations.[18]

Titanium tetrachloride is a strong Lewis acid which has been observed to react with epoxides to provide β-chlorotitanates.[32] The oxophilicity of titanium and the relative acidity of the Ti-alcohol complex can be tempered by replacing chloride by alkoxy groups, such as isopropoxy. The titanium tetraalkoxides have been shown to be effective in catalyzing aldol condensations[32] and β-hydroxyl epoxide-initiated olefin-terminated cyclizations.[21] Furthermore, Stork[33] has demonstrated the use of the closely related $Zr(O\text{-}iPr)_4$ in promoting intramolecular Michael additions, leading to angularly methylated trans-hydrindenones.

Finally, zinc iodide[34] was selected to catalyze epoxy-initiated cyclizations based on the assumption that the intermediate Zn-alcohol complex, generated in the cyclization step, would be a weak protic acid. This assumption is substantiated by Marshall's successful closure of an acid-sensitive diene-aldehyde in his synthesis of occidentaldol.[34a]

For our particular study, we examined the ability of the following five Lewis acids to promote epoxy-initiated pyrrole-terminated cationic cyclization: $EtAlCl_2$; Et_2AlCl; $Ti(O\underline{i}\text{-}Pr)_3Cl$; ZnI_2; and $BF_3 \cdot OEt_2$/TEA. The first four Lewis acids had provided poor to excellent yields of cyclized products during our furan-terminated cyclization studies[7a];

however, the aluminum-based Lewis acids afforded considerable quantities of allylic alcohol by-products. From our initial experiments, we discovered that standard $BF_3 \cdot OEt_2$ conditions generally used to catalyze epoxy-initiated cyclizations had to be modified. Tempering the Lewis acidity of $BF_3 \cdot OEt_2$ was accomplished with ethereal solvents (Et_2O, THF) and tertiary amine bases, such as triethylamine. Having considered the requirements for the Lewis acids in this study, we began our examination with the moderated $BF_3 \cdot OEt_2$ (R_2O, Et_3N) reaction conditions.

N-(epoxyalkyl) pyrrole 8 was treated with $BF_3 \cdot OEt_2$ (1 equiv.), Et_3N (1 equiv.) in THF at -45°C to provide a single product 14 in 70% yield (See Table II). Examination of the spectroscopic data (IR, ^1H NMR, EI/MS) obtained for product 14 revealed the nature of the product. Indolizidine precursor 14 resulted from an unanticipated 6-endocyclic ring closure. The observation of cyclization exclusively at the less-substituted terminus of the epoxide was unforeseen in light of our experiences with a similar 5-exo/6-endo furan-terminated cyclization[7a] and the prior studies of van Tamelen.[3a,b] In the analogous epoxide initiated-furan terminated cyclization, the ring-opened allylic alcohol was formed to the complete exclusion of closure to form the five-membered ring.[7a] The failure to form a five-membered ring is likely the result of poor overlap between the developing cationic center at the internal carbon of the oxirane with the π-system of the pyrrole nucleus. Lack of

flexibility in the N-alkyl side chain which possesses but two sp^3-carbon atoms precludes this overlap from occurring. Indeed, by analogy to the work of Stork[35a], we anticipate that "Markovnikov" attack of the nucleophilic pyrrole-α-carbon upon the more substituted carbon of the Lewis acid complexed epoxide would result in a severe bond angle distortion. Furthermore, van Tamelen has examined a polyene cyclization with an identical orientation of the π-system nucleophile relative to the mono-substituted epoxide and has obtained the "anti-Markovnikov" cyclization product, albeit in 2% yield.[35b] Our observation of exclusive "anti-Markovnikov" attack on N-epoxyalkyl pyrrole 8 to give 14 in 70% yield is indeed noteworthy.

In a similar fashion, 8 was subjected to $EtAlCl_2$ (2 equiv., CH_2Cl_2, -78°C), Et_2AlCl (2 equiv., CH_2Cl_2, -78°C), $Ti(O\underline{i}\text{-}Pr)_3Cl$ (3 equiv., CH_2Cl_2, 0°C-25°C) and ZnI_2 (3 equiv., PhH, 25°C) to provide 14 in 23%, 32%, 45% and 33% yields, respectively. It should be noted that these and other cyclization yields determined in this study are for optimized reaction conditions and represent virtually all of the recovered material.

N-(epoxyalkyl) pyrrole 9, which has been further biased toward C-O bond cleavage at the internal carbon of the oxirane, was treated with $BF_3 \cdot OEt_2$ in THF containing an equivalent of TEA to yield exclusively the 6-endo product 16 in 32% yield; none of the possible by-products associated with epoxide opening were detected. The alkyl aluminum

halides; $EtAlCl_2$, Et_2AlCl and ZnI_2, yielded only **16** in 42%, 44% and 67% yields, respectively. Surprisingly, the generally mild $Ti(O\underline{i}\text{-}Pr)_3Cl$ afforded an intractable mixture of unstable products which apparently did not contain **16**.

Epoxy-pyrrole **10**, which was expected to yield only 6-endo product **17** by analogy to our earlier work in the furan area[7a], was treated with moderated $BF_3 \cdot OEt_2$ (TEA, THF) providing a single cyclized alcohol **17** in an excellent 91% yield as a white crystalline solid (mp = 79-81°C). Good to excellent yields were obtained (60-74%) with the remaining Lewis acids used in this study (See Table II). Similarly, <u>N</u>-(epoxyalkyl) pyrrole **11** led to uniformly high (72-81%) yields of the expected 6-exo product **18** after treatment with the Lewis acids shown in Table II.

The next substrate examined was the <u>N</u>-(epoxyalkyl) pyrrole **12** which is the precursor to the 6-exo **19** and the 7-endo cyclized alcohol **20**. An analogous 5-(3-furyl)-1,2-epoxy pentane provided only the corresponding 6-exo cyclized product with a variety of Lewis acids.[7a] Therefore, we anticipated similar behavior when the furyl moiety was replaced with pyrrole as the terminator. In the event, treatment of **12** with $BF_3 \cdot OEt_2$ (TEA, THF) afforded the 6-exo product **19**, albeit in only 20% yield. However, treatment of **12** with $EtAlCl_2$ (CH_2Cl_2, -78°C) yielded a mixture of two compounds, the expected <u>N</u>-α-dialkyl pyrrole product **19** (35%) and the previously unobserved 7-endo alcohol **20** (45%). The isolation of the 7-endo product as the major cyclized

material suggests that the more nucleophilic pyrrole terminator coupled with the relatively mild reaction conditions are conspiring to yield the product of an assisted SN^2 substitution at the less sterically encumbered oxirane carbon.[36]

The final cyclization precursor **13** provided the expected 7-exo alcohol **21** (See Table II) as the only cyclized product with the five Lewis acids studied. The yield of **21** ranged from a disappointing 21% using moderated $BF_3 \cdot OEt_2$ (TEA, THF) to an excellent 85% using $Ti(OiPr)_3Cl$ (See Table II). Exposure of **13** to ZnI_2 provided, in addition to cyclized product **21**, the corresponding iodohydrin in a yield which was dependent upon the reaction solvent (PhH, 21%; Et_2O, 49%).

These results demonstrate the pyrrole moiety to be an excellent cationic cyclization terminator in epoxide-initiated cyclizations. In general, the ring size obtained is predictable, providing mixtures only in the case of *N*-(epoxyalkyl) pyrrole **12**. In addition, it is interesting to note that the 7-endo mode of closure can compete effectively with the expected 6-exo pathway leading to **12**. It is particularly noteworthy that the exclusive products obtained from epoxy-pyrroles **8** and **9** are the "anti-Markovnikov" cyclized materials. Finally, the yields of cyclized products obtained ranged from moderate to excellent; however, closer scrutiny of Table II does not reveal any general trends which would assist in the selection of

"optimum" reaction conditions. The most favorable reaction conditions must be determined on an individual basis.

EXPERIMENTAL

PYRROLES AS TERMINATORS IN CATIONIC CYCLIZATIONS. THE PREPARATION OF 5,6,7,8-TETRAHYDRO-INDOLIZIDINES AND 6,7,8,9-TETRAHYDRO-[5H]-PYRROLO[1,2A]-AZEPINES.

EXPERIMENTAL SECTION

General. Tetrahydrofuran (THF) and benzene were dried by distillation under argon from sodium benzophenone ketyl; methylene chloride was dried by distillation under argon from calcium hydride; triethylamine (TEA) was dried by distillation under argon from calcium hydride; t-butanol was dried by distillation under argon from sodium; pyridine was dried by distillation under argon from calcium hydride. Boron trifluoride etherate ($BF_3 \cdot OEt_2$) was dried by distillation at reduced pressure from calcium hydride. Petroleum ether refers to 35-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Columbia Chemical Industries, Inc., Columbus, Wisconsin, and was used as received. Osmium tetraoxide was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin and prepared as a 0.5M solution in t-butanol. Ethylaluminum dichloride and diethyl aluminum chloride were purchased as hexane solutions from Alfa Products, Danvers, Massachusetts, and used as received. All other reagents were used as received unless otherwise stated; all reactions were performed under argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrometer or a Perkin-Elmer Model 167 spectrometer with polystyrene as standard. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian T-60 at 60MHz, a Varian CFT-20 at 80MHz, 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 followed: chemical shifts (multiplicity: s = singlet, brs = broad singlet, dd = doublet of doublets, d = doublet, t = triplet, q = quartet, m = multiplet, coupling constant (Hz), integration). Electron impact (EI/MS, 70eV) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. Exact Mass Mass Spectrometry is presently being performed at the University of Chicago under the direction of Professor David G. Lynn.

Flash column chromatography was performed according to the procedure of Still[37] *et. al.* by using the Whatman silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (o.d.) is listed in millimeters.

General Procedure for the N-Alkylation of Pyrroles with ω-Iodo Epoxides.

2-Methyl-5-(*N*-pyrrolyl)-1,2-epoxypentane 11.

To anhydrous ether (40mL) at room temperature under argon was added 18-crown-6 ether (0.53g, 2.0mmol) and potassium t-butoxide (2.58g, 23.0mmol) followed immediately by pyrrole (1.34g, 1.39mL, 20.0mmol). The resulting off-white suspension was stirred for 15 minutes. To this mixture was added a solution of 23[a] (5.20g, 23.0mmol) in ether (18mL) over 15 minutes. The mixture was stirred at room temperature for 20h, diluted with H_2O (100mL) and cast into ether (100mL) and H_2O (100mL). The aqueous layer was separated and washed with ether (2 x 80mL). The combined ether layers were washed with brine (200mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 200g, 60mm o.d., ether-petroleum ether 30:70, 60mL fractions) using the flash technique. Fractions 24-32 provided 1.13g, 34%, of 11 as a pale yellow, free-flowing liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.45 (m, 2), 6.35 (m, 2), 3.29 (t, J=6Hz, 2), 2.10 (s, 2), 1.38 (m, 2), 1.10 (m, 2), 0.93 (s, 3); IR (neat): 3100, 3040, 2920, 1290, 1090, 720 cm^{-1}; EI-MS (70eV): 165 (M^+, 73.3), 148 (37.7), 134 (38.7), 120 (60.5), 81 (53.5), 80 (base), 68 (60.7).

Anal. C, H, N.

2-Methyl-4-(N-pyrrolyl)-1,2-Epoxybutane 9.

According to the general procedure for N-alkylation of pyrroles with ω-iodoepoxides, the reaction of 0.34g (5mmol) of pyrrole with KOtBu (0.56g, 5mmol) and 18-crown-6 ether (44mg, 0.17mmol) in benzene (8mL) followed by the addition of ω-iodoepoxide 22[7,25] gave 0.302g (40%) of 9 after purification by chromatography on a column of silica gel. ^{1}H-NMR (60MHz): δ = 6.43 (t, J=1.5Hz, 2), 5.90 (brt, J=1.5Hz, 2), 3.88 (t, J=6.5Hz, 2), 2.3 (m, 2), 1.85-2.20 (m, 2), 1.22 (s, 3); IR (neat): 3100, 3020, 2930, 2870, 1500, 1450, 1380 (br), 1285, 1090, 905, 800, 730 cm^{-1}; EI-MS (70eV): 151 (M^+, 68), 120 (33), 106 (14), 95 (12.8), 80 (base).

Anal. C, H, N.

1-Benzyloxy)-4-methyl-pent-3-ene.

To a suspension of oil-free NaH (1.42g, 59mmol) in dry THF (100mL), chilled in an ice-H_2O bath to 0°C, was added 4-methyl-pent-3-en-1-ol[38] (5.78g, 57.8mmol) over 30 min. The mixture was warmed to 25°C, stirred for 30 min, then a catalytic amount of tetrabutylammonium iodide (214mg, 0.578mmol) was added followed by the addition of a solution of benzyl bromide (9.99g, 58.4mmol) in THF (10mL) over 40 min. The resulting suspension was stirred at 25°C for 5h, quenched by cautiously adding water (100mL) and extracted with Et_2O (3 x 100mL). The combined Et_2O layers were washed

with brine (300mL), dried ($MgSO_4$) and concentrated *in vacuo* to 11.0g, 100%, of the benzyl ether as a pale yellow liquid which was used without further purification. ^1H-NMR (60MHz): δ = 7.38 (s, 5), 5.10 (m, 1), 4.45 (s, 2), 3.48 (t, J=8Hz, 2), 2.50-2.0 (m, 2), 1.70 (s, 3), 1.63 (s, 3); EI-MS (70eV): 190 (M^+, 1.05), 175 (1.97), 147 (1.48), 132 (8.50), 107 (26.6), 91 (base), 69 (76.7), 41 (76.0).

1-(Benzyloxy)-4-methylpentan-3,4-diol.

To a solution of benzyl ether (3.85g, 20.26mmol) and N-methylmorpholine N-oxide hydrate[39] (3.56g, 26.34mmol) in acetone (13mL) and water (5.0mL) was added at room temperature a solution of osmium tetraoxide[39] (2.02mL, 1.01mmol, 0.5M) in t-butanol. The resulting deep purple solution faded within minutes to a light maroon color where it remained for 15 minutes before returning to a deep purple cast. The mixture was stirred at room temperature for 24h. A major portion of the solvents were removed at reduced pressure and the aqueous residue was acidified with cold 2N aqueous HCl followed by the addition of 10% aqueous sodium bisulfite (10mL). The aqueous mixture was saturated with sodium chloride and extracted with ethyl acetate (6 x 50mL). The combined organic phases were washed with 10% aqueous sodium bisulfite (300mL), brine (300mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide 4.03g of a pale yellow, viscous liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 200g,

60mm o.d., ethyl acetate, 75-100mL fractions) using the flash technique to provide 3.50g, 77%, of mono-protected triol as a water-white viscous liquid which was immediately converted to the corresponding acetonide.

^{1}H-NMR (60MHz): δ = 7.30 (s, 5), 4.50 (bs, 2), 3.70 (t, J=6Hz, 2), 3.50 (m, 1), 3.15 (s, 2), 2.0-1.56 (m, 2), 1.23 (s, 3), 1.15 (s, 3); EI-MS (70eV): 224 (M^+, 0.20), 206 (0.18), 188 (0.44), 178 (0.65), 165 (1.32), 148 (0.87), 123 (8.25), 107 (15.1), 91 (base).

<u>1-(Benzyloxy)-4-Methyl-3,4-Di-O-Isopropylidene-pentane-3,4-Diol</u>.

To a solution of the O-Benzyldiol (3.50g, 15.62mmol) in dry acetone (50mL) was added two drops of concentrated sulfuric acid and solid sodium sulfate (4.0g). The mixture was stirred at room temperature overnight then quenched by suspending solid sodium bicarbonate in the reaction mixture for 15 min. The mixture was then filtered through a pad of celite topped with a layer of anhydrous magnesium sulfate and concentrated *in vacuo* to give 4.0g, 97%, of the desired acetonide as a water-white viscous liquid.

^{1}H-NMR (60MHz): δ = 7.32 (s, 5), 4.58 (s, 2), 3.69 (m, 3), 1.80 (m, 2), 1.43 (s, 3), 1.37 (s, 3), 1.28 (s, 3), 1.10 (s, 3); EI-MS (70eV): 264 (M^+, 0.85), 249 (base), 206 (18.8), 175 (4.46), 147 (25.4), 123 (38.2), 107 (13.8), 91 (73.3), 84 (16.7).

4-Methyl-3,4-Di-O-Isopropylidene-pentane-1,3,4-triol.

A solution of benzylether-acetonide (4.00g, 15.2mmol) in ethanol (60mL) was hydrogenated at 65 psi over 10% palladium on charcoal (0.98g) for 24h. The catalyst was removed by filtration and the solution was concentrated *in vacuo* to afford 2.54g, 98%, of the deprotected triol as a water-white viscous liquid.

^{1}H-NMR (60MHz): δ = 7.33 (s, 5), 4.55 (s, 2), 3.64 (m, 3), 1.78 (m, 2), 1.41 (s, 3), 1.32 (s, 3), 1.25 (s, 3), 1.10 (s, 3); IR (neat): 3480, 2950, 1460, 1370, 1100, 750, 700 cm^{-1}; EI-MS (70eV): 174 (M^+, 1.05), 159 (19.3), 117 (14.6), 99 (34.8), 85 (50.8), 71 (23.4), 59 (61.4), 43 (base).

General Procedure for the Tosylation of ω-Hydroxy Acetonides.

2-Methyl-2,3-Di-O-Isopropylidene-pentane-2,3,5-triol-5-p-Toluenesulfonate.

To a solution of the ω-hydroxy acetonide (2.54g, 14.60mmol) in dry pyridine (8mL), chilled in an ice-water bath, was added p-toluenesulfonyl chloride (3.48g, 18.25mmol) in one portion. The reaction mixture was stirred at 0°C for 2h and then placed in a freezer (-20°C) overnight. The cooled reaction mixture was allowed to come to room temperature, cast into ice-conc. HCl (50g/50mL), and extracted with ether (100mL). The ether layer was washed with 1N aqueous HCl (100mL), water (100mL), saturated aqueous sodium bicarbonate (100mL), brine (100mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 4.57g, 95%, of

the acetonide tosylate as a pale yellow, viscous liquid which was used without further purification.

General Procedure for the Iodination of Acetonide-Tosylates. 5-Iodo-2-Methyl-2,3-Di-O-Isopropylidene-pentane-2,3-Diol (26).

To a solution of the corresponding acetonide-tosylate (8.22g, 25.06mmol) in acetone was added anhydrous sodium iodide (4.25g, 27.68mmol). The resulting yellow-brown mixture was heated under reflux for 5h, cooled to room temperature, filtered, and the filtrate taken up in ether (150mL). The organic layer was washed with 10% aqueous sodium bisulfite (2 x 150mL), water (150mL), saturated aqueous sodium bicarbonate (150mL), brine (150mL), dried (Na_2SO_4) and concentrated *in vacuo* to provide 6.0g (84%) of **26** as a pale yellow, free-flowing liquid. The crude product was purified by bulb-to-bulb distillation: $bp_{2.0}$ = 89°C, to yield 5.69g, 80%, of **26** as a water-white, free-flowing liquid.

^{1}H-NMR (60MHz): δ = 3.45 (m, 1), 3.32 (m, 2), 2.10 (m, 2), 1.50 (s, 3), 1.40 (s, 3), 1.29 (s, 3), 1.18 (s, 3); IR (neat): 2940, 1450, 1400, 1230, 1060, 830 cm^{-1}; EI-MS (70eV): 284 (M^+, 2.57), 269 (70.5), 239 (5.08), 227 (30.5), 212 (20.5), 127 (4.38), 99 (34.8), 71 (23.4), 59 (61.5), 43 (base).

1,2-Di-O-Isopropylidene-butane-1,2-Diol-4-p-Toluenesulfonate

A solution of the corresponding ω-hydroxy acetonide[28] (8.42g, 57.7mmol) in dry pyridine (30mL), cooled to 0°C in an ice-water bath, was reacted with p-toluenesulfonyl chloride (14.66g, 76.9mmol) according to the general procedure for tosylation of ω-hydroxy acetonides to yield 15.0g, 87%, of the tosylate acetonide as a pale yellow, viscous liquid which was used in the next step without further purification.

