1991

Approaches to indole alkaloids

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Order Number 9126180

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Approaches to indole alkaloids

by

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A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1991

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DEDICATION

This dissertation is dedicated to my late grandparents, Joseph and Rose Bougie and Ruben and Henriette Van Vonderen. These are the people who, through direct contact and through my parents, have instilled the values of education and hard work into me.

I would also like to dedicate this dissertation to the late Caitlin Rose Bougie, the newest member of our Bougie clan.

GENERAL INTRODUCTION

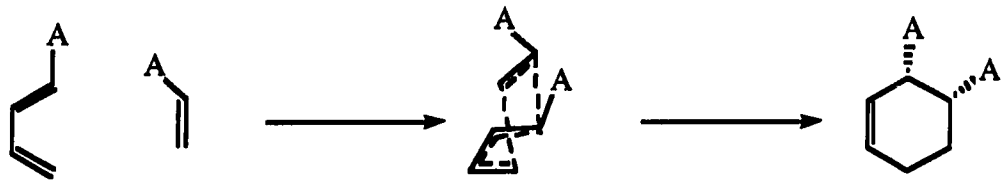
The intramolecular Diels-Alder reaction has been known to organic chemists for decades. However, utilization of this reaction for the synthesis of indole containing natural products has been limited. We have studied the application of the intramolecular Diels-Alder reaction on indole derivatives to determine the requirements for the tether and have applied our new found knowledge towards the synthesis of strychnine.

This dissertation is divided into two parts. The first part will deal with the intramolecular Diels-Alder reaction utilizing the indole nucleus. The second part will address our efforts toward the synthesis of strychnine.

PART I: THE INTRAMOLECULAR DIELS-ALDER REACTION AND THE INDOLE NUCLEUS

HISTORICAL

Since its discovery, the Diels-Alder reaction has been studied extensively and has become synthetically very useful. Its synthetic utility has been proven in the synthesis of numerous natural and biologically active compounds. This reaction is useful because it has the capability of setting up to four stereogenic centers with predictable results. Its concerted mechanism yields this predictability through the endo transition state and secondary orbital interactions. An illustration of this reaction is depicted below. A diene and a dienophile come together with the activating groups near each other. The two components align such that the π orbitals can interact. The stereochemical and regiochemical outcome is as depicted.

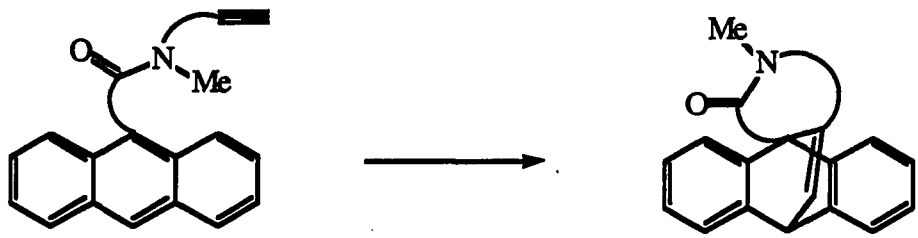


A Diels-Alder reaction consists of two components, a 4π and a 2π system. Hence it is also known as a [4 + 2] cyclization. The 4π system is an electron-rich diene whereas the 2π system is an electron-deficient dienophile. These requirements are necessary to obtain the proper interactions between the HOMO (highest occupied molecular orbital) of the diene and the LUMO (lowest unoccupied molecular orbital) of the dienophile.[1] The intramolecular version simply connects both components together, but subtle aspects can affect the course of the reaction.

Utilization of the intramolecular Diels-Alder reaction can be very advantageous from a synthetic point of view. This version of the [4 + 2] cyclization assembles two new rings

simultaneously and produces a product with functional groups for further manipulation. The intramolecular Diels-Alder reaction has been exhaustively reviewed within the last 15 years. [2a-f]