4-Iodo-1,2-Di-O-Isopropylidene-butane-1,2-Diol (24).

A solution of the tosylate acetonide (15.0g, 50mmol) in acetone (dried over $CaCl_2$, 200mL) was reacted with anhydrous sodium iodide (8.25g, 55mmol) according to the general procedure. The crude iodo acetonide **24** was purified by bulb-to-bulb distillation, B.P.$_{0.7}$ = 52°C, to provide 10.1g, 79%, of **24** as a water-white, free-flowing liquid.
^{1}H-NMR (60MHz, CCl_4): δ = 4.08 (m, 2), 3.60 (m, 1), 3.22 (t, J=8Hz, 2), 2.02 (m, 2), 1.38 (s, 3), 1.31 (s, 3); IR (neat): 2980, 2940, 2880, 1370, 1230, 1160, 1060, 840 cm^{-1}; EI-MS (70ev): 256 (M^+, 0.87), 241 (base), 218 (6.79), 199 (9.66), 181 (30.9), 101 (13.7), 72 (22.0), 59 (18.7), 43 (95.3).

5-Hydroxy-1,2-Di-O-Isopropylidene-pentane-1,2-Diol.

To a solution of the 1,2,5-Pentanetriol[29] (4.13g, 34.4mmol) in acetone (50mL, dried over $CaCl_2$) at room

temperature was added two drops of conc. HCl together with anhydrous Na_2SO_4 (6.0g). The reaction mixture was stirred for 3h at room temperature then solid $NaHCO_3$ was suspended in the mixture and stirring was continued for an additional 25 min. The reaction mixture was filtered and concentrated *in vacuo* to 4.98g, 90%, of the hydroxy acetonide as a slightly cloudy, viscous liquid which was purified by distillation: $bp_{0.1}$ = 70°C.

^{1}H-NMR (60MHz, CD_3CN): δ = 4.10 (m, 2), 3.53 (m, 3), 2.80 (brs, 1), 1.60 (m, 4), 1.4 (s, 3), 1.32 (s, 3); EI-MS (70eV): 160 (M^+, 1.00), 145 (6.39), 117 (6.27), 99 (24.5), 101 (15.7), 83 (18.9), 59 (60.1), 43 (base).

1,2-Di-O-Isopropylidene-pentane-1,2-Diol-p-Toluenesulfonate.

A solution of the hydroxy acetonide (2.85g, 17.8mmol) in dry pyridine (10mL), chilled to 0°C in an ice-water bath, was reacted with p-toluene sulfonyl chloride (4.52g, 23.7mmol) according to the general procedure to yield 4.08, 85%, of the acetonide-tosylate as a cloudy, pale yellow viscous liquid which was used without further purification.

5-Iodo-1,2-Di-O-Isopropylidene-pentane-1,2-Diol (28).

A solution of the tosylate acetonide (4.23g, 13.43mmol) in acetone (50mL, dried over $CaCl_2$) was reacted with anhydrous sodium iodide (2.32g, 15.44mmol) according to the general procedure for iodination of tosylate acetonides to provide 2.94g, 76%, of **28** as a pale yellow, free-flowing

liquid. The crude product was purified by Kugelrohr distillation, B.P.$_{0.01}$ = 68-70°C, to yield a colorless free-flowing liquid.

^{1}H-NMR (60MHz): δ = 4.1 (m, 2), 3.45 (m, 1), 3.20 (t, J=6Hz, 2), 2.15 (m, 2), 1.60 (m, 2), 1.35 (s, 3), 1.30 (s, 3); IR (neat): 2960, 1370, 1230, 1180, 1080, 850 cm^{-1}; EI-MS

1,2-Di-O-Isopropylidene-hexane-6-p-Toluenesulfonate.

A solution of the hydroxy acetonide[30] (11.12g, 63.9mmol) in dry pyridine (33mL), chilled to 0°C in an ice-water bath, was reacted with p-toluenesulfonyl chloride (16.2g, 85mmol) according to the general procedure to give 18.95g, 90%, of the tosylate acetonide as a colorless viscous liquid which was used without further purification.

6-Iodo-1,2-Di-O-Isopropylidene-hexane-1,2-diol (30).

A solution of the tosylate acetonide (18.84g, 57.44mmol) in acetone (180mL, dried over $CaCl_2$) was reacted with anhydrous sodium iodide (9.48g, 63.2mmol) according to the general procedure. The crude iodo-acetonide 30 was purified by bulb-to-bulb distillation: bp$_{0.01}$ = 87°C, to give 15.17g, 93%, of 30 as a water-white liquid.

^{1}H-NMR (60Hz): δ = 4.08 (m, 2), 3.50 (m, 1), 3.20 (t, J=7Hz, 2), 1.90 (m, 2), 1.60 (m, 2), 1.42 (s, 3), 1.39 (s, 3); IR (neat): 2920, 1450, 1370, 1225, 1170, 1060, 850 cm^{-1}; EI-MS (70eV): 284 (M^+, 11.9), 269 (base), 227 (8.85), 209 (22.6), 127 (4.38), 101 (13.5), 81 (76.3), 72 (37.8), 43 (89.3).

General Procedure for the N-Alkylation of Pyrroles with ω-Iodo Acetonides.

1,2-Di-O-Isopropylidene-6-(N-pyrrolyl)hexane-1,2-diol (31).

To anhydrous ether (60mL) at room temperature under argon was added 18-crown-6 ether (0.793g, 3.0mmol) and potassium t-butoxide (3.82g, 34.0mmol), followed immediately by pyrrole (2.08mL, 30.0mmol). The resulting off-white suspension was stirred at room temperature for 15 min. A solution of 30 (9.37g, 33.0mmol) in ether (22mL) was then added over 20 min. The reaction mixture was stirred at room temperature for 24h, diluted with H_2O (100mL) and cast into ether (100mL) and water (50mL). The aqueous layer was separated and washed with ether (2 x 75mL). The combined ether layers were washed with brine (200mL), dried (Na_2SO_4), and concentrated *in vacuo* to provide a yellow liquid. The crude product was purified by chromatography on a column of silica·gel (60-230 mesh, 120g, 50mm o.d., ether-petroleum ether 1:1, 75mL fractions) using the flash technique. Fractions 7-14 yielded 6.56g, 98%, of 31 as a pale yellow, free-flowing liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.46 (t, J=1Hz, 2), 6.34 (t, J=1Hz, 2), 3.70 (m, 2), 3.27 (m, 1), 3.25 (t, J=8Hz, 2), 1.42 (s, 3), 1.32 (s, 3), 1.65-0.9 (m, 6); IR (neat): 2940, 1370, 1240, 1060, 720 cm^{-1}; EI-MS (70eV): 223 (M^+, 26.1),

208 (8.21), 165 (18.6), 148 (55.2), 81 (base), 72 (35.3), 43 (53.5).

Anal. C, H, N.

General Procedure for the Deprotection of the Pyrrole Acetonides.

6-(N-pyrrolyl)hexane-1,2-diol (35).

To a solution of the pyrrole-acetonide 31 (1.045g, 4.69mmol) in methanol (250mL) at 25°C was added p-toluenesulfonic acid (0.951g, 0.50mmol). The mixture was allowed to stir for 2h then quenched by suspending solid $NaHCO_3$ for 5 min. in the reaction mixture. The mixture was filtered and concentrated *in vacuo* to provide a yellow viscous liquid together with some solid $NaHCO_3$. The crude diol was purified by chromatography on a column of silica gel (60-230 mesh, 100g, 50mm o.d., EtOAc, 75mL fractions) using the flash technique. Fractions 7-15 yielded 0.775g, 90%, of 35 as a yellow viscous liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.51 (t, J=2Hz, 2), 6.35 (t, J=2Hz, 2), 3.81 (brs, 1), 3.55 (m, 2), 3.41 (m, 1), 3.35 (t, J=7Hz, 2), 3.34 (t, J=7Hz, 2), 3.30 (brs, 1), 1.25 (m, 6); IR (neat): 3360 (br), 2920, 1280, 1070, 730 cm^{-1}; EI-MS (70eV): 183 (M^+, 44.4), 166 (7.34), 152 (12.3), 134 (15.2), 81 (base), 80 (78.2), 41 (44.3).

General Procedure for the Mono-Tosylation of the Pyrrolyl-1,2-Diols.

Preparation of 6-(N-pyrrolyl)hexane-1,2-diol-1-p-Toluenesulfonate (35, R_4=pTs, R_5=H).

To a solution of diol 35, R_4=R_5=H (0.75g, 4.10mmol) in dry pyridine (18mL), chilled in an ice-water bath, was added in one portion p-toluenesulfonyl chloride (0.90g, 4.72mmol) and a crystal of 4,4-dimethylaminopyridine. The resulting deep-red colored mixture was stirred at RT for 48h. The mixture was then cast into ice-conc. HCl (100g/100mL) and extracted with ether (150mL). The ether layer was washed with 1N aqueous HCl (100mL), water (100mL), brine (100mL), dried (Na_2SO_4), and concentrated *in vacuo* to provide a green viscous liquid (1.4g). The crude tosylate was purified by chromatography on a column of silica gel (60-230 mesh, 100g, 50mm o.d., EtOAc, 40mL fractions) using the flash technique. Fractions 3-7 yielded 1.28g, 93%, of 35 as an orange viscous liquid.

^{1}H-NMR (60MHz, C_6D_6): δ = 7.70 (d, J=8Hz, 2), 6.70 (d, J=8Hz, 2), 6.40 (m, 2), 6.27 (m, 2), 3.95 (brs, 1), 3.74 (m, 2), 3.30 (m, 3), 1.89 (s, 3), 1.08 (m, 4); IR (neat): 3500, 3100, 2920, 1600, 1360, 1180, 970, 730 cm^{-1}; EI-MS (70eV): 337 (M^+, 0.81), 182 (1.43), 166 (5.20), 165 (19.7), 134 (10.2), 122 (16.7), 107 (20.5), 91 (46.9), 81 (base).

General Procedure for the Formation of the Pyrrolyl Epoxides.

6-(N-pyrrolyl)-1,2-epoxyhexane (13).

To a suspension of potassium t-butoxide (0.775g, 6.91mmol) in dry THF (40mL), cooled in a dry ice-CCl_4 bath to -23°C, was added dropwise over 15 min. a solution of 35 (2.025g, 6.01mmol) in dry THF (20mL). The resulting magenta-colored mixture was stirred at -23°C for 15 min., warmed to RT, diluted with water (24mL), and cast into ether (200mL) and water (100mL). The organic layer was separated, washed with brine (200mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield a pale yellow, free-flowing liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 100g, 50mm o.d., Et_2O-petroleum ether 30:70, 50mL fractions) using the flash technique. Fractions 7-13 provided 0.87g, 88%, of 13 as a pale yellow, free-flowing liquid.

^{1}H-NMR (250MHz): δ = 6.61 (t, J=1Hz, 2), 6.10 (t, J=1Hz, 2), 3.85 (t, J=6Hz, 2), 2.75 (m, 1), 2.69 (t, J=3Hz, 1), 2.40 (m, 1), 1.78 (m, 2), 1.45 (m, 4); IR (neat): 3100, 3050, 2920, 1500, 1290, 1100, 730 cm^{-1}; EI-MS (70eV): 165 (M^+, 15.5), 147 (1.98), 134 (13.2), 120 (13.8), 106 (14.6), 94 (15.9), 81 (base), 80 (78.6), 53 (40.1).

Anal. C, H, N.

1,2-Di-O-Isopropylidene-4-(N-Pyrrolyl)butane-1,2-diol (25).

A mixture of pyrrole (1.38mL, 20mmol), 18-crown-6 ether (0.53g, 2.0mmol) and potassium t-butoxide (2.58g, 23mmol) in anhydrous ether (40mL) was stirred at room temperature for 30 min. To the suspension was added a solution of 24 (5.76g, 22.5mmol) in anhydrous ether (15mL) over 15 min. The reaction mixture was stirred at room temperature for 18h and worked up according to the general procedure for the preparation of pyrrole acetonides. Flash chromatography on a column of silica gel provided 3.73g, 95%, of 25 as a pale yellow liquid.

^{1}H-NMR (60MHz, CCl_4): δ = 6.41 (t, J=2Hz, 2), 5.87 (t, J=2Hz, 2), 3.83 (m, 4), 3.28 (m, 1), 1.80 (m, 2), 1.28 (s, 3), 1.20 (s, 3); IR (neat): 3100, 2980, 294-, 2880, 1500, 1370, 1290, 1250, 1220, 1160, 1090, 1065, 860, 730 cm^{-1}; EI-MS (70eV): 196 (M^+1, 2.97), 195 (M^+, 24.4), 180 (1.17), 137 (10.4), 120 (43.0), 106 (4.34), 94 (30.1), 81 (base), 80 (73.9), 43 (36.0).

4-(N-Pyrrolyl)butane-1,2-diol (32, R_4=R_5=H).

A solution of 25 (0.14g, 0.77mmol) in methanol (20mL) was stirred with pyridinium-p-toluenesulfonate (0.015g, 0.06mmol) at room temperature for 32h and was worked up according to the general procedure for the deprotection of pyrrole acetonides. Flash chromatography on a column of

silica gel gave 0.10g (89%) of pyrrole-diol **32** as a pale yellow, viscous liquid.

^{1}H-NMR (60MHz, CCl_4): δ = 6.38 (t, J=2Hz, 2), 5.83 (t, J=2Hz, 2), 3.89 (t, J=7Hz, 2), 3.50 (m, 2), 3.26 (m, 3), 2.62 (m, 2); IR (CCl_4): 3400, 2930, 2870, 1500, 1280, 1240, 1090, 1060, 720 cm^{-1}; EI-MS (70eV): 156 (M^+1, 4.24), 155 (M^+, 38.3), 137 (1.78), 124 (4.17), 120 (5.60), 106 (2.44), 94 (6.40), 81 (base), 80 (80.0), 68 (15.1), 53 (22.2).

4-(N-Pyrrolyl)butane-1,2-diol-1-p-Toluenesulfonate (**32**, R_4=pTs, R_5=H).

A solution of 0.098g (0.632mmol) of **32** (R_4=R_5=H) in dry pyridine (4mL), chilled to 0°C in an ice-water bath, was reacted with p-toluenesulfonyl chloride (0.132g, 0.692mmol). The mixture was stirred overnight and worked up according to the general procedure for the tosylation of pyrrole diols. Flash chromatography on a column of silica gel yielded 0.177g, 91%, of the glycol mono-tosylate **32** (R_4=pTs, R_5=H) as a pale yellow, viscous liquid.

^{1}H-NMR (60MHz, CCl_4): δ = 7.72 (d, J=8Hz, 2), 6.73 (d, J=8Hz, 2), 6.42 (t, J=2Hz, 2), 6.28 (t, J=2Hz, 2), 3.97 (br s, 1), 3.77 (t, J=6Hz, 2), 3.30 (m, 3), 1.87 (s, 3), 1.32 (m, 2); EI-MS (70eV): 309 (M^+, 0.41), 172 (1.08), 155 (2.72), 137 (35.5), 120 (11.3), 106 (2.92), 94 (43.3), 81 (22.2), 80 (base), 68 (9.61), 67 (14.0), 53 (22.2).

4-(N-Pyrrolyl)-1,2-epoxybutane (8).

To a suspension of potassium t-butoxide (0.076g, 0.68mmol) in dry THF (8mL), cooled to -78°C in a dry ice-*i*-PrOH bath, was added a solution of 0.174g (0.567mmol) of **32** (R_4=pTs, R_5=H) in THF (3mL) over 3 min. The mixture was stirred at -78°C for 10 min and worked up according to the general procedure for the formation of the epoxy-pyrroles. Flash chromatography on a column of silica gel provided 0.070g, 90%, of **8** as a pale yellow, free-flowing liquid. ^{1}H-NMR (60MHz): δ = 6.62 (t, J=2Hz, 2), 6.10 (t, J=2Hz, 2), 4.00 (t, J=7Hz, 2), 2.78 (m, 2), 2.37 (m, 1), 1.91 (m, 2); IR (neat): 3040, 2985, 2920, 2860, 1500, 1350, 1285, 1090, 1065, 910, 720 cm^{-1}; EI-MS (70eV): 137 (M^+, 48.4), 120 (3.71), 106 (14.0), 94 (12.7), 81 (20.3), 80 (base), 67 (13.9), 53 (29.3), 39 (26.4).
Anal. C, H, N.

2-Methyl-2,3-Di-O-Isopropylidene-5-(N-pyrrolyl)pentane-1,2-diol (27).

To anhydrous ether (20mL) at room temperature under argon was added 18-crown-6 ether (0.264g, 1.0mmol), potassium t-butoxide (1.23g, 11.0mmol), and pyrrole (0.694mL, 10mmol). The resulting suspension was stirred at room temperature for 15 min, and a solution of **26** (3.00g, 10.56mmol) in anhydrous ether (7mL) was then added over 5 min. The mixture was stirred at room temperature for 24h

and was worked up according to the general procedure for the preparation of pyrrole acetonides. Flash chromatography on a column of silica gel yielded 2.21g, 99%, of **27** as a pale yellow liquid.

^{1}H-NMR (80MHz): δ = 6.70 (brs, 2), 6.25 (brs, 2), 4.10 (m, 2), 3.60 (m, 1), 1.90 (m, 2), 1.50 (s, 3), 1.38 (s, 3), 1.22 (s, 3), 1.12 (s, 3); IR (neat): 3100, 2980, 2930, 2860, 1500, 1450, 1370, 1280, 1220, 1120, 1000, 730 cm^{-1}; EI-MS (70eV): 224 (M^+1, 4.80), 223 (M^+, 17.1), 208 (6.09), 178 (5.65), 166 (14.5), 148 (16.5), 81 (base), 80 (37.8), 59 (13.5), 43 (32.4).

2-Methyl-5-(N-pyrrolyl)pentane-2,3-diol (**33**, R_4=R_5=H).

A solution of **27** (1.10g, 4.83mmol) in methanol (250mL) was stirred with p-toluenesulfonic acid (0.0938g, 0.493mmol) at room temperature for 24h and worked up according to the general procedure for the deprotection of pyrrole acetonides. Flash chromatography on a column of silica gel yielded 0.708g, 78%, of **33** (R_4=R_5=H) as a yellow viscous liquid.

^{1}H-NMR (60MHz, CCl_4): δ = 6.40 (t, J=2Hz, 2), 5.83 (t, J=2Hz, 2), 3.90 (t, J=6Hz, 2), 3.60 (t, J=7Hz, 1), 3.20 (brs, 1), 1.95-1.55 (m, 3), 1.25 (s, 3), 1.15 (s, 3); IR (neat): 3400, 2940, 2860, 1500, 1450, 1370, 1280, 1110, 1050, 720 cm^{-1}; EI-MS (70eV): 166 (M-17, 6.86), 165 (M-18, 33.8), 150 (49.8), 148 (14.6), 121 (21.8), 106 (21.6), 81 (base), 80 (52.7), 59 (36.0), 43 (28.1).

2-Methyl-5-(N-pyrrolyl)pentane-2,3-diol-3-p-Toluenesulfonate (33, R_4=H, R_5=pTs).

A solution of 0.708g (3.87mmol) of 33 (R_4=R_5=H) in dry pyridine (17mL), chilled to 0°C in an ice-water bath, was reacted with p-toluenesulfonyl chloride (0.848g, 4.45mmol). The mixture was stirred for 1h at 0°C and overnight at room temperature, then was worked up according to the general procedure for the tosylation of pyrrole-diols. Flash chromatography on a column of silica gel gave 0.522g, 40%, of 33 (R_4=H, R_5=pTs) as an orange viscous liquid. .389g, 55%, of 33 (R_4=R_5=H) was recovered unreacted.
^{1}H-NMR (60MHz, C_6D_6): δ = 7.68 (d, J=8Hz, 2), 6.73 (d, J=8Hz, 2), 6.53 (t, J=2Hz, 2), 6.20 (t, J=2Hz, 2), 4.50 (t, J=4Hz, 1), 3.82 (t, J=6Hz, 2), 2.39 (brs, 1), 1.92 (?, 3), 1.70 (m, 2), 1.00 (s, 3), 0.98 (s, 3); EI-MS (70eV): 337 (M^+, 1.12), 182 (2.95), 165 (63.8), 150 (100), 132 (9.49), 121 (44.6), 106 (40.8), 80 (34.4).

2-Methyl-5-(N-pyrrolyl)-2,3-epoxypentane (10).

To a suspension of potassium t-butoxide (0.049g, 0.44mmol) in dry THF (4mL), cooled to -78°C in a dry ice-*i*-PrOH bath, was added a solution of 0.125g (0.371mmol) of 33 (R_4=H, R_5=pTs) in THF (1mL). The mixture was stirred at -78°C for 15 min and worked up according to the general procedure for the preparation of epoxy pyrroles. Flash

chromatography on a column of silica gel provided 0.053g, 86%, of **10** as a pale yellow, free-flowing liquid.

^{1}H-NMR (60MHz): δ = 6.52 (t, J=2Hz, 2), 6.02 (t, J=2Hz, 2), 4.12 (t, J=7Hz, 2), 2.82 (t, J=7Hz, 2), 1.70 (brs, 1), 1.10 (s, 3), 0.99 (s, 3); IR (CCl_4): 3050, 2980, 2920, 2860, 1500, 1280, 1090, 910, 720 cm^{-1}; EI-MS (70eV): 166 (M^+1, 4.70), 165 (M^+, 36.9), 150 (47.3), 135 (5.40), 121 (25.7), 106 (63.6), 94 (21.3), 81 (50.6), 80 (88.7), 71 (32.0), 68 (45.3), 43 (base).

Anal. C, H, N.

1,2-Di-O-Isopropylidine-5-(N-pyrrolyl)pentane-1,2-diol (**29**).

To anhydrous ether (20mL) at room temperature was added 18-crown-6 ether (0.264g, 1.0mmol) potassium t-butoxide (1.29g, 11.5mmol) and pyrrole (0.69mL, 10mmol). The suspension was stirred at room temperature for 15 min then a solution of iodo-acetonide **28** (2.85g, 10.56mmol) in anhydrous ether (7mL) was added over 10 min. The mixture was stirred at room temperature for 19h and worked up according to the general procedure for the preparation of pyrrole-acetonides. Flash chromatography on a column of silica gel gave 1.82g, 87%, of **29** as a pale yellow, free-flowing liquid.

^{1}H-NMR (60MHz, CCl_4): δ = 6.52 (t, J=2Hz, 2), 6.00 (t, J=2Hz, 2), 3.88 (m, 4), 3.38 (m, 1), 2.15-1.50 (m, 4), 1.32 (s, 3), 1.25 (s, 3); IR (CCl_4): 3100 2880, 2940, 2870, 1500,

1450, 1380, 1280, 1230, 1160, 1060, 850, 730 cm^{-1}; EI-MS (70eV): 210 (M^+1, 3.91), 209 (M^+, 26.4), 194 (2.41), 166 (0.55), 151 (24.5), 134 (53.0), 93 (36.7), 81 (base), 80 (62.4), 72 (30.2), 43 (54.4).

5-(N-Pyrrolyl)pentane-1,2-diol (34, R_4=R_5=H).

A solution of 29 (1.00g, 4.78mmol) in methanol (130mL) was stirred with pyridinium-p-toluenesulfonate (0.12g, 0.478mmol) at room temperature for 32h and worked up according to the general procedure for the deprotection of pyrrole-acetonides. Flash chromatography on a column of silica gel provided 0.735g, 91%, of 34 (R_4=R_5=H) as a pale yellow, viscous liquid.

^{1}H-NMR (60MHz): δ = 6.67 (t, J=2Hz, 2), 6.15 (t, J=2Hz, 2), 3.94 (t, J=7Hz, 2), 2.72 (t, J=4Hz, 2), 2.43 (m, 1), 2.12-1.20 (m, 4); IR (neat): 3360, 2920, 2860, 1500, 1450, 1280, 1090, 1060, 730 cm^{-1}; EI-MS (70eV): 170 (M^+1, 8.20), 169 (M^+, 85.5), 152 (10.2), 149 (12.6), 138 (10.9), 134 (11.8), 120 (54.1), 95 (25.7), 85 (45.1), 81 (99), 80 (base), 68 (64.1), 53 (27.4), 43 (45.8).

5-(N-Pyrrolyl)pentane-1,2-diol-1-p-toluenesulfonate (34, R_4=pTs, R_5=H).

A solution of 0.29g (1.74mmol) of 34 (R_4=R_5=H) in dry pyridine (7mL), chilled to 0°C in an ice-water bath, was reacted with p-toluenesulfonyl chloride (0.393g, 2.06mmol). The mixture was stirred for 1h at 0°C and overnight at room

temperature and was worked up according to the general procedure for the tosylation of pyrrole-diols. Flash chromatography on a column of silica gel yielded 0.462g, 83%, of 34 (R_4=pTs, R_5=H) as a yellow viscous liquid. ^{1}H-NMR (250MHz, C_6D_6): δ = 7.75 (d, J=8Hz, 2), 6.72 (d, J=8Hz, 2), 6.43 (t, J=2Hz, 2), 6.30 (t, J=2Hz, 2), 4.02 (brs, 1), 3.81 (m, 2), 3.54 (m, 1), 3.31 (t, J=7Hz, 2), 1.84 (s, 3), 1.60 (m, 1), 1.40 (m, 1), 1.02 (m, 2); IR (neat): 3100, 3050, 2930, 2885, 1500, 1280, 1090, 1070, 730 cm^{-1}; EI-MS (70eV): 152 (M^+1, 20.4), 151 (M^+, 64.9), 134 (38.4), 120 (44.1), 106 (12.6), 93 (19.0), 81 (48.9), 80 (base), 68 (32.5), 53 (14.3).

Anal. C, H, N.

General Procedure for Cyclization of Pyrrole Epoxides with $BF_3 \cdot OEt_2$ and Et_3N.

Preparation of 8-Hydroxymethyl-8-Methyl-5,6,7,8-Tetrahydro-indolizidine (18).

To a solution of 11 (0.1g, 0.6mmol) in dry THF (15mL), cooled to -42°C in a dry ice-CH_3CN bath, was added Et_3N (0.083mL, 0.6mmol) followed by freshly distilled $BF_3 \cdot OEt_2$ (0.074mL, 0.6mmol). The reaction was allowed to slowly warm to room temperature overnight and then was quenched with saturated aqueous $NaHCO_3$ (10mL). The mixture was cast into ether (75mL) and saturated aqueous $NaHCO_3$ (50mL). The organic layer was separated, washed with 1N aqueous HCl (50mL), water (50mL), brine (50mL), dried (Na_2SO_4), and

concentrated *in vacuo* to provide a yellow viscous liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 25g, 30mm o.d., Et_2O-petroleum ether 30:70, 15mL fractions) using the flash technique. Fractions 15-20 provided 0.073g, 73%, of **18** as a pale yellow, viscous liquid which solidified upon cooling. ^1H-NMR (250MHz, C_6D_6): δ = 6.35 (m, 1), 6.31 (t, J=2Hz, 1), 6.05 (m, 1), 3.55 (d, J=11Hz, 1), 3.42 (d, J=11Hz, 1), 3.31 (t, J=6Hz, 2), 2.62 (brs, 1), 1.75 (m, 1), 1.48 (m, 2), 1.27 (m, 1), 1.20 (s, 3); IR (neat): 3280, 2940, 1450, 1350, 1050, 720 cm^{-1}; EI-MS (70eV): 165 (M^+, 12.7), 147 (6.56), 134 (base), 118 (9.97), 80 (8.30), 44 (54.4), 40 (88.2). Anal. C, H, N.

General Procedure for Cyclization of Pyrrole-Epoxides with $EtAlCl_2$.

To a solution of **11** (0.1g, 0.606mmol) in dry CH_2Cl_2 (5 mL), chilled in a dry ice-CCl_4 bath, was added $EtAlCl_2$ (0.82 mL, 1.21mmol, 1.47M in hexane) over 2 min. The reaction mixture was stirred for 25 minutes at -24°C then quenched with saturated aqueous NH_4Cl (5mL). The mixture was cast into Et_2O (50mL) and 1N aqueous HCl (50mL). The organic layer was separated, washed with brine (50mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield a pale yellow, viscous liquid. The crude product was purified by chromatography on a column of silica gel using the flash technique to provide 0.081g, 81%, of **18**.

General Procedure for Cyclization of Pyrrole-Epoxides with Et_2AlCl.

Preparation of 18.

To a solution of 11 (0.104g, 0.63mmol) in dry CH_2Cl_2, cooled to -40°C in a dry ice-CH_3CN bath, was added Et_2AlCl (0.86mL, 1.26mmol, 1.47M in hexane). The mixture was stirred at -40°C for 10 min then quenched by cautiously adding 1N aqueous HCl (10mL). The mixture was cast into Et_2O (50mL) and 1N aqueous HCl (50mL). The organic layer was separated, washed with brine (50mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield a yellow viscous liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 25g, 30mm o.d., EtOAc-petroleum ether 40:60, 15mL fractions) using the flash technique. Fractions 5-10 provided 0.084g, 81%, of 18.

General Procedure for Cyclization of Pyrrole-Epoxides with $Ti(O\text{-}iPr)_3Cl$.

Preparation of 18.

To a solution of 11 (0.142g, 0.861mmol) in dry CH_2Cl_2 (20mL), chilled in an ice-water bath, was added $Ti(O\text{-}iPr)_3Cl$[40] (3.44mL, 2.58mmol), 0.75M in CH_2Cl_2). The mixture was stirred for 15 min and then quenched with saturated aqueous NH_4Cl (15mL). The solution was cast into Et_2O (75mL) and saturated aqueous NH_4Cl (75mL). The organic layer was separated, washed with 1N aqueous HCl (75mL),

water (75mL), brine (75mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an orange viscous liquid. The crude product was purified by chromatography on a column of silica gel using the flash technique to give 0.115g, 80%, of **18**.

General Procedure for Cyclization of Pyrrole-Epoxides with $ZnI_2 \cdot OEt_2$.

Preparation of **18**.

To a solution of **11** (0.1g, 0.6mmol) in dry benzene (15mL) at room temperature was added freshly prepared $ZnI_2 \cdot OEt_2$[41] (0.472g, 1.2mmol) in one portion. Within 5 min, the colorless suspension became orange in color and the reaction was complete. The mixture was quenched with saturated aqueous NH_4Cl (10mL) and was cast into Et_2O (50mL) and saturated NH_4Cl (50mL). The organic layer was separated, washed with 10% aqueous $Na_2S_2O_3$ (50mL), water (50mL), saturated aqueous $NaHCO_3$ (50mL), brine (50mL), dried (Na_2SO_4) and concentrated *in vacuo* to provide a pale orange viscous liquid. The crude product was purified by chromatography on a column of silica gel using the flash technique to give 0.072g, 72%, of **18**.

Cyclization of **8** with Et_2AlCl.

Preparation of 7-Hydroxy-5,6,7,8-Tetrahydroindolizidine (**14**).

To a solution of **8** (0.1g, 0.73mmol) in dry CH_2Cl_2 (5mL), chilled to -23°C in a dry ice-CCl_4 bath, was added Et_2AlCl (1.0mL, 1.47mmol, 1.47M in hexane). The mixture was

stirred at -23°C for 30 min and then quenched by cautiously adding 1N aqueous HCl (5mL). The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 30g, 30mm o.d., EtOAc-petroleum ether 1:1, 20mL fractions) using the flash technique. Fractions 6-12 provided 0.032g, 32%, of **14** as a pale yellow, viscous liquid.

^{1}H-NMR (250MHz): δ = 6.54 (brs, 1), 6.14 (m, 1), 5.84 (brs, 1), 4.15 (m, 1), 3.96 (m, 2), 3.13 (dd, J=16.6,4.2Hz, 1), 2.77 (dd, J=16.6,8.3Hz, 1), 2.03 (m, 2); IR (CCl_4): 3380, 3100, 2940, 1490, 1430, 1320, 1200, 1070, 980, 700 cm^{-1}; EI-MS (70eV): 137 (M^+, 2.31), 118 (0.31), 108 (1.51), 93 (2.79), 44 (16.8), 40 (base).

Anal. C, H, N.

Cyclization of **9** with Et_2AlCl.

Preparation of 7-Hydroxy-7-methyl-5,6,7,8-Tetrahydroindolizidine (**16**).

To a solution of **9** (0.085g, 0.566mmol) in dry CH_2Cl_2 (5mL), cooled to -78°C in a dry ice-*i*-PrOH bath, was added Et_2AlCl (0.76mL, 1.13mmol, 1.47M in hexane). The mixture was stirred at -78°C for 2h and then quenched by cautiously adding 1N aqueous HCl (5mL). The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole-epoxides with Et_2AlCl. The crude

product was purified by chromatography on a column of silica gel (230-400 mesh, 30g, 30mm o.d., EtOAc-petroleum ether 30:70, 15mL fractions) using the flash technique. Fractions 8-13 provided 0.038g, 44%, of 16 as a pale yellow, viscous liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.42 (m, 1), 6.37 (t, J=2Hz, 1), 6.01 (brs, 1), 3.65 (m, 1), 3.32 (m, 1), 2.50 (s, 2), 1.34 (m, 3), 0.97 (s, 3); IR (neat): 3420, 2900, 1450, 1380, 1330, 1120, 700 cm^{-1}; EI-MS (70eV): 151 (M^+, 61.9), 136 (6.72), 120 (8.70), 108 (23.2), 93 (base), 80 (52.5), 66 (18.0), 43 (31.6).

Anal. C, H, N.

Cyclization of 10 with Et_2AlCl.

Preparation of 7-Hydroxy-8,8-dimethyl-5,6,7,8-Tetrahydro-indolizidine (17).

To a solution of 10 (0.023g, 0.139mmol) in dry CH_2Cl_2 (1.0mL), cooled to -78°C in a dry ice-i-PrOH bath, was added Et_2AlCl (0.19mL, 0.279mmol, 1.47M in hexane). The mixture was stirred at -78°C for 20 min and then quenched by the addition of saturated aqueous NH_4Cl (3 mL). The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole-epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 15g, 20mm o.d., EtOAc-petroleum ether 30:70, 15mL fractions) using the flash technique. Fractions

7-12 provided 0.014g, 61%, of 17 as a pale yellow, viscous liquid which solidified on cooling. mp = 79-81°C; ^{1}H-NMR (250MHz, C_6D_6): δ = 6.34 (m, 1), 6.30 (m, 1), 6.07 (m, 1), 3.55 (m, 1), 3.30 (m, 2), 1.56 (m, 2), 1.45 (brs, 1), 1.20 (s, 3), 1.18 (s, 3); IR (CCl_4): 3460, 2920, 1450, 1370, 1190, 1180, 1080, 1050, 850, 700 cm^{-1}; EI-MS (70eV): 165 (M^+, 48.9), 150 (base), 132 (9.12), 121 (47.0), 106 (38.1), 80 (13.7).

Anal. C, H, N.

Cyclization of 12 with $Ti(O\text{-}iPr)_3Cl$.

Preparation of 8-Hydroxymethyl-5,6,7,8-Tetrahydroindolizidine (19).

To a solution of 12 (0.050g, 0.33mmol) in dry CH_2Cl_2 (5mL), chilled in an ice-water bath, was added $Ti(O\text{-}iPr)_3Cl$ (0.50mL, 1.0mmol, 2.0M in CH_2Cl_2. The mixture was stirred at 0°C for 1h, warmed to room temperature and allowed to stir for an additional 45 min. The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole-epoxides with $Ti(O\text{-}iPr)_3Cl$. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 20g, 200mm o.d., EtOAc-petroleum ether 30:70, 10mL fractions) using the flash technique. Fractions 10-14 provided 0.032g, 64%, of 19 as a pale yellow, viscous liquid.

Cyclization of 12 with Et_2AlCl.

Preparation of 19 and 6-Hydroxy-6,7,8,9-Tetrahydro[5H]-pyrrolo[5H]pyrrolo[1,2a]azepine (20).

A solution of 12 (0.055g, 0.36mmol) in dry CH_2Cl_2 (?mL) was reacted with Et_2AlCl (0.49mL, 0.72mmol, 1.47M in hexane) according to the general procedure for cyclization of pyrrole-epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 20g, 20mm o.d., EtOAc-petroleum ether 40:60, 15mL fractions) using the flash technique. Fractions 6-8 provided 0.020g, 37%, of 19, and fractions 10-13 yielded 0.026g, 48%, of 20 as a water-white liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.31 (brs, 1), 6.18 (t, J=1.5Hz, 1), 6.10 (brs, 1), 3.32 (brs, 1), 3.20 (t, J=6.0Hz, 2), 3.16 (m, 1), 2.69 (brd, J=15.4Hz, 1), 2.63 (dd, J=15.4,9.4Hz, 1), 1.41 (m, 2), 1.09 (m, 2); IR (CCl_4): 3460, 2920, 1430, 1350, 1280, 1020, 700 cm^{-1}; EI-MS (70eV): 151 (M^+, base), 150 (49.3), 134 (6.55), 122 (18.7), 106 (20.6), 94 (75.3), 80 (36.5), 53 (9.77), 41 (10.4).

Anal. C, H, N.

Cyclization of 13 with $Ti(O\text{-}iPr)_3Cl$.

Preparation of 5-Hydroxymethyl-5,7,8,9-Tetrahydro[5H]pyrrolo-[1,2a]azepine (21).

To a solution of 13 (0.104g, 0.630mmol) in dry CH_2Cl_2 (15mL), chilled in an ice-water bath, was added $Ti(O\text{-}iPr)_3Cl$ (0.945mL, 1.89mmol, 2.0M in CH_2Cl_2). The mixture was

stirred at 0°C for 1h, then warmed to room temperature and stirred for an additional 3h. The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole-epoxides with $Ti(O\text{-}iPr)_3Cl$. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30g, 30mm o.d., EtOAc-petroleum ether 30:70, 25mL fractions) using the flash technique. Fractions 8-13 yielded 0.088g, 85%, of **21** as a pale yellow, viscous liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.35 (m, 1), 6.18 (t, J=2Hz, 1), 5.99 (brs, 1), 3.85 (dd, J=10.8,6.7Hz, 1), 3.58 (dd, J=10.8,7.5Hz, 1), 3.31 (brq, J=7.7Hz, 2), 2.61 (m, 1), 1.74 (m, 1), 1.60 (m, 1), 1.32 (m, 2), 1.15 (m, 2); IR (CCl_4): 3580, 2920, 2860, 1480, 1290, 1110, 1080, 1030, 700 cm^{-1}; EI-MS (70eV): 165 (M^+, 19.4), 134 (base), 118 (5.85), 106 (7.02), 93 (3.00), 80 (17.8).

Anal. C, H, N.

Cyclization of **13** with $ZnI_2 \cdot OEt_2$.

Preparation of **21** and 1-Iodo-2-hydroxy-6-(N-pyrrolyl)hexane.

A solution of **13** (0.105g, 0.636mmol) in anhydrous ether (10mL) was reacted with freshly prepared $ZnI_2 \cdot OEt_2$ (0.477g, 1.212mmol) for 3h at room temperature according to the general procedure for cyclization of pyrrole-epoxides with $ZnI_2 \cdot OEt_2$. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30g, 30mm o.d., EtOAc-petroleum ether 30:70, 20mL fractions) using the flash

technique. Fractions 5 and 6 gave 0.091g, 49%, of 1-iodo-2-hydroxy-6-(N-pyrrolyl)hexane as a pale yellow, viscous liquid. Fractions 9-13 provided 0.273g, 26%, of 21 as a pale yellow, viscous liquid.

^{1}H-NMR (250MHz, C_6D_6): δ = 6.46 (t, J=1Hz, 2), 6.34 (t, J=1Hz, 2), 3.27 (t, J=6Hz, 2), 2.92 (m, 1), 2.75 (t, J=4Hz, 1), 2.64 (t, J=6Hz, 1), 1.45 (brs, 1), 1.24 (m, 2), 1.00 (m, 4); IR (neat): 3440, 2920, 1290, 1100, 730 cm^{-1}; EI-MS (70eV): 166 (M-1, 8.07), 151 (5.80), 134 (4.54), 81 (8.11), 61 (13.8), 43 (base).

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PYRROLES AS TERMINATORS IN CATIONIC CYCLIZATIONS. THE PREPARATION OF 5,6,7,8-TETRAHYDRO-INDOLIZIDINES AND 6,7,8,9-TETRAHYDRO-[5H]-PYRROLO[1,2A]-AZEPINES.

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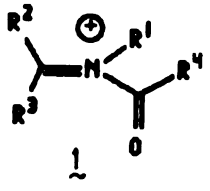
INTRODUCTION

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS.

INTRODUCTION

N-acyliminium ions (1) have been recognized as valuable intermediates in the synthesis of alkaloids and related nitrogen-containing compounds.[1] Many examples of intramolecular cyclizations involving 1 as a cyclization initiator reacting with an appropriately nucleophilic terminator function are known. Notable among these are the syntheses of alkaloids, such as perhydrohistrionicotoxin (H_{12}-HTX)[2], vertaline[3], gephyrotoxin[4], and the necine bases.[5]



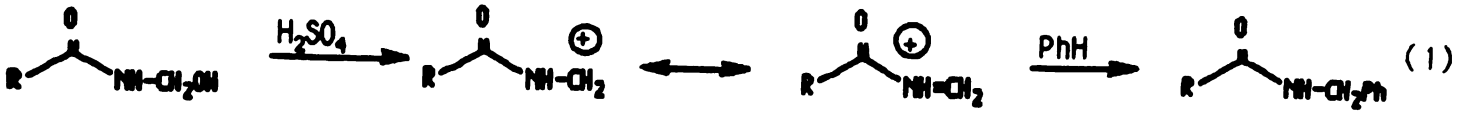
1

R^1, R^2, R^3 = aryl, alkyl, or H
R^4 = C or heteroatom

Figure 1

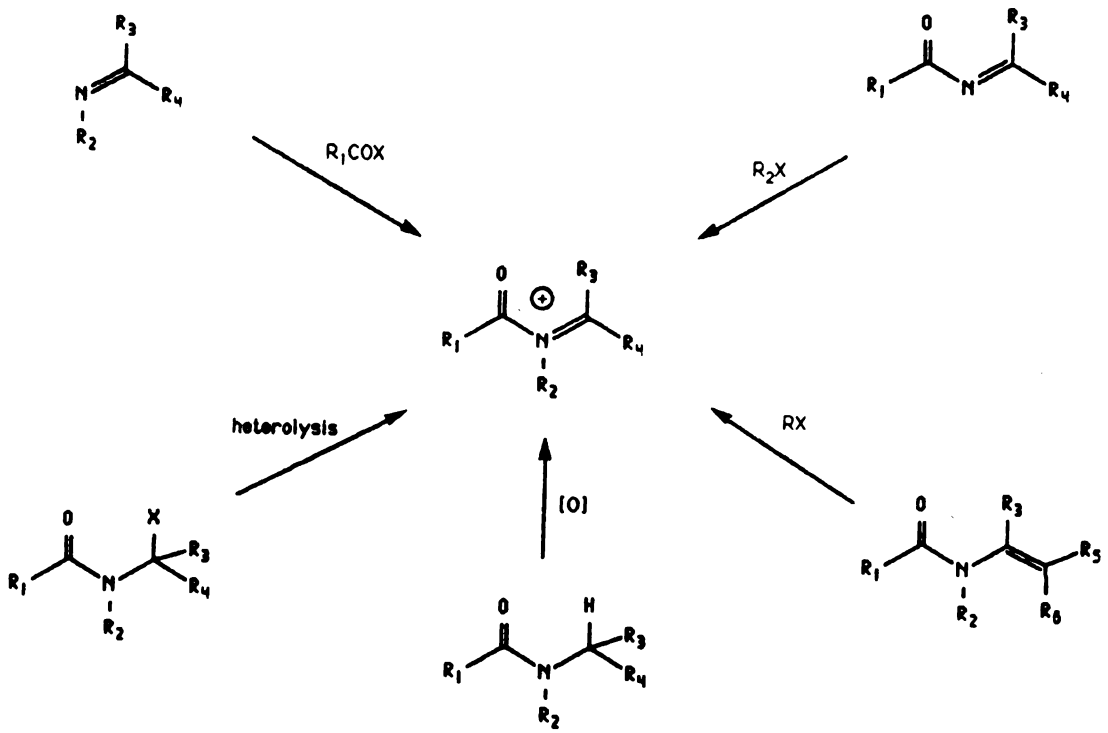
The relatively high reactivity of the N-acyliminium ions (See Figure 1) has been appreciated since the beginning of this century when the Tscherniac-Einhorn reaction (Eq. 1) was discovered.[6] The acid-catalyzed cleavage of N-(α-

hydroxyalkyl) amides (See Eq. 1) still remains as one of the most direct and successful routes to N-acyliminium ions.



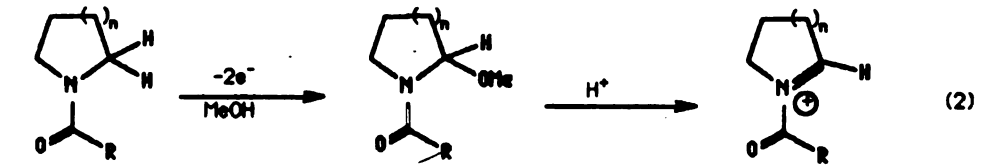
(1)

Scheme I depicts this method and several other techniques for the generation of N-acyliminium ions. Protonation of ene-amides[7], N-acylation of imines[8], and N-alkylation of acylimines[9] have been examined but are not generally employed to prepare N-acyliminium ions in synthetic sequences.



Scheme I

The development of two new and versatile methods for the preparation of carbinolamides and N-(α-alkoxyalkyl) amides have spurred further examination of the synthetic potential of N-acyliminium ions (Eq. 2 and 3). These two methods, the electrochemical oxidation of amides[10] and the pH-controlled $NaBH_4$ reduction of cyclic imides[11], are depicted in Equations 2 and 3, respectively. Recently, a further improvement in the preparation of the carbinolamide precursor of cyclic N-acyliminium ions 3 has been reported by Chamberlin ($NaBH_4$, MeOH, -4°C).[5b]



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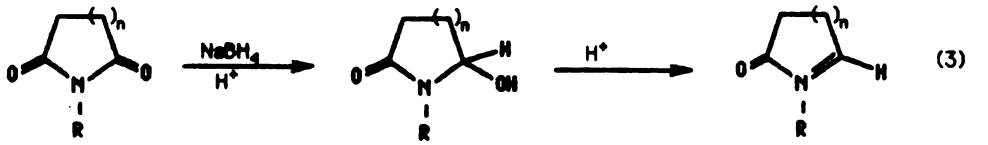


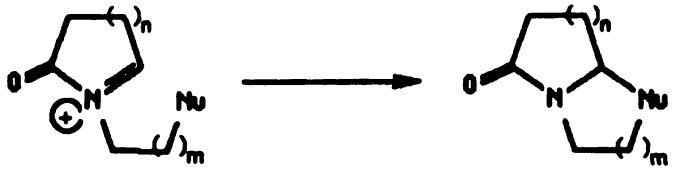
(3)

3

The fate of the N-acyliminium ions produced upon treatment of carbinolamides with acid depends upon the structure of the starting imide (Eq. 3) and the nature of the termination step. The N-acyliminium ion can suffer deprotonation to yield an enamide[12], be captured inter- or intramolecularly by olefinic[13], acetylenic[13b,e;14], allylic-

[15,16] and properglic silanes[15], allenic[17], or aromatic[18] terminators, or be quenched by a heteroaromatic nucleophile.[19] These terminator moieties are quite useful; however, the spectrum of terminator functions which have been found to be compatible with the conditions required to generate N-acyliminium ions is not as broad as those employed in cationic polyene cyclizations.[22]

Other research in our laboratories has centered upon 2- and 3-substituted furans as cyclization terminators in annulation sequences.[20] The majority of these examples have employed epoxides[20a,21], allylic alcohols[20b,22], and enones[20b,23] as cyclization initiators, thus providing routine access only to terpenoid-type compounds. Should N-acyliminium ion precursors containing furan-terminated chains be constructed and should the furyl moiety prove to be sufficiently robust so as to survive intact during N-acyliminium ion formation and subsequent cyclizations, then a variety of biologically active alkaloids could be considered potential targets for total synthesis. For this process to be general, we must be able to prepare a variety of skeletal types including linearly-fused, spirocyclic and bridged. Possible N-acyliminium ion precursors to those target structures are depicted in Figure 2.



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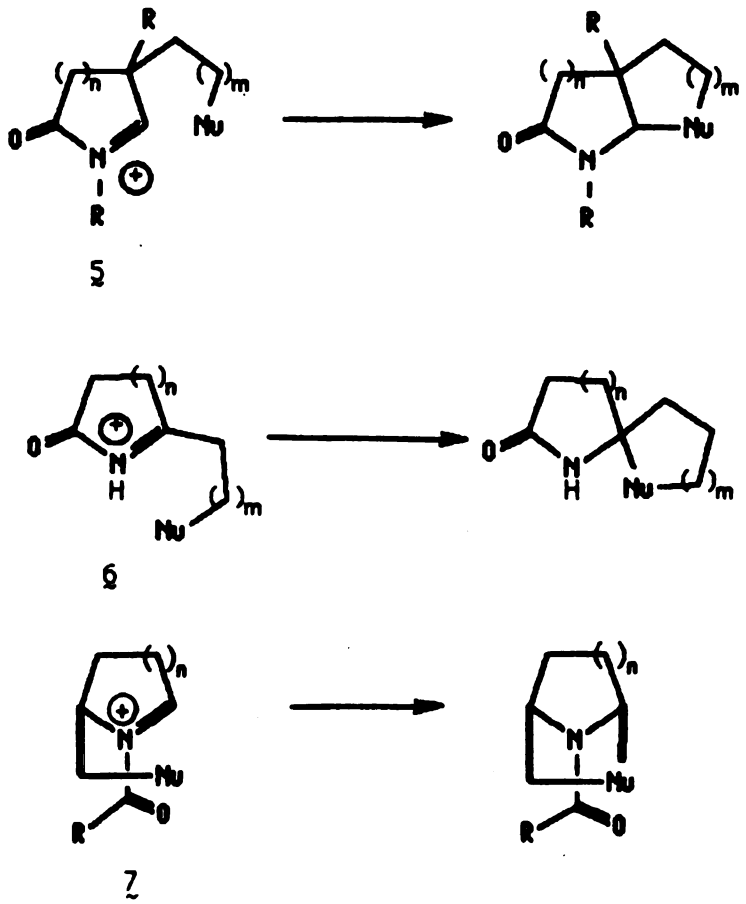


Figure 2. N-acyliminium ion skeltal types

N-acyliminium ions 4 and 5 will provide linearly-fused, bicyclic products in which the size of the rings formed can be readily varied. Their cyclization products could be converted to pyrrolizidine, indolizidine, and quinolizidine

alkaloids (from 4); or indole- and quinoline-type alkaloids (from 5). Similarly, N-acyliminium ions 6 and 7 could lead to a variety of spirocyclic- and bridged-alkaloid precursors.

Design and Synthesis of Cyclization Substrates

Our initial investigations in this area were directed toward compounds which might result from the cyclization of the readily prepared N-acyliminium ion 4. If we assume that Nu = 3- or 2-furyl (Figure 2, 4), then the resulting products should be readily converted to a variety of indolizidine and quinolizidine alkaloids (Figure 3, Eqs. 4 and 5) with the furyl moiety providing useful residual functionality after standard manipulations.

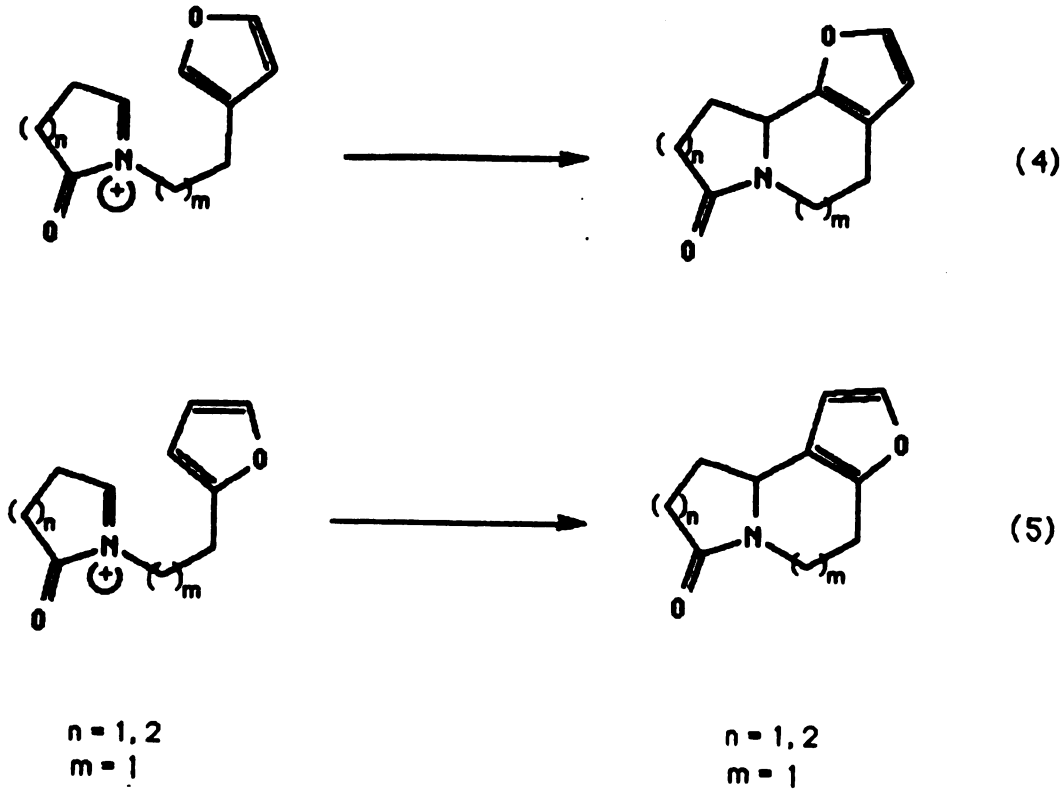
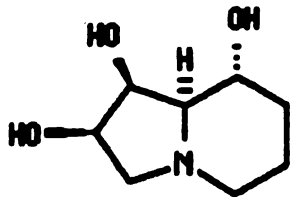


Figure 3

Some representative examples of the indolizidine alkaloids are the powerful α-mannosidase inhibitor swainsonine 8[24] and the related enzyme inhibitor castanospermine 9.[25] The Dedrobates alkaloids, gephyrotoxin 10[4] and perhydrogephyrotoxin 11[26] together with the Elaeokanine alkaloids A - C (12-14)[27], which have no unusual bioactivity, might also be considered members of this class of alkaloids. A few simple examples of quinolizidines include lupinine 15[28] and its stereoisomer epilupinine 16.[5b,29]

Of the structures depicted in Figure 4, we chose the less complex Elaeokanine alkaloids 12-14 and lupinine 15, or its isomer epilupinine 16, as our initial synthetic targets. However, first we must demonstrate that the 2- and 3-furyl moieties are sufficiently nucleophilic and stable terminator functions for N-acyliminium ion-initiated cyclizations. Additionally, we hoped to show that the N-alkyl chain of these cyclization precursors can be readily modified to routinely provide access to six- and seven-membered linearly-fused carbocyclic ring systems, such as those shown in Equations 6-9.

As is illustrated in Equations 6-9, 2- and 3-furyl alcohols 19, 26, 33 and 40 will serve as the source of the furyl moieties. Coupling, utilizing the Mitsunobu protocol[30], so successfully employed by Hart[3,4d,26c], Chamberlin[5], Speckamp[14,15,27e], and others, with succinimide or glutarimide, should afford imides 20, 23, 27, 30, 34, 37,



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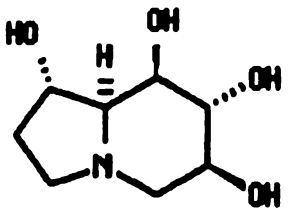

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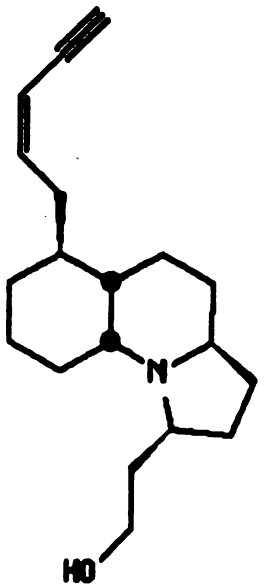

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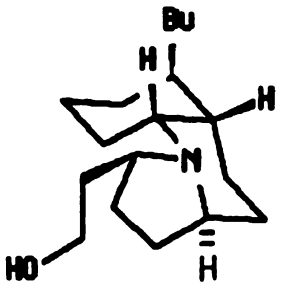

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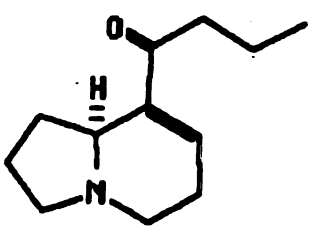

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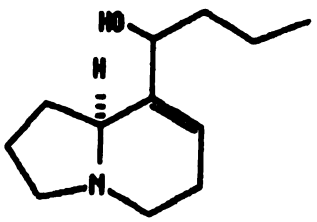

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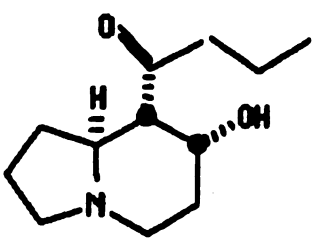

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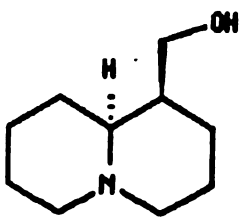

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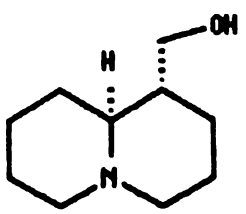

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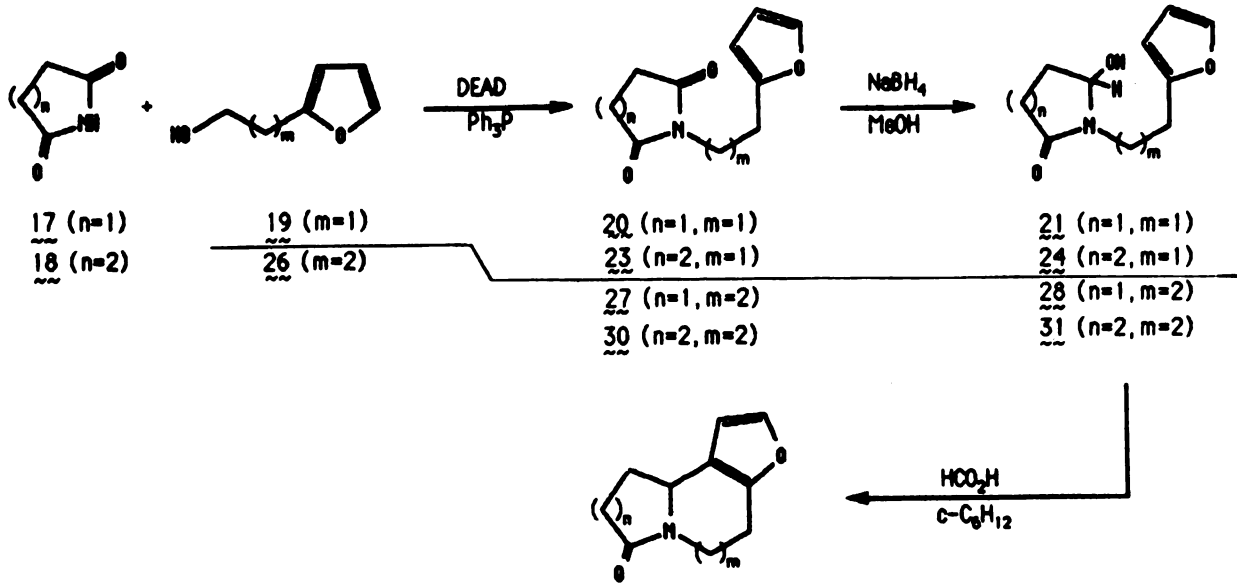
Figure 4. Indolizidines and Quinolizidines



17 (n=1)
18 (n=2)

19 (m=1)
26 (m=2)

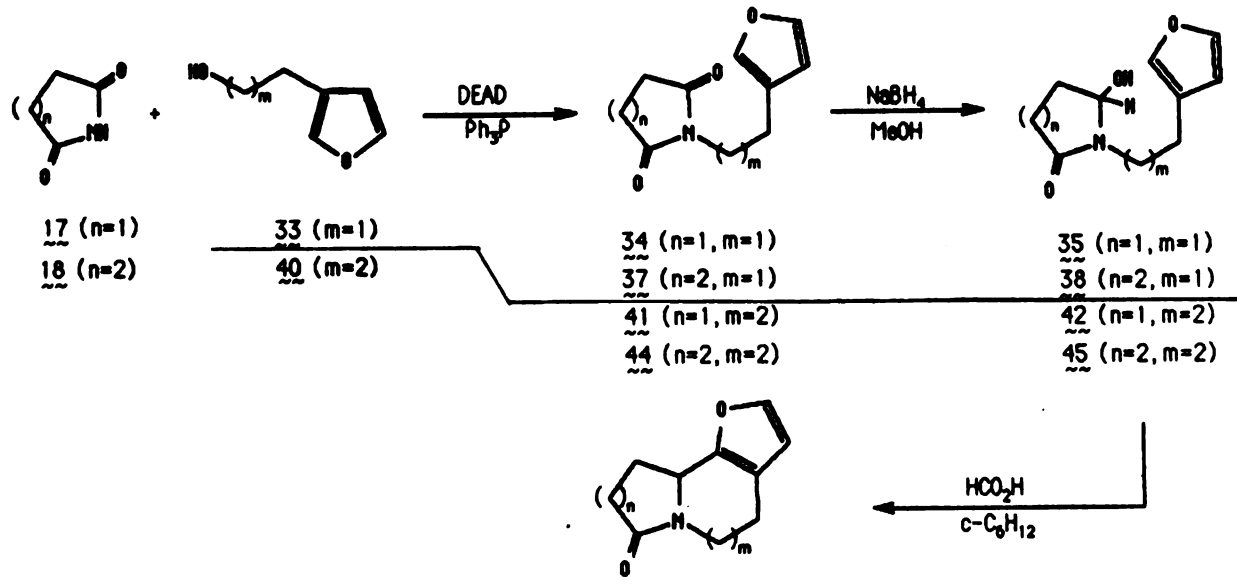
20 (n=1, m=1)
23 (n=2, m=1)
27 (n=1, m=2)
30 (n=2, m=2)

21 (n=1, m=1)
24 (n=2, m=1)
28 (n=1, m=2)
31 (n=2, m=2)

(6)

(7)

22 (n=1, m=1)
25 (n=2, m=1)
29 (n=1, m=2)
32 (n=2, m=2)



17 (n=1)
18 (n=2)

33 (m=1)
40 (m=2)

34 (n=1, m=1)
37 (n=2, m=1)
41 (n=1, m=2)
44 (n=2, m=2)

35 (n=1, m=1)
38 (n=2, m=1)
42 (n=1, m=2)
45 (n=2, m=2)

(8)

(9)

36 (n=1, m=1)
39 (n=2, m=1)
43 (n=1, m=2)
46 (n=2, m=2)

41 and 44. Reduction to the carbinolamide and subsequent cyclization could lead to the corresponding cyclized products (See Eqs. 6-9). In the event, treatment of 2-(2-furyl)ethanol 19 (m=1)[31] with either succinimide 17 (n=1) or glutarimide 18 (n=2) in the presence of diethyl azodicarboxylate (DEAD) and triphenyl phosphine (Ph_3P) provided N-substituted imides 20 (n=1, m=1) and 23 (n=2, m=1) in 31% and 51% yields, respectively, after chromatography. Similarly, the Mitsunobu reaction of 3-(2-furyl)propanol 26 (m=2) with succinimide 17 and glutarimide 18 led to imides 27 (69%) and 30 (53%). With the complement of imides 20, 23, 27 and 30 designed to examine the effects of preformed (5 or 6) ring and forming ring (6 or 7) size upon the N-acyliminium ion-initiated furan (2-3 position) terminated cyclization in hand, we next examined the reduction-cyclization sequence. Sodium borohydride reduction of 20, 23, 27 and 30, according to the procedure of Chamberlin[5b] ($NaBH_4$, MeOH, -4°C), provided the corresponding carbinolamides 21, 24, 28 and 31 in 88%, 95%, 94% and 95% yields, respectively. Carbinolamide 21 was then subjected to the cyclization conditions we had successfully employed in our sequences with allylic alcohol and enone initiators.[20b] Exposure of 21 to a two-phase mixture of anhydrous HCO_2H and c-C_6H_{12} for 2-3 minutes gave the desired indolizidine alkaloid precursor 22 in 70% yield. The time before workup (2-3 min.) was found to be crucial as lengthening of the reaction time (5-10 min.) caused a

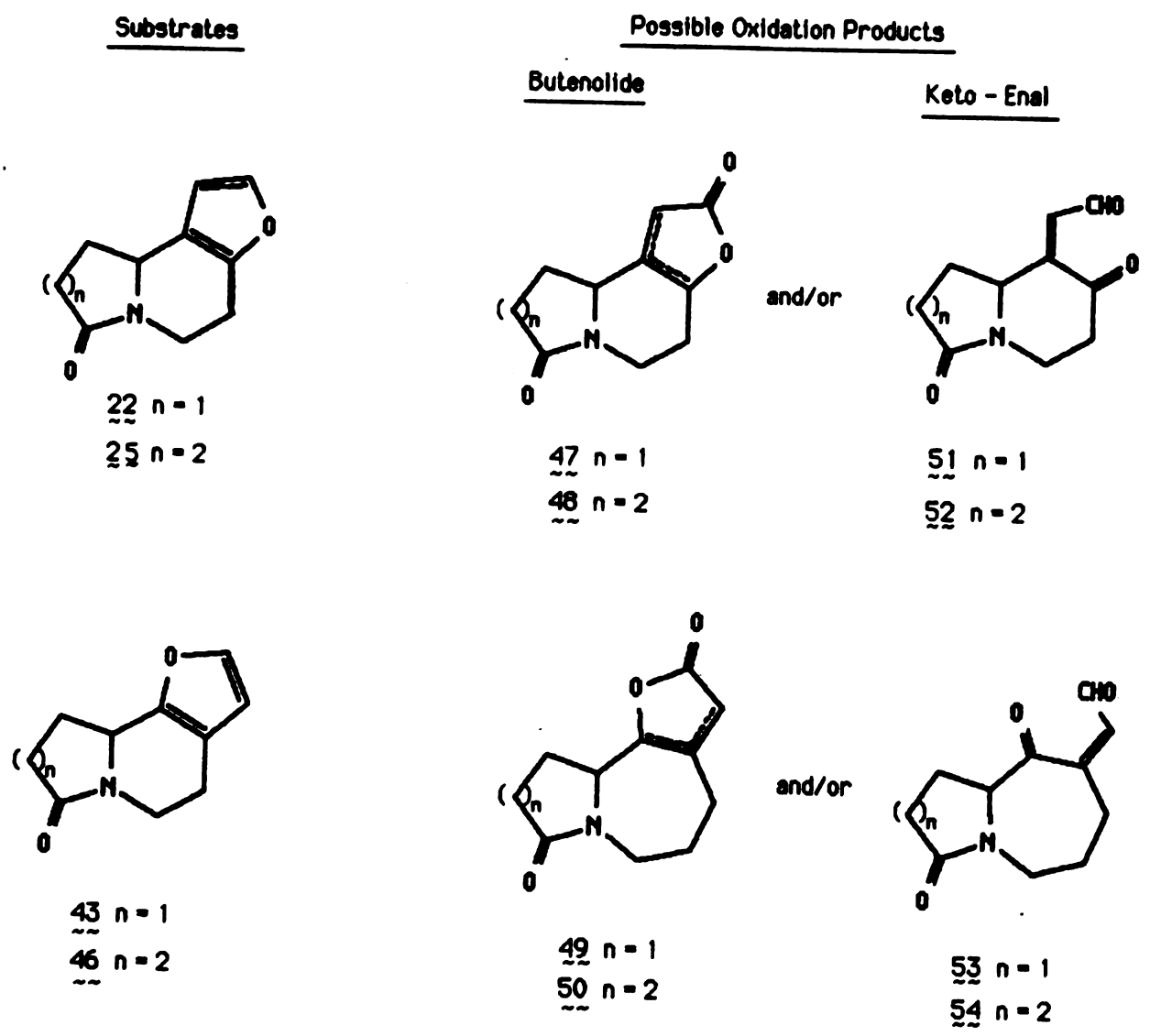
substantial reduction in yield and a poor mass balance. The isolation of a good yield of **22** is noteworthy in that it is but our second example of the previously unknown and relatively disfavored 2-substituted-to-3-furyl cyclization.[20b] Similarly, carbinolamide **24** afforded quinolizidine precursor **25** in 71% yield after purification by chromatography. The seven-membered ring precursors **28** and **31** were examined extensively, and we were unable to prepare either the 5,7-membered ring compound **29** or the 6,7-fused **32** under a variety of reaction conditions (*e.g.*, i. HCO_2H, c-C_6H_{12}; ii. MsCl, Et_3N; iii. HCl, aq. THF).

Based upon our previous experience in furan-terminated cationic cyclization[20b], we expected not to encounter such forming-ring size problems in the electronically favored 3-to-2-closure (Eqs. 8 and 9). Therefore, we prepared the requisite imides **34** (100%), **37** (100%), **41** (56%), and **44** (84%) from glutarimide or succinimide, 2-(3-furyl)ethanol **33** (m=1)[32] and 3-(3-furyl)propanol **40** (m-2) and subjected these materials to the standard reduction and cyclization conditions. 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 **36**, **39**, **43** and **46** after brief treatment with HCO_2H/cC_6H_{12}.

Furan Manipulations - The Preparation of Alkaloid Precursors

With the desired cyclized substrates (See Eqs. 6-9) in hand, the next important transformation to be examined was the crucial oxidative cleavage of the 2,3-Disubstituted furyl moiety. Of the six possible (**22**, **25**, **36**, **39**, **43** and **46**) cyclized materials to be subjected to various oxidative methods, we chose as representative examples the indolizidine and quinolizidine precursors **22** and **25**, respectively, and the seven-membered, 3- to 2-cyclized substrates **43** and **46**. Successful oxidation of substrates **22**, **25**, **43** and **46** could afford either the corresponding butenolides (**47** - **50**) or cleaved products, the keto-enals (**51** - **54**), as a function of the conditions employed for the oxidation (See Figure 5).

FIGURE 5: Oxidation of 2,3-Disubstituted Furans



Numerous methods for transforming a wide variety of variously substituted furans into their corresponding butenolides or keto-enals have been reported. Of these methods, we initially investigated oxidation with mCPBA in CH_2Cl_2 buffered with $NaHCO_3$[33] or unbuffered[33,34], the chrominum VI-based reagents (PCC[35] and variants, such as 2-CNPCC[36]; and the more classical Clauson-Kaas oxidation, Br_2

in buffered CH_3OH)[37], followed by hydrolysis of the intermediate α,α'-dimethoxy-dihydro furan derivative.[33,37c,38]

In the event, the readily available quinolizidine precursor **25** was subjected to the oxidation methods mentioned above. Thus, treatment of **25** with mCPBA under a variety of reaction conditions (2.2 equiv., CH_2Cl_2, 0°C to reflux[33,34]; 2.2 equiv., $NaHCO_3$, 0°C to reflux[33]; 2.2 equiv., NaOAc, HOAc) followed by reductive ($NaBH_4$) workup[39]; and finally, 2.2 equiv., CH_2Cl_2, 0°C to 25°C followed by trifluoroacetic acid (TFA) quench[33], led only to recovery of the starting material **25** or a number of unidentified products with overall poor mass-balance. Similarly ineffective in oxidizing the furyl residue of **25** was PCC, CH_2Cl_2, 25°C to reflux[35] and the more reactive 2-CNPCC, CH_2Cl_2, 25°C to reflux.[36] Clauson-Kaas oxidation (Br_2, Na_2CO_3, MeOH, -30°C)[37] of the indolizidine precursor **25** did provide the corresponding α,α'-dimethoxy-dihydro derivative in 77% yield; 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[38a]; H_2O, 45°C[38d]; ii. 1N HCl, H_2O, 45°C[38a]; iii. 2% aqueous H_2SO_4, 25°C).[38c]

Other methods that have been successfully employed in oxidizing related substituted furan systems, but which failed to oxidatively open the furyl residue in **25**, were NBS, NaOAc, dioxane-H_2O, followed by $NaBH_4$ reduction[40] and

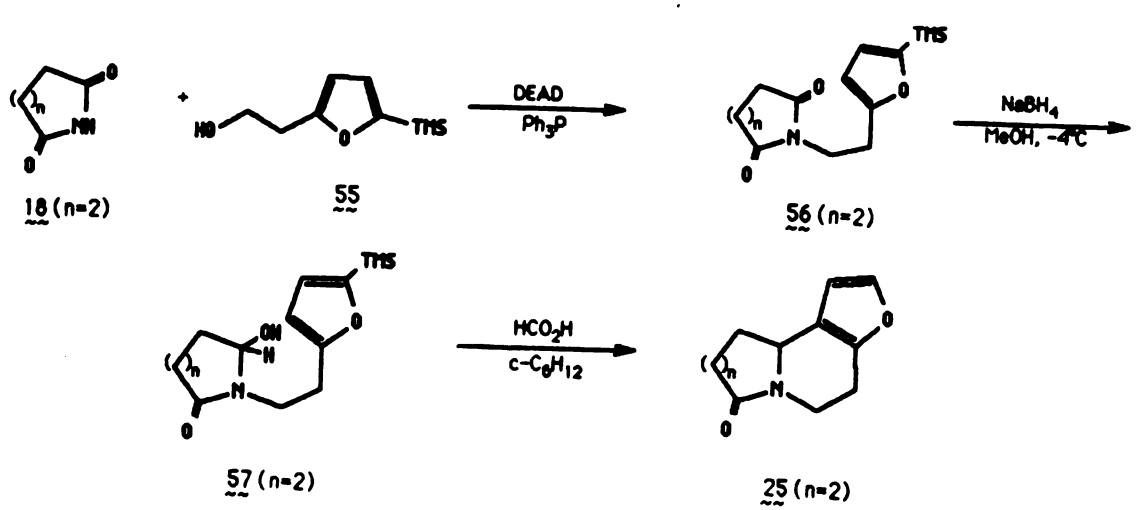
$Ce^{IV}(NH_4)_2(NO_3)_6$, H_2O-CH_3CN, 25°C.[41] We can safely conclude after this extensive examination of chemical oxidants that furan cleavages are non-standard operations which are extremely substrate dependent.

Since standard and other esoteric methods for oxidizing the furyl moiety of substrate **25** 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.[42]

Treatment of **45** and or **46** with $^1O_2$, generated by bubbling oxygen through solution of substrates in CH_3OH or CH_2Cl_2 and either rose bengal[43], hematoporphrin[42], or tetrahydroporphrin[42,44] as sensitizers at 25°C using either a medium-pressure Hanovia lamp or a 500W Tungsten filiment source, failed to provide any of the desired products and, in general, resulted in poor mass-recovery. Consequently, the temperature at which the photolyses were performed was lowered to -78°C[44c]; and the crude photolysis mixtures were quenched with reducing agents, including $NaBH_4$ in MeOH or i-PrOH[45] and Ph_3P.[43f,44b] 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 (See Figure 5). 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 experiences in oxidizing furans[48] and the studies of others[44c,47], we decided to increase the nucleophilicity of the furyl moiety in cyclized substrate **25** by introducing a TMS group at the unsubstituted-α'-position. Following a procedure by German workers, who successfully silylated analogous pyrrole systems using Et_3N and TMSOTf at 5°C to 25°C[48], we exposed furan **25** to TMSOTf in 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 methanol leading to recovery of **25**.

Alternatively, the silyl group could be introduced intact on the furyl piece prior to the Mitsunobu coupling reaction as is outlined in Scheme II.

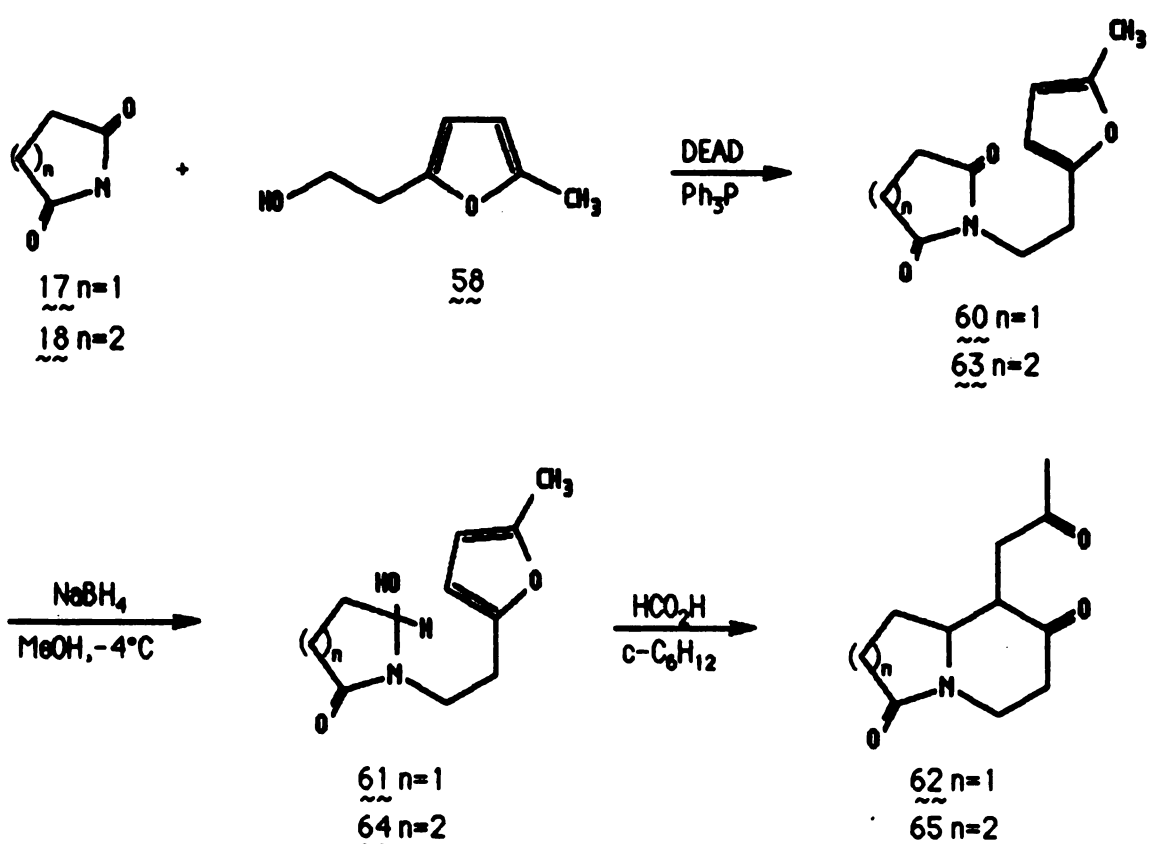


18 (n=2) 55 56 (n=2) 57 (n=2) 25 (n=2)

Scheme II

The coupling of 2-(5-Trimethylsilyl-2-furyl) ethanol 55[49] with glutarimide 18 (n=2) using the Mitsunobu procedure (DEAD, Ph_3P)[30] provided imide 56 in 87% yield after chromatography. Reduction ($NaBH_4$, MeOH, -4°C)[5b] yielded cyclization precursor 57 in quantitative crude yield. Attempted cyclization of carbinolamide 57 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 25.

Recently, we[50] have discovered that that introduction of an alkyl group at an unsubstituted-α'-position of a similarly unreactive 2,3-disubstituted furyl moiety increased its reactivity towards standard oxidizing



17 n=1
18 n=2

58

60 n=1
63 n=2

61 n=1
64 n=2

62 n=1
65 n=2

Scheme III

reagents. Because of our concern for the survival of the system under the strongly basic conditions required to introduce a CH_3- onto the cyclized **25**, we elected to employ the strategy depicted in Scheme III and utilize a furyl piece with the requisite group already in place.

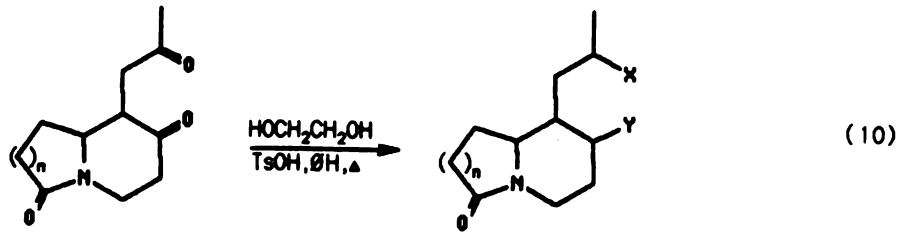
Hence, the required imides, **60** (n=1, 55%) and **63** (n=2, 83%), were prepared from succinimide **17** (n=1) or glutarimide **18** (n=2) and 2-(5-methyl-2-furyl) ethanol **58**. Reduction provided crude carbinolamides **61** and **64** in quantitative yields. Subjecting these two substrates to the standard cyclization conditions (HCO_2H, c-C_6H_{12}, 2 to 3 min.) afforded, to our delight, diones **62** (n=1) and **65** (n=2) in 35% and 64% yields, respectively. Diones **62** and **65** were obtained as a mixture of epimers. This observation is unique in that the hydrolysis of the putative furan intermediate is essentially unprecedented. Our experience in the parent systems and in a related perhydrohistrionicotoxin spiro-cyclization[52] 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[53] and or allylic strain.[54]

With both quinolizidine **65** and indolizidine **62** precursors in hand, we next examined their conversion to the relatively simple naturally occurring alkaloids, lupinine **15** or epilupinine **16** and elaeokanine A **12**. Considering first

the dione **65** (n=2), 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 function is crucial to the successful completion of the synthesis.

Dione **65** was subjected to the "standard" ketalization conditions ($HOCH_2CH_2OH$, TsOH, PhH, Δ)[55] affording a disappointing ~2 to 1 mixture of "ring" ketalized material **68** to "side chain" ketalized compound **69** in 75% yield (see Eq. 10). The predominant formation of "ring" ketalized material **68** was demonstrated when the ketalized substrate, obtained from the standard ketalization technique[55], was submitted to $NaBH_4$ reduction. The ^1H-NMR (250MHz) spectrum of the product ketal-alcohol revealed that the methyl singlet of dione **65** now appeared as a pair of doublets (~ 3:1 ratio) indicating that the major product under these conditions was not **69** but hydroxy ketal **68** (X=H,OH) prepared as a mixture of epimers at the carbinol center.

However, treatment of **65** under the recently reported kinetically-controlled ketalization conditions ($TMSOCH_2CH_2OTMS$, -23°C to 25°C, 10 mol% TMSOTf)[56] yielded exclusively the "side chain" ketalized product **69** in 77% yield.

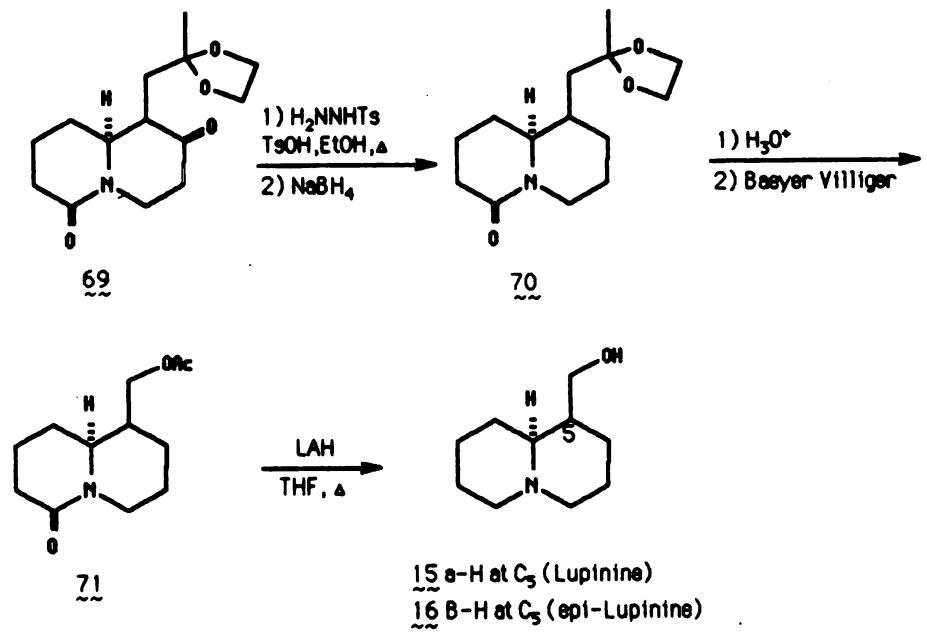


(10)

62 (n=1)
65 (n=1)

66 X=(=O), Y=(-OCH2CH2O-), n=1
67 X=(-OCH2CH2O-), Y=(=O), n=1
68 X=(=O), Y=(-OCH2CH2O-), n=2
69 X=(-OCH2CH2O-), Y=(=O), n=2

With the exclusive formation of the monoketal **69**, we envisioned the completion of the synthesis of lupinine **15** or epi-lupinine **16** as described in Scheme IV. Formation of the tosylhydrazone derivative from mono-ketal **69** (H_2NNHTS, TsOH, EtOH, Δ)[57] and subsequent reductive deoxygenation ($NaBH_4$, MeOH, 0°C)[57d] should afford compound **70**. Deprotection (H_3O^+)[58] followed by Baeyer-Villiger oxidation[59] could provide acetate **71**. Finally, LAH reduction of both the acetate and amide carbonyl functions[5b] in **71** should lead cleanly to either lupinine **15** or epi-lupinene **16**.



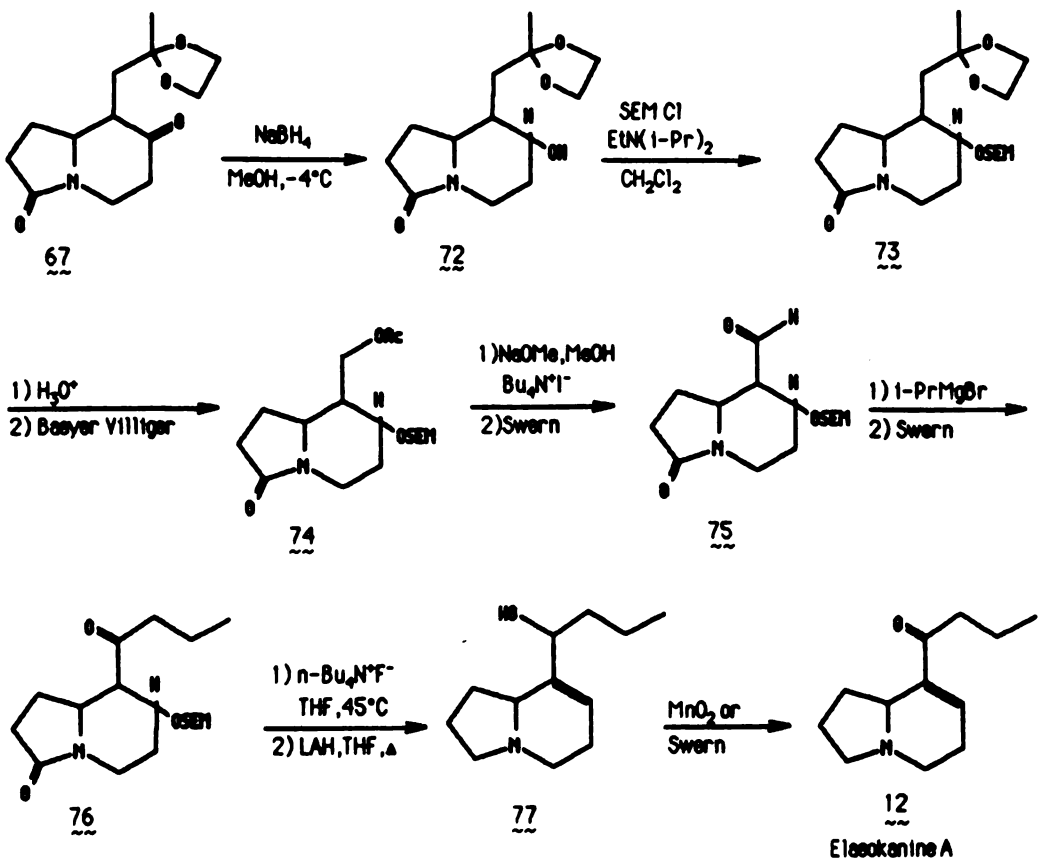
69 → 70 → 71 → 15 α-H at C_5 (Lupinine) + 16 β-H at C_5 (epi-Lupinine)

Scheme IV

Some preliminary studies of the Baeyer-Villiger oxidation conducted on the inseparable 2:1 mixture of ketals **69** and **68** revealed that this oxidation was not as trivial as initially presumed. For example, reacting the mixture of ketals under a variety of Baeyer-Villiger conditions, such as mCPBA (2.2 equiv.), CH_2Cl_2, Δ^{60}; 30% H_2O_2, NaOH, MeOH, 25°C[61]; 30% H_2O_2, NaOH, EtOH, Δ^{62}; TFAA, 30% H_2O_2, CH_2Cl_2, wet TFA[63], gave either recovered starting material or a variety of unidentifiable products with poor mass-recovery. However, subjecting the mixture of ketals **69** and **68** to Noyori's conditions (3 equiv. CF_3CO_2H, 3 equiv. $NaHPO_4$, CH_2Cl_2, 0° to 25°C)[59,64] resulted in the complete disappearance of **69** and the appearance of ^{1}H-NMR resonances consistant with an acetate functional group.

The successful completion of the synthesis of quinolizidine alkaloids, lupinine **15** or epi-lupinine **16**, appears to be assured; and all that remains to be accomplished is the removal of the ring ketone carbonyl prior to deketalization, Baeyer-Villiger cleavage and LAH reduction. These transformations are currently being examined.

In order to convert indolizidine precursor **67** to an elaeokanine alkaloid, selective ketalization of the dione is again paramount. Fortunately, with this particular dione system, the solution to the problem was much more straightforward than in the analogous substrate **65**. To our



Scheme V

delight, standard ketalization techniques performed on **62** (n=1) gave only the "side chain" ketalized material **67** in 70% yield with no formation of the "ring-ketalized" substrate **68** observed (See Eq. 10). From the mono-ketal **67**, we envisioned preparing elaeokanine A **12** as illustrated in Scheme V.

Reduction ($NaBH_4$, MeOH, 0°C) of **67** proceeded cleanly to provide the hydroxy-ketal **72** in 81% unoptimized yield. Protection of the secondary hydroxyl function as the SEM-

ether (SEMCl, i-Pr_2NEt, CH_2Cl_2, 40°C)[65] followed by ketal deprotection (H_3O^+) and subsequent Baeyer-Villiger oxidation (TFPA, Na_2HPO_4, CH_2Cl_2)[59,64] of the 2-propyl ketone side chain could yield acetate 74. Acetate hydrolysis (K_2CO_3/aq. MeOH)[66], Swern oxidation (DMSO, $(CO)_2Cl_2$, CH_2Cl_2)[67] of the primary hydroxyl followed by treatment of the aldehyde 75 with i-PrMgBr[68] and oxidation of the resulting alcohol (Swern) should give ketone 76. "Dehydration" of 76, followed by LAH reduction, could afford the allylic alcohol 77. Finally, oxidation of the allylic alcohol (MnO_2)[69] should provide Elaeokanine A 12. Furthermore, with some minor modifications to one or more of the steps presented in Scheme V, the synthesis of the remaining Elaeokanine alkaloids could be realized.

In conclusion, we have demonstrated that 2- and 3-furyl moieties are sufficiently nucleophilic and stable 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-to-2-furyl closure (all) and the regioisomeric 2-to-3-furyl closure (5,6- and 6,6-membered rings only) being realized. In general, cyclization yields were uniformly high; additionally, the utility of these linearly-fused, bicyclic substrates was demonstrated by illustrating the chemical manipulations of the furyl residue necessary to transform 22 and 25 into precursors of the bioactive

alkaloids lupinine **15** or epi-lupinine **16** and Elaeokanine A **12**.

The ease with which the cyclization precursors can be prepared, coupled with their demonstrated structural flexibility (yielding a variety of preformed (5 or 6) and formed (6 or 7) ring systems with important residual functionality present), will undoubtedly lend itself to the preparation of other more challenging biologically active alkaloid structures.

EXPERIMENTAL

STUDIES DIRECTED TOWARDS THE SYNTHESIS OF SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS.

EXPERIMENTAL SECTION

General. Tetrahydrofuran (THF) and benzene were dried by distillation under argon from sodium benzophenone ketyl; methylene chloride was dried by distillation under argon from calcium hydride; triethylamine (TEA) was dried by distillation under argon from calcium hydride; t-butanol was dried by distillation under argon from sodium; pyridine was dried by distillation under argon from calcium hydride. Formic acid (98%) was purchased from Fluka and was used as received. Diethyl azodicarboxylate and Ph_3P were purchased from Aldrich Chemical Company, Milwaukee, Wisconsin and were used as received. Petroleum ether refers to 35-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Columbia Chemical Industries, Inc., Columbus, Wisconsin, and was 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 Pye-Unicam SP-1000 infrared spectrometer or a Perkin-Elmer Model 167

spectrometer with polystyrene as standard. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian T-60 at 60MHz, a Varian CFT-20 at 80MHz, 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 followed: chemical shifts (multiplicity: s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet, coupling constant (Hz), integration). Electron impact (EI/MS, 70eV) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system.

Flash column chromatography was performed according to the procedure of Still *et. al.* by using the Whatman silica gel mentioned and elated with the solvents mentioned. The columns outer diameter (o.d.) is listed in millimeters.

General Procedure for the Preparation of N-Substituted Imides (20, 23, 27, 30, 34, 37, 41 and 44).

Preparation of N-(2-(2-Furyl)-ethyl)-2,5-pyrrolidinedime (20).

To a solution of 2-furyl ethanol (2.24g, 20mmol), triphenylphosphine (5.77g, 22mmol), succinimide (1.98g, 20mmol), and THF (16.7mL), chilled in an ice-H_2O bath, was

added to a solution of diethyl azodicarboxylate (3.83g, 22mmol) in THF (8.9mL) over 20 min. The mixture was stirred at 25°C for 48h and then concentrated *in vacuo* to a yellow viscous liquid. Ether-petroleum ether (1:1) was added to the residue resulting in the precipitation of a white solid ($Ph_3P=O$) which was removed by filtration. The filtrate was concentrated *in vacuo* to provide 3.52g of a viscous pale yellow liquid which was purified by chromatography on a column of silica gel (60-230 mesh, 170 g, 60mm o.d., ethyl acetate-petroleum ether 35:65, 100mL fractions) using the flash technique. Fractions 12-25 provided 1.21g, 31%, of **20** as an off-white crystalline solid. mp = 65-69°C. ^{1}H-NMR (250MHz): δ = 7.27 (m, 1), 6.22 (m, 1), 6.01 (m, 1), 3.75 (t, J=8.3Hz, 2), 2.88 (t, J=8.3Hz, 2), 2.63 (s, 4); IR (neat): 3450, 2930, 2860, 1770, 1700, 1400, 1170, 1125, 815 cm^{-1}; EI-MS (70eV): 193 (M^+, 0.31), 126 (8.15), 113 (43.14), 112 (35.5), 100 (base), 81 (86.3).

N-(2-(2-Furyl)-ethyl)-2,6-piperidinedione (23).

According to the general procedure for the preparation of N-substituted imides, 2-furyl ethanol (2.24g, 20mmol), triphenylphosphine (5.77g, 22mmol), and glutarimide (2.26 g, 20mmol) in THF (16.7mL) was allowed to react with diethyl azodicarboxylate (3.83g, 22mmol) to provide 5.15g of crude product. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 230g, 20mm o.d., ethyl acetate-petroleum ether 35:65, 125mL fractions) using

the flash technique. Fractions 13-28 provided 2.10g, 51%, of **23** as a viscous yellow liquid.

^{1}H-NMR (60MHz): δ = 7.30 (m, 1), 6.27 (m, 1), 6.02 (m, 1), 4.07 (t, J=8.0Hz, 2), 2.85 (t, J=8.0Hz, 2), 2.59 (t, J=6.5 Hz, 4), 1.90 (m, 2); IR (neat): 3.30, 2860, 1725, 1670, 1350, 920, 735 cm^{-1}; EI-MS (70eV): 207 (M^+, 8.07), 140 (0.44), 126 (0.78), 98 (4.63), 94 (base), 81 (13.0).

N-(2-(3-Furyl)-ethyl)-2,5-pyrrolidinedione (**34**).

According to the general procedure for the preparation of N-substituted imides, 3-furyl ethanol (1.12g, 10mmol), triphenylphosphine (2.88g, 11mmol), and succinimide (0.99 g, 10mmol) in THF (8.3mL) were allowed to react with diethyl azodicarboxylate (1.91g, 11mmol) in THF (4.5mL) for 24h to provide 4.20g of crude product. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 120g, 50mm o.d., ethyl acetate-petroleum ether 30:70, 75mL fractions) using the flash technique. Fractions 19-27 provided 1.90g, 98%, of **34** as a viscous pale yellow liquid together with a white solid.

^{1}H-NMR (250MHz): δ = 7.32 (m, 1), 7.23 (m, 1), 6.28 (bs, 1), 3.90 (t, J=6.7Hz, 2), 3.51 (t, J=6.7Hz, 2), 2.73 (m, 4); IR (neat): 3260, 1750, 1700, 1400, 1140, 870, 660 cm^{-1}; EI-MS (70eV): 193 (M^+, 13.6), 126 (57.0), 112 (7.23), 94 (base), 84 (20.1), 81 (25.3).

N-(2-(3-Furyl)-ethyl)-2,6-piperidinedione (37).

According to the general procedure for the preparation of N-substituted imides, 3-furyl ethanol (1.12g, 10mmol), triphenylphosphine (2.88g, 11mmol), and glutarimide (1.13 g, 10mmol) in THF (8.3mL) was allowed to react with diethyl azodicarboxylate (1.92g, 11mmol) in THF (4.5mL) for 24h to provide 4.33g of crude product. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 120g, 50mm o.d., ethyl acetate-petroleum ether 1:1, 75mL fractions) using the flash technique. Fractions 7-12 yielded 2.03g, 98%, of 37 as a viscous pale yellow liquid together with a white solid.
^{1}H-NMR (250MHz): δ = 7.31 (m, 1), 7.15 (bs, 1), 6.30 (bs, 1), 3.91 (t, J=7.8Hz, 2), 3.42 (t, J=7.8Hz, 2), 2.61 (m, 4), 1.90 (m, 2); IR ($CHCl_3$): 3420, 1730, 1670, 1350, 1125, 870 cm^{-1}; EI-MS (70eV): 208 (15.0), 207 (38.2), 177 (14.7), 176 (16.4), 140 (45.5), 126 (4.09), 98 (12.6), 94 (base), 81 (4.78).

N-(3-(2-Furyl)-propyl)-2,5-pyrrolidindione (27).

According to the general procedure for the preparation of N-substituted imides, 3-(2-furyl)propanol (4.0g, 31.75 mmol), triphenylphosphine (8.32g, 31.75mmol) and succinimide (3.52g, 35.60mmol) in THF (50mL) was allowed to react with diethyl azodicarboxylate (5.52g, 31.75mmol) in THF (8mL) for 36 h. The crude product was purified by chromatography on a

column of silica gel (60-230 mesh, 200 g, 50mm o.d., ethyl acetate, petroleum ether 2:3, 60mL fractions) using the flash technique. Fractions 10-15 provided 4.08g, 62%, of **27** as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 7.25 (m, 1), 6.22 (m, 1), 5.98 (m, 1), 3.54 (t, J=7.3Hz, 2), 2.63 (m, 4), 2.61 (t, J=8.0Hz, 2), 1.91 (m, 2); IR (neat): 3450, 3240, 1770, 1700, 1435, 1400, 1150, 730 cm^{-1}; EI-MS (70eV): 208 (M^++1, 2.04), 207 (M^+, 11.3), 113 (15.1), 108 (base), 95 (33.9), 81 (73.7), 67 (13.6), 55 (47.6).

N-(3-(2-Furyl)-propyl)-2,6-piperidinedione (**30**).

According to the general procedure for the preparation of N-substituted imides, 3-(2-furyl)propanol (4.0g, 31.75mmol), triphenylphosphine (8.32g, 31.75mmol), and glutarimide (4.02g, 35.60mmol) in THF (50mL) was allowed to react with diethyl azodicarboxylate (5.52g, 31.75mmol) in THF (8mL) for 36 h. The crude product was purified by preparative liquid chromatography (300mL/min) eluting with ethyl acetate-hexane, 30:70, to provide 3,69g, 53%, of **30** as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 7.25 (m, 1), 6.23 (m, 1), 5.99 (m, 1), 3.81 (t, J=7.3Hz, 2), 2.61 (t, J=8.3Hz, 2), 2.59 (t, J=6.7Hz, 4), 1.86 (m, 4); IR (neat): 3300, 3000, 1730, 1680, 1370, 1280, 1125, 1140, 1055, 1000, 935, 730 cm^{-1}; EI-MS (70eV): 221 (M^+, 8.16), 140 (6.42), 126 (11.2), 108 (100), 98 (16.8), 81 (74.8).

N-(3-(3-Furyl)-propyl)-2,5-pyrrolidinedione (41).

According to the general procedure for the preparation of N-substituted imides, 3-(3-furyl)propanol (2.52g, 20mmol), triphenylphosphine (6.03g, 23mmol), and succinimide (1.98g, 20mmol) in THF (16.7mL) was allowed to react with diethyl azodicarboxylate (4.01g, 23mmol) in THF (8.9mL) for 24 h. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 230g, 60mm o.d., ethyl acetate-petroleum ether 30:70, 75-100 mL fractions) using the flash technique. Fractions 15-26 provided 2.31g, 56%, of 41 as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 7.35 (m, 1), 7.24 (bs, 1), 6.28 (bs, 1), 3.57 (t, J=8.3Hz, 2), 2.65 (m, 4), 2.45 (t, J=8.3Hz, 2), 1.86 (m, 2); IR ($CHCl_3$): 3400, 2965, 1720, 1690, 1480, 1400, 1210, 1150, 1050 cm^{-1}; EI-MS (70eV): 208 (M^++1, 3.46), 207 (M^+, 15.03), 126 (4.22), 113 (6.64), 108 (base), 95 (35.6), 84 (12.6), 81 (20.6).

N-(3-(3-furyl)-propyl)-2,6-piperidinedione (44).

According to the general procedure for the preparation of N-substituted imides, 3-(3-furyl)propanol (2.52g, 20mmol), triphenylphosphine (6.03g, 23mmol), and glutarimide (2.26g, 20mmol) in THF (16.7mL) was allowed to react with diethyl azodicarboxylate (4.01g, 23mmol) in THF (8.9mL) for 48 h. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 250g, 60mm o.d., ethyl acetate-

petroleum ether 30:70, 100 mL fractions) using the flash technique. Fractions 18-31 provided 3.70g, 84%, of **44** as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 7.34 (m, 1), 7.24 (bs, 1), 6.27 (bs, 1), 3.82 (t, J=8.3Hz, 2), 2.62 (t, J=6.3Hz, 4), 2.45 (t, J=8.3Hz, 2), 1.89 (m, 2), 1.80 (m, 2); IR (neat): 3410, 2995, 1720, 1660, 1350, 1215, 1160, 1125, 1040 cm^{-1}; EI-MS (70eV): 221 (M^+, 7.97), 141 (27.0), 127 (8.04), 108 (base), 98 (39.0), 95 (18.7), 81 (26.4).

General Procedure for the Reduction of N-substituted Imides (**20**, **23**, **27**, **30**, **34**, **37**, **41** and **44**).

Preparation of N-(2-(2-Furyl)-ethyl)-5-hydroxy-2-pyrrolidinone (**21**).

Sodium borohydride (1.52g, 40mmol) was added all at once to a solution of the N-substituted imide (**20**, 769mg, 3.98mmol) in methanol (40mL) and chilled to -5°C in an ice-salt bath. The mixture was stirred at -5°C for 1h then cast into a rapidly stirred mixture of saturated aqueous $NaHCO_3$ (40mL) and CH_2Cl_2 (40mL) and chilled to 0°C in an ice-H_2O bath. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 40mL), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford 684mg, 88%, of the crude carbinol amide **21** as a viscous water-white liquid, which was used without further purification.

^{1}H-NMR (250MHz): δ = 7.28 (m, 1), 6.26 (m, 1), 6.05 (m, 1), 4.95 (bs, 1), 3.57 (m, 2), 3.63 (bs, 1), 2.88 (t, J=7.0Hz, 2), 2.51 (m, 1), 2.23 (m, 2), 1.85 (m, 1); IR (neat): 3320, 2920, 1690, 1660, 1450, 1285, 1170, 1070, 985, 920, 670 cm^{-1}; EI-MS (70eV): 196 (M^++1, 1.32), 195 (M^+, 10.0), 177 (4.30), 176 (7.55), 142 (3.94), 114 (24.8), 94 (80.9), 68 (58.9), 46 (base).

N-(2-(2-Furyl)-ethyl)-6-hydroxy-2-piperidinone (24).

According to the general procedure for the reduction of N-substituted imides sodium borohydride (1.14g, 30mmol) was added to imide 23 (621mg, 3.0mmol) in MeOH (30mL) at -5°C and stirred for 1h to provide 620mg, 98%, of the crude carbinol amide 24 as a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 55g, 40mm o.d., ethyl acetate-petroleum ether 4:1, 50mL fractions) using the flash technique. Fractions 9-18 provided 480mg, 76%, of a white crystalline solid. mp = 87-90°C.

^{1}H-NMR (250MHz): δ = 7.32 (m, 1), 6.29 (m, 1), 6.05 (m, 1), 5.85 (m, 1), 5.06 (m, 1), 3.72 (t, J=8.0Hz, 2), 2.90 (t, J=8.0Hz, 2), 2.50 (t, J=8.8Hz, 2), 2.37 (m, 2), 2.27 (m, 2); IR ($CHCl_3$): 3570, 3320, 2930, 1705, 1600, 1320, 1060, 970, 835 cm^{-1}; EI-MS (20eV): 210 (M^++1, 1.87), 209 (M^+, 9.55), 192 (3.40), 191 (18.2), 128 (8.3), 110 (24.3), 94 (61.7), 82 (31.8), 71 (29.4), 45 (base).

N-(2-(3-Furyl)-ethyl)-5-hydroxy-2-pyrrolidinone (35).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.60g, 42mmol) was added to imide 34 (0.811g, 4.20mmol) in MeOH (41mL) at -3°C and stirred for 1h to yield 0.671g, 82%, of the crude carbinol amide 35 as a viscous pale yellow liquid together with a white solid.

^{1}H-NMR (250MHz): δ = 7:32 (m, 1), 7.23 (bs, 1), 6.29 (bs, 1), 5.10 (bs, 1), 3.84-3.29 (m, 3), 2.61 (m, 2), 2.24 (m, 2), 1.86 (m, 2); IR ($CHCl_2$): 3430, 2960, 1770, 1690, 1480, 1350, 1080, 1030 cm^{-1}; EI-MS (70eV): 178 (M^++1-H_2O, 31.3), 177 (M^+-H_2O, 56.6), 176 (base), 149 (11.8), 148 (24.9), 121 (13.0), 120 (35.8), 110 (3.65), 82 (2.29), 65 (14.6).

N-(2-(3-Furyl)-ethyl)-6-hydroxy-2-piperidinone (38).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.50g, 39.4mmol) was added to imide 37 (0.816g, 3.94mmol) in MeOH (38mL) at -4°C and stirred for 1h to provide 0.55g, 67%, of the crude carbinol amide 38 as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 7.37 (m, 1), 7.25 (m, 1), 6.33 (bs, 1), 4.37 (m, 1), 3.90 (m, 1), 3.24 (m, 1), 2.73 (m, 2), 2.38 (m, 2), 1.99 (m, 2), 1.63 (m, 2); IR ($CHCl_3$): 3420, 2960, 1730, 1640, 1470, 1350, 1220, 1070, 1030 cm^{-1}; EI-MS (70eV): 210 (M^++1, 0.74), 209 (M^+, 4.49), 181 (5.26), 191 (2.23), 142 (2.50), 128 (22.0), 110 (27.9), 94 (base), 82 (48.3).

N-(3-(2-Furyl)-propyl)-5-hydroxy-2-pyrrolidinone (28).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.90g, 50mmol) was added to imide 27 (2.03g, 9.8mmol) in MeOH (100mL) at -4°C and stirred for 45 min. to afford 1.93g, 94%, of the crude carbinol amide 28 as a viscous pale yellow liquid.
^{1}H-NMR (250MHz): δ = 7.30 (m, 1), 6.27 (m, 1), 6.02 (m, 1), 4.91 (dd, J=6.0,2.0Hz, 1), 3.53 (m, 2), 2.65 (t, J=8.3Hz, 2), 2.50 (m, 2), 2.29 (m, 2), 2.00 (m, 2); IR ($CHCl_3$): 3900, 3300, 1730, 1680, 1470, 1380, 1340, 1230, 1060, 880 cm^{-1}; EI-MS (70eV): 192 (8.5), 191 (M^+-H_2O, 43.0), 108 (49.9), 97 (88.2), 81 (46.0), 68 (base).

N-(3-(2-Furyl)-propyl)-6-hydroxy-2-piperidinone (31).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.90g, 50mmol) was added to imide 30 (2.21g, 10mmol) in MeOH (100mL) at -4°C and stirred for 45 min to yield 2.0g, 90%, of the crude carbinol amide 31 as a viscous pale yellow liquid which crystallized upon cooling (-20°C) to give an off-white solid. mp = 58-64°C.
^{1}H-NMR (250MHz): δ = 7.29 (m, 1), 6.27 (m, 1), 6.02 (m, 1), 4.47 (m, 1), 3.68 (m, 2), 2.64 (t, J=7.8Hz, 2), 2.58 (m, 4), 1.98 (m, 2), 1.65 (m, 2); IR ($CHCl_3$): 3580, 3330, 2940, 1720, 1620, 1470, 1330, 1140, 1070, 1000, 930 cm^{-1}; EI-MS (70eV): 224 (M^++1, 1.78), 223 (M^+, 11.5), 205 (53.9), 176

(4.28), 149 (12.5), 110 (37.9), 108 (base), 81 (42.0), 68 (26.0).

N-(3-(3-Furyl)-propyl)-5-hydroxy-2-pyrrolidinone (42).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (3.82g, 100.5mmol) was added to imide 41 (2.18g, 10.52mmol) in MeOH (100mL) at -4°C and stirred for 1h to provide 1.85g, 84%, of the crude carbinol amide 42 as a viscous pale yellow liquid.
^{1}H-NMR (250MHz): δ = 7.38 (m, 1), 7.27 (m, 1), 6.30 (bs, 1), 5.22 (m, 0.5), 4.94 (m, 0.5), 3.34 (m, 2), 2.45 (t, J=8.3Hz, 2), 2.40 (m, 4), 1.85 (m, 2); IR ($CHCl_3$): 3400, 3290, 2940, 1720, 1675, 1460, 1210, 1050, 870 cm^{-1}; EI-MS (70eV): 210 (M^++1, 6.23), 209 (M^+, 17.4), 192 (34.3), 191 (65.0), 142 (4.40), 128 (8.37), 115 (13.7), 108 (base), 81 (60.9), 68 (55.4).

N-(3-(3-Furyl)-propyl)-6-hydroxy-2-piperidinone (45).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (5.17g, 136mmol) was added to imide 44 (3.0g, 13.57mmol) in MeOH (136mL) at -4°C and stirred for 1.25h to yield 3.02g, 99%, of the crude carbinol amide 45 as a viscous pale yellow liquid.
^{1}H-NMR (250MHz): δ = 7.34 (m, 1), 7.24 (m, 1), 6.28 (m, 1), 6.00 (m, 1), 5.14 (m, 1), 3.5 (t, J=8.3Hz, 2), 2.46 (m, 4), 2.28 (m, 2), 1.84 (m, 4); IR (neat): 3310, 2960, 1720, 1670, 1500, 1350, 1260, 1165, 1125, 870, 780 cm^{-1}; EI-MS (70eV):

206 (M^++1-H_2O, 19.4), 205 (M^+-H_2O, base), 177 (5.76), 149 (5.58), 135 (21.5), 108 (68.4), 98 (31.4), 82 (48.9), 68 (33.3).

General Procedure for the Cyclization of Carbinol Amides (21, 24, 35, 38, 42, 45).

Preparation of 1-Aza-4,5-(2,3b-furyl)bicyclo[4.3.0]nonan-9-one (21).

To a vigorously stirred solution of the carbinol amide 21 (0.207g, 1.06mmol) in cyclohexane (17mL) at 25°C was rapidly added anhydrous HCO_2H (4.25mL). The two-phase mixture was stirred for 3 min. then immediately cast into CH_2Cl_2 (50mL) and H_2O (75mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with brine (150mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield 220mg of crude cyclized material 22. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40g, 30mm o.d., ethyl acetate-petroleum ether 4:1, 30mL fractions) using the flash technique. Fractions 8-13 yielded 0.139mg, 74%, of 22 as a viscous water-white liquid. ^{1}H-NMR (250MHz): δ = 7.27 (m, 1), 6.20 (m, 1), 4.98 (m, 2), 4.42 (m, 1), 2.78 (m, 2), 2.33 (m, 2), 1.94-1.62 (m, 2); IR ($CHCl_3$): 3000, 2860, 1675, 1420, 1310, 1220, 1110, 900 cm^{-1}; EI-MS (70eV): 178 (M^++1, 20.8), 177 (M^+, base), 176 (66.2), 148 (11.1), 134 (10.5), 120 (45.5), 107 (9.88), 91 (27.0), 65 (25.0).

Cyclization of Carbinol Amide (24).

According to the general procedure for the cyclization of carbinol amides, a two-phase mixture of HCO_2H (6.0mL), carbinol amide 24 (326mg, 1.56mmol), and cyclohexane (25mL) was stirred vigorously at 25°C for 3 min. to yield 0.28g of a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 32g, 30mm o.d., ethyl acetate-petroleum ether 4:1, 20mL fractions) using the flash technique. Fractions 13-22 provided 0.211g, 71%, of 25 as a viscous water-white liquid. ^{1}H-NMR (250MHz, C_6D_6): δ = 7.02 (bs, 1), 5.84 (m, 1), 5.12 (dd, J=12.5,5.0Hz, 1), 3.78 (m, 2), 2.55 (m, 2); IR ($CHCl_3$): 3000, 2945, 1625, 1465, 1440, 1415, 1350, 1330, 1310, 1220, 1160, 1140, 1115 cm^{-1}; EI-MS (70eV): 192 (M^++1, 14.6), 191 (M^+, base), 163 (11.8), 162 (20.5), 148 (7.75), 135 (41.9), 121 (54.5), 120 (57.7), 104 (26.1), 91 (30.3), 77 (29.3), 55 (73.1).

Cyclization of Carbinol Amide (35).

According to the general procedure for the cyclization of carbinol amides, a two-phase mixture of HCO_2H (1.0mL), carbinol amide 35 (50mg, 0.256mmol), and cyclohexane (4.0mL) was stirred vigorously at 25°C for 3 min. to yield a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 15g, 20mm o.d., ethyl acetate-petroleum ether 4:1, 10mL

fractions) using the flash technique. Fractions 10-22 provided 30mg, 66%, of **38** as a white crystalline solid. mp = 84-87°C.

^{1}H-NMR (250MHz): δ = 7.28 (m, 1), 6.21 (m, 1), 4.69 (m, 1), 4.35 (dd, J=19,5.8Hz, 2), 2.87 (m, 2), 2.70-2.35 (m,2), 1.89 (m, 2); IR ($CHCl_3$): 3000, 2860, 1680, 1420, 1310, 1220, 1110, 1040, 900 cm^{-1}; EI-MS (70eV): 177 (M^++1, 64.8), 176 (M^+, base), 149 (11.6), 148 (25.1), 134 (6.48), 120 (38.4), 107 (6.69), 91 (15.8), 65 (19.2), 39 (48.6).

Cyclization of Carbinol Amide (38).

According to the general procedure for the cyclization of carbinol amides, a two-phase mixture of HCO_2H (2.4mL), carbinol amide **38** (128mg, 0.612mmol), and cyclohexane (9.5mL) was stirred vigorously at 25°C for 2 min. to afford a viscous white-water liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30g, 30mm o.d., ethyl acetate-petroleum ether 4:1, 30mL fractions) using the flash technique. Fractions 9-15 provided 83mg, 71%, of **39** as a white crystalline solid. mp = 82-84°C.

^{1}H-NMR (250MHz): δ = 7.25 (m, 1), 6.21 (m, 1), 4.98 (m, 2), 4.50 (m, 1), 2.65 (m, 2), 2.39 (m, 2), 1.92-1.55 (m, 4); IR ($CHCl_3$): 2965, 2860, 1630, 1440, 1415, 1310, 1220, 1165, 1120, 1035 cm^{-1}; EI-MS (70eV): 192 (M^++1, 13.7), 191 (M^+, base), 190 (M^+-1, 85.1), 163 (16.4), 162 (26.1), 148 (8.78), 135 (29.3), 121 (45.0), 120 (54.0), 91 (19.5), 55 (48.5).

Cyclization of Carbinol Amide (42).

According to the general procedure for the cyclization of carbinol amides, a two-phase mixture of HCO_2H (3.1mL), carbinol amide 42 (1.66g, 7.94mmol), and cyclohexane (124mL) was stirred vigorously at 25°C for 3 min. to yield a tan solid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 50g, 40mm o.d., ethyl acetate-petroleum ether 4:1, 50mL fractions) using the flash technique. Fractions 7-14 provided 757mg, 50%, of 43 as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 7.20 (m, 1), 6.14 (m, 1), 4.75 (m, 1), 4.30 (m, 2), 2.88 (m, 2), 2.56 (m, 2), 2.00-1.71 (m, 4); IR (neat): 3420, 2940, 2860, 1660, 1460, 1405, 1330, 1280, 1210, 920 cm^{-1}; EI-MS (70eV): 192 (M^{+}+, 23.4), 191 (M^{+}, base), 190 (M^{+}-1, 98.3), 163 (35.8), 162 (37.6), 148 (12.5), 135 (33.5), 134 (46.4), 120 (28.5), 107 (39.8), 91 (34.0), 77 (38.9), 55 (44.8).

Cyclization of Carbinol Amide (45).

According to the general procedure for the cyclization of carbinol amides, a two-phase mixture of HCO_2H (3.6mL), carbinol amide 45 (2.09g, 9.0mmol), and cyclohexane (144mL) was stirred vigorously for 3 min. to yield 2.08g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 60g, 40mm o.d., ethyl acetate-petroleum ether 4:1, 50mL

fractions) using the flash technique. Fractions 6-17 provided 1.23g, 67%, of **46** as a white solid. mp = 72-74°C. ^{1}H-NMR (250MHz): δ = 7.23 (m, 1), 6.19 (m, 1), 4.62 (t, J=5.0Hz, 2), 4.56 (t, J=4.2Hz, 1), 2.72 (m, 2), 2.43 (m, 2), 2.09 (m, 2), 1.91 (m, 2), 1.78 (m, 2); IR ($CHCl_3$): 3380, 2940, 2870, 1620, 1460, 1410, 1330, 1280, 1210, 1130, 920, 880 cm^{-1}; EI-MS (70eV): 206 (M^++1, 14.6), 205 (M^+, 92.3), 206 (M^+-1, 18.7), 177 (18.9), 176 (12.8), 162 (16.7), 149 (22.1), 135 (base), 134 (31.6), 120 (22.5), 107 (18.9), 91 (21.1), 77 (22.8), 55 (33.8).

Clauson-Kaas Oxidation of **46**.

To a solution of **46** (39mg, 0.19mmol) and Na_2CO_3 (40mg, 0.38mmol) in anhydrous methanol (0.25mL), cooled in a dry-CCl_4 ice bath to -22°C, was added a cooled (-22°C) solution of bromine in methanol (0.20mL, 0.19mmol, 1.0M) over five min. The mixture was stirred at -22°C for 90 min. then cast into CH_2Cl_2 (15mL) and brine (15mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 15mL). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$, brine (15mL each), dried ($MgSO_4$) and concentrated *in vacuo* to provide 39mg, 77%, of the α,α'-dimethoxy-dihydro derivative as a mixture of diastereomers.

^{1}H-NMR (250MHz): δ = 5.76 (m, 0.5), 5.71 (m, 0.5), 5.66 (m, 0.5), 5.29 (m, 0.5), 4.63 (m, 0.5), 4.55 (m, 0.5), 3.73 (m, 0.5), 3.68 (m, 0.5), 3.49 (s, 1.5), 3.44 (s, 1.5), 3.15 (s, 1.5), 3.03 (s, 1.5), 2.66-1.60 (m, 12); IR (CCl_4): 3380,

2960, 2880, 1660, 1620, 1460, 1420, 1250, 1090, 1010, 800 cm^{-1}; EI-MS (70eV): 268 (10.0), 267 (5.41), 252 (3.06), 236 (18.5), 235 (48.0), 220 (3.78), 207 (18.53), 168 (12.4), 153 (14.3), 137 (17.5), 123 (22.6), 112 (43.0), 84 (35.0), 69 (34.3), 55 (base).

Preparation of N-(2-(5-Trimethylsilyl-2-furyl)ethyl)-2,6-piperidinedione (56, n=2).

According to the general procedure for the preparation of N-substituted imides, to glutarimide (781mg, 6.90mmol), triphenylphosphine (2.07g, 7.90mmol), and 2-(5-trimethylsilyl-2-furyl) ethanol 55 (1.27g, 6.9mmol) in THF (5.8mL) was added a solution of diethyl azodicarboxylate (1.38g, 7.9mmol) in THF (3.1mL) over 20 min. to yield 3.0g of a viscous orange liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 120g, 50mm o.d., ethyl acetate-petroleum ether 1:1, 50-75mL fractions) using the flash technique. Fractions 11-19 provided 1.67g, 87%, of 56 as a viscous yellow liquid. ^{1}H-NMR (250MHz): δ = 6.50 (d, J=4.2Hz, 1), 6.03 (d, J=4.2Hz, 1), 4.07 (t, J=8.3Hz, 2), 2.90 (t, J=8.3Hz, 2), 2.62 (t, J=6.3Hz, 4), 1.90 (m, 2), 0.24 (s, 9); IR (neat): 3320, 2970, 1730, 1675, 1360, 1255, 1135, 1040, 1015, 930, 850 cm^{-1}; EI-MS (70eV): 280 (M^++1, 0.94), 279 (M^+, 4.31), 264 (2.44), 197 (0.50), 176 (2.04), 166 (67.4), 151 (34.4), 141 (3.44), 114 (7.56), 98 (8.73), 74 (24.6), 59 (68.1).

Preparation of N-(2-(5-Trimethylsilyl-2-furyl)ethyl)-6-hydroxy-2-piperidineone (57, n=2).

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (1.08g, 28.4mmol) was added all at once to imide 56 (793mg, 2.84mmol) in MeOH (28mL) at -5°C and stirred for 1h to provide 785mg, 98%, of the crude carbinol amide 57 as a viscous pale yellow liquid which was used without further purification. ^{1}H-NMR (250MHz): δ = 6.50 (d, J=3.05Hz, 1), 6.02 (d, J=3.05Hz, 1), 4.66 (m, 1), 3.68 (m, 2), 2.95 (m, 2), 2.32 (m, 2), 2.07-1.54 (m, 5), 0.21 (s, 9); IR (neat): 3320, 2970, 1740, 1620, 1490, 1340, 1250, 1190, 1090, 990, 845, 760 cm^{-1}; EI-MS (70eV): 281 (M^+, 0.38), 263 (M^+-H_2O, 1.77), 248 (0.51), 220 (1.33), 205 (0.61), 176 (5.08), 166 (28.2), 151 (12.42), 130 (4.64), 104 (19.9), 84 (29.9), 59 (44.2).

Cyclization of Carbinol Amide 57 (n=2).

According to the general procedure for the cyclization of N-ω-furyl-carbinol amides, a two-phase mixture of HCO_2H (7.5mL), carbinol amide 57 (546mg, 1.94mmol) and cyclohexane (31mL) was stirred vigorously at 25°C for 3 min. to yield 458mg of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 32g, 30mm o.d., ethyl acetate-petroleum ether 5:1, 30-50mL fractions) using the flash technique. Fractions 9-16 provided 235mg, 63%, of desilylated cyclized material 25 as a viscous water-white liquid.

^{1}H-NMR (250MHz): δ = 7.31 (m, 1), 6.25 (m, 1), 5.12 (m, 2), 4.47 (m, 1), 2.84 (m, 2), 2.66-2.28 (m, 4), 1.96-1.50 (m, 2); IR ($CHCl_3$): 2945, 1620, 1465, 1440, 1350, 1220, 1160, 1145, 1115 cm^{-1}; EI-MS (70eV): 192 (M^++1, 9.89), 191 (M^+, 50.0), 174 (3.60), 162 (9.75), 148 (3.74), 135 (19.8), 120 (27.6), 110 (33.8), 98 (26.5), 77 (16.8), 55 (base).

Preparation of N-(2-(5-Methyl-2-furyl)-ethyl)-2,5-pyrrolidindione (60).

According to the general procedure for the preparation of N-substituted imides, to succinimide 17 (1.27g, 12.86mmol), triphenylphosphine (3.88g, 14.79mmol), and 2-(5-methyl-2-furyl) ethanol 58 (1.62g, 12.86mmol) in THF (10.8mL) was added a solution of diethyl azodicarboxylate (2.58g, 14.79mmol) in THF (5.7mL) over 20 min. to provide 4.38g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 130g, 50mm o.d., ethyl acetate-petroleum ether 30:70, 50-75mL fractions) using the flash technique. Fractions 15-22 yielded 1.46g, 55%, of 60 as a white solid. mp = 71-75°C.

^{1}H-NMR (250MHz): δ = 5.88 (m, 1), 5.78 (m, 1), t, J=7.5Hz, 2), 2.83 (t, J=7.5Hz, 2), 2.64 (s, 4), 2.20 (s, 3); IR (CCl_4): 3450, 3300, 2940, 2860, 1770, 1700, 1435, 1400, 1365, 1340, 1240, 1170, 1125, 820 cm^{-1}; EI-MS (70eV): 208 (M^++1, 0.53), 207 (M^+, 5.17), 176 (1.24), 164 (0.59), 149

(0.37), 138 (0.90), 108 (base), 95 (53.7), 59 (18.6), 55 (28.4).

Preparation of N-(2-(5-Methyl-2-furyl)-ethyl)-2,6-piperidindione (63).

According to the general procedure for the preparation of N-substituted imides, to glutarimide (4.52g, 40mmol), triphenylphosphine (12.06g, 46mmol), and 2-(5-methyl-2-furyl) ethanol 58 in THF (33.4mL) was added a solution of diethyl azodicarboxylate (8.01g, 46mmol) in THF (17.8mL) over 30 min. to afford 1.18g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 250g, 60mm o.d., ethyl acetate-petroleum ether 30:70, 100-125mL fractions) using the flash technique. Fractions 12-22 yielded 7.32g, 83%, of 63 as a white solid. mp = 64-67°C.

^{1}H-NMR (60MHz): δ = 5.92 (m, 2), 4.12 (t, J=8.0Hz, 2), 2.87 (t, J=8.0Hz, 2), 2.70 (t, J=6.0Hz, 4), 2.38 (s, 3), 2.02 (m, 2); IR (CCl_4): 3400, 3280, 2980, 1730, 1680, 1570, 1430, 1390, 1360, 1235, 1170, 1130, 1040, 1025 cm^{-1}; EI-MS (70eV): 221 (M^+, 2.14), 140 (6.36), 127 (12.8), 126 (19.4), 114 (33.6), 108 (base), 95 (75.8), 71 (13.2), 55 (15.2).

Reduction of Imide 60.

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (2.07g, 54.6mmol)

was added all at once to imide **60** (1.13g, 5.46mmol) in MeOH (55mL) at -4°C and stirred for 1h to provide 1.13g, 99%, of the carbinol amide **61** as a viscous pale yellow liquid which was used without further purification.

^{1}H-NMR (250MHz): δ = 5.89 (m, 1), 5.81 (m, 1), 4.98 (m, 1), 3.55 (m, 2), 3.63 (bs, 1), 2.82 (t, J=7.0Hz, 2), 2.50 (m, 1), 2.25 (m, 2), 1.85 (m, 1); IR (CCl_4): 3340, 2920, 1680, 1570, 1460, 1430, 1290, 1225, 1070, 1030, 980 cm^{-1}; EI-MS (70eV): 209 (M^+, 10.2), 191 (M^+, $-H_2O$, 12.6), 176 (10.8), 131 (7.82), 127 (12.4), 114 (8.98), 108 (base), 104 (25.0), 96 (22.5), 95 (21.1), 85 (10.2), 68 (19.6).

Reduction of Imide **63**.

According to the general procedure for the reduction of N-substituted imides, sodium borohydride (3.44g, 90.5mmol) was added all at once to imide **63** (2.0g, 9.05mmol) in MeOH (90mL) at -4°C and stirred for 45 min. to provide 1.98g, 98%, of the carbinol amide **64** as a viscous pale yellow liquid which was used without further purification.

^{1}H-NMR (250MHz): δ = 5.92 (m, 1), 5.85 (m, 1), 4.73 (bs, 1), 3.66 (m, 2), 3.37 (bs, 1), 2.89 (t, J=7.0Hz, 2), 2.36 (m, 2), 2.26 (s, 3), 2.13-1.6 (m, 4); IR (neat): 3280, 2940, 1720, 1615, 1560, 1480, 1330, 1215, 1075, 1015, 980, 850, 780 cm^{-1}; EI-MS (70eV): 223 (M^+, 4.56), 205 (M^+-H_2O, 1.58), 176 (0.47), 128 (2.97), 116 (2.01), 108 (base), 99 (4.14), 95 (12.1), 82 (7.66), 55 (7.56).

Cyclization of Carbinol Amide **64**.

According to the general procedure for the cyclization of carbinol amides, a two-phase mixture of HCO_2H (27.5mL), carbinol amide **64** (1.44g, 6.46mmol) and cyclohexane (110mL) was stirred vigorously at 25°C for 3 min. to yield 1.34g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 70g, 40mm o.d., ethyl acetate-methanol-triethylamine 20:1:0.5, 50mL fractions) using the flash technique. Fractions 9-14 provided 0.922g, 64%, of the dione **65** as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 4.98 (m, 1), 3.58 (m, 2), 2.89 (m, 3), 2.54 (m, 4), 2.24 (s, 3), 2.0-1.54 (m, 4); ^{13}C-NMR (250MHz): δ = 207.8, 206.3, 170.0, 58.8, 51.4, 41.1, 40.2, 39.0, 32.3, 30.0, 27.9, 18.8; IR (CCl_4): 3420, 2960, 2880, 1770, 1700, 1470, 1445, 1420, 1350, 1260, 1170, 975 cm^{-1}; EI-MS (70eV): 224 (M^++1, 2.32), 205 (6.05), 190 (0.83), 180 (18.8), 166 (base), 165 (38.6), 152 (3.88), 138 (4.64), 124 (4.19), 110 (48.2), 98 (32.1), 55 (34.4).

Cyclization of Carbinol Amide **61**.

According to the general procedure to the cyclization of carbinol amides, a two-phase mixture of HCO_2H (22mL), carbinol amide **61** (1.17g, 5.6mmol) and cyclohexane (90mL) was stirred at 25°C for 2 min. to yield 1.10g of a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 60g,

40mm o.d., ethyl acetate-methanol-triethylamine 20:1:0.5, 30-50mL fractions) using the flash technique. Fractions 8-15 provided 0.406g, 35%, of the dione **65** as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 4.37 (m, 1), 3.50 (m, 2), 2.85 (m, 3), 2.44 (m, 2), 2.26 (m, 2), 2.19 (s, 3), 1.72 (m, 2); IR ($CHCl_3$): 3000, 2910, 1720, 1690, 1490, 1450, 1370, 1320, 1270, 1230, 1175 cm^{-1}; EI-MS (70eV): 210 (M^++1, 1.59), 191 (1.84), 166 (21.3), 152 (base), 123 (17.0), 108 (30.9), 96 (71.9), 84 (55.9), 68 (34.0), 55 (83.8), 43 (90.7).

General Procedure for the Thermodynamically-Controlled Ketalization of Diones **62** and **65**.

Preparation of Mono-ketals **68** and **69** (n=2).

To a solution of the dione (**65**) (868mg, 3.80mmol) and ethylene glycol (0.32mL, 5.7mmol) in anhydrous benzene (32mL) was added a crystal of, TsOH, and this mixture was refluxed overnight using a Dean-Stark apparatus to remove water. The mixture was cooled to 25°C then filtered through a pad layered with $MgSO_4$, K_2CO_3, and silica gel (230-400 mesh). The filtrate was concentrated *in vacuo* to afford 757mg, 75%, of a mixture of mono-ketals **68** and **69** as a viscous pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 80g, 40mm o.d., ethyl acetate-methanol-triethyl amine 20:1:0.5, 40mL fractions) using the flash technique. Fractions 7-12 provided 632mg, 62%, of an inseparable *ca.*

2:1 mixture of mono-ketals **68** and **69** as a viscous pale yellow liquid.

^{1}H-NMR (250MHz): δ = 4.76 dq, J=13.3,4.90,2.45Hz, 0.67), 4.40 (dt, J=13.3,4.90Hz, 0.33), 3.94 (m, 4), 3.78 (m, 1.34), 3.58 (m, 0.66), 3.28 (m, 0.67), 3.03 (m, 0.33), 2.82-2.18 (m, 6), 2.13 (s, 1.5), 1.88-1.30 (m, 4), 1.53 (s, 1.5); IR (CCl_4): 2960, 2900, 1720, 1640, 1445, 1350, 1260, 1160, 1120, 1055, 950 cm^{-1}; EI-MS (70eV): 268 (M^++1, 4.32), 267 (M^+, 5.56), 224 (6.60), 209 (84.4), 190 (5.56), 179 (29.8), 166 (14.7), 150 (36.3), 137 (33.6), 110 (20.4), 99 (base), 55 (61.5).

Ketalization of Dione **62** (n=1).

According to the general procedure for the thermodynamically controlled ketalization of diones, to dione **62** (215mg, 1.02mmol) and ethylene glycol (95mg, 1.53mmol) in anhydrous benzene (10mL) was added a crystal of $TsOH\cdot H_2O$, and the mixture was refluxed overnight to yield 182mg, 70%, of the crude mono-ketal **67** as a viscous pale yellow liquid without any contamination of the isomeric mono-ketal **66**.

^{1}H-NMR (250MHz): δ = 4.00 (m, 6), 3.42 (m, 1), 2.83 (m, 1), 2.42-1.70 (m, 6), 1.49 (m, 2), 1.34 (s, 3); IR (CCl_4): 2970, 2920, 2900, 1695, 1430, 1260, 1150, 1105, 1050, 950 cm^{-1}; EI-MS (70eV): 254 (M^++1, 2.47), 253 (M^+, 0.56), 210 (25.0), 195 (27.8), 182 (1.62), 165 (9.24), 151 (2.10), 111 (15.0), 99 (88.3), 87 (base).

General Procedure for the Reduction of Mono-ketals **67** and **68**.

Preparation of Alcohol **72**.

To a solution of the mono-ketal **67** (130mg, 0.512mmol) in anhydrous methanol (5.0mL), chilled in an ice-H_2O bath to 0°C, was added $NaBH_4$ (97mg, 2.56mmol) all at once. The mixture was stirred for 3h at 0°C then cast into CH_2Cl_2 (50mL) and saturated aqueous $NaHCO_3$ (50mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30mL). The combined organic layers were washed with brine (100mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield 106mg, 81%, of alcohol **72** as a viscous water-white liquid. ^{1}H-NMR (250MHz): δ = 3.96 (m, 7), 3.38 (m, 1), 2.79 (m, 1), 2.37-1.59 (m, 7), 1.44 (m, 2), 1.30 (s, 3); IR (CCl_4): 3360, 2980, 2900, 1680, 1460, 1270, 1140, 1105, 1050, 950 cm^{-1}; EI-MS (70eV): 255 (M^+, 1.52), 210 (6.08), 195 (8.85), 180 (1.53), 167 (35.0), 149 (base), 99 (21.1), 69 (38.0), 57 (44.8).

Reduction of Mono-ketal **68**.

According to the general procedure for the reduction of mono-ketals, to mono-ketal **58** in anhydrous methanol (2.5mL), chilled in an ice-H_2O bath to 0°C, was added $NaBH_4$ in one portion, and the mixture stirred for 3h to provide 65mg, 95%, of the corresponding epimeric alcohols as a 3:1 mixture.

^{1}H-NMR (250MHz): δ = 4.81 (m, 1), 4.07 (m, 6), 3.33 (m, 1), 3.00 (m, 1), 2.82-2.26 (m, 6), 1.84 (m, 2), 1.71-1.48 (m, 2), 1.21 (d, 6.3Hz, 3), 1.19 (d, 6.3Hz, 1); IR (CCl_4): 3360, 2940, 2865, 1630, 1460, 1270, 1180, 1100, 950 cm^{-1}; EI-MS (70eV): 270 (M^++1, 1.11), 269 (M^+, 4.94), 254 (1.38), 224 (4.30), 210 (4.91), 205 (6.88), 190 (1.28), 163 (10.1), 149 (6.49), 135 (6.81), 99 (78.7), 69 (28.4), 55 (base).

General Procedure for the Kinetically-Controlled Ketalization of Dione 65 (n=2).

Preparation of Mono-ketal 69.

To anhydrous CH_2Cl_2 (0.25mL) and TMSOTf (16mg, 0.0717mmol, 10mol%), cooled to -23°C in a dry ice-CCl_4 bath, was added dropwise Bis-1,2-trimethylsiloxyethane (177mg, 0.8604mmol) over 3 min. followed by the addition of a solution of the dione 65 (160mg, 0.717mmol) in CH_2Cl_2 (0.75mL) over 5 min. The mixture was allowed to slowly warm to 25°C, stirred for 24 h, quenched by the addition of dry pyridine (7 drops), and the mixture cast into CH_2Cl_2 (10mL) and saturated aqueous $NaHCO_3$ (15mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10mL). The combined CH_2Cl_2 layers were washed with 5% aqueous HCl (30mL), brine (50mL), dried (Na_2SO_4-Na_2CO_3 1:1) and concentrated *in vacuo* to 180mg of 69 as a viscous yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 40g, 30mm o.d., ethyl

acetate-methylene chloride-methanol 8:1:1, 20mL fractions) using the flash technique. Fractions 7-10 provided 147mg, 77%, of the mono-ketal **69** as a viscous pale yellow liquid. ^{1}H-NMR (250MHz): δ = 4.40 (dt, J=13.0,4.9Hz, 1), 3.92 (m, 4), 3.56 (m, 2), 3.02 (m, 1), 2.74 (m, 2), 2.48 (dd, J=13.0,8.3Hz, 2), 2.33 (t, J=6.3Hz, 2), 2.23-1.55 (m, 4), 1.52 (t, 3); IR (CCl_4): 2960, 2880, 1720, 1640, 1445, 1260, 1180, 1120, 960, 910 cm^{-1}; EI-MS (70eV): 268 (M^++1, 2.00), 267 (M^+, 16.3), 224 (4.33), 209 (5.45), 191 (8.99), 180 (7.87), 166 (21.1), 147 (52.7), 108 (59.5), 99 (84.1), 55 (base).

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