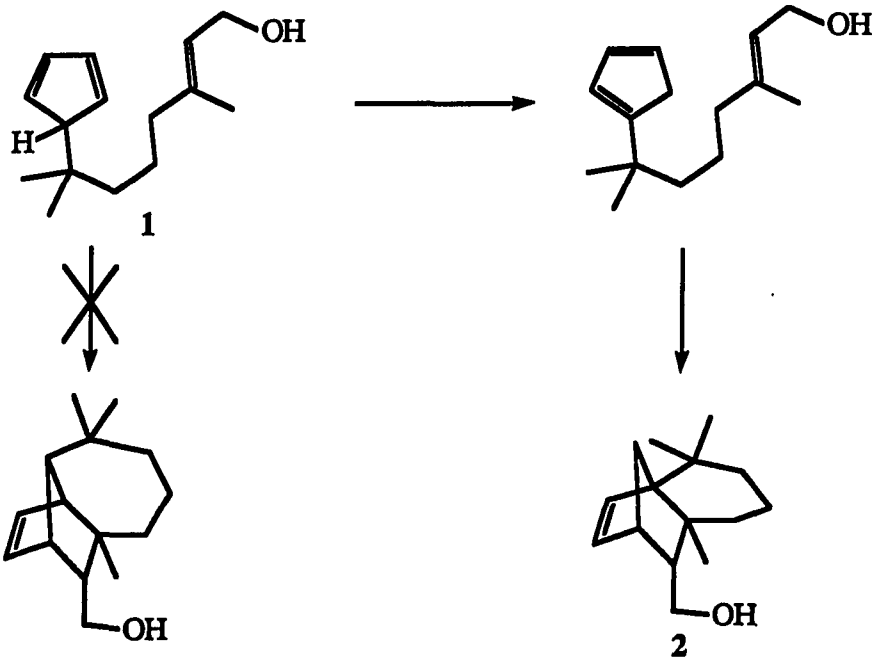
These reviews cover many aspects of the intramolecular Diels-Alder reaction. One very important aspect is the tether that joins the diene and the dienophile. It appears that if the tether is short, the two π systems cannot align properly for cyclization and longer chains start to require similar conditions as their bimolecular counterparts.[2b] Entropy considerations alone suggest that the rates should decrease in the order 3> 4> 5 membered chain lenghts.[2e] Thus, a series of 9-anthracenecarboxamides containing ethynyl dienophiles was studied with chain lengths of 3, 4 and 5 atoms.[3] These compounds



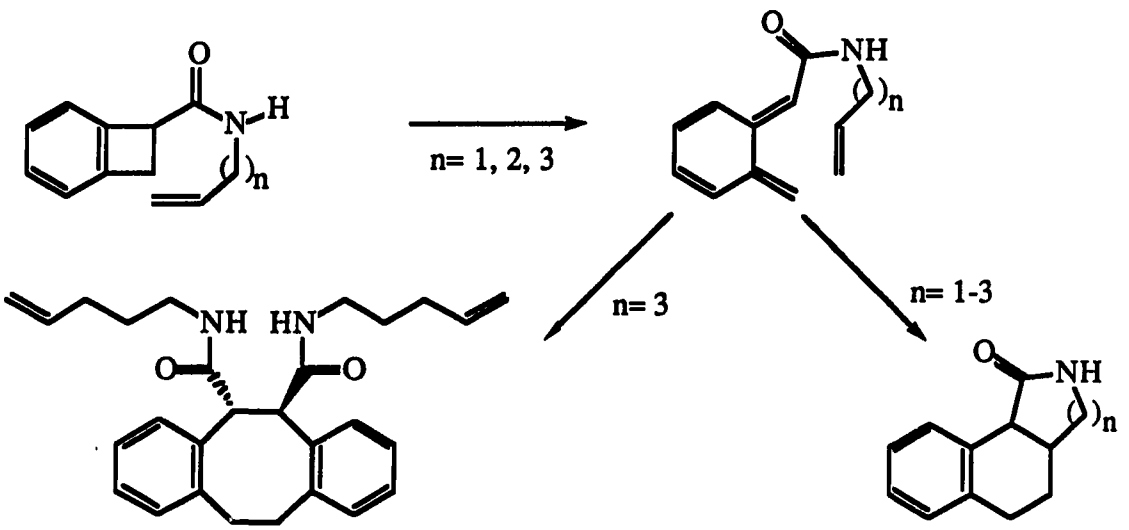
chain lenght of 3, 4 and 5 atoms

cyclized at 110°C, 140°C and 220°C, respectively. The temperature required for the last example is similar to that for the corresponding bimolecular reaction. The most common tether length is three or four atoms, yielding 6-5 and 6-6 ring systems, respectively.

Brieger reported the [4 + 2] cyclization of the cyclopentadiene derivative **1**.[4] The only product isolated was the norbornene **2** with no trace of the expected product.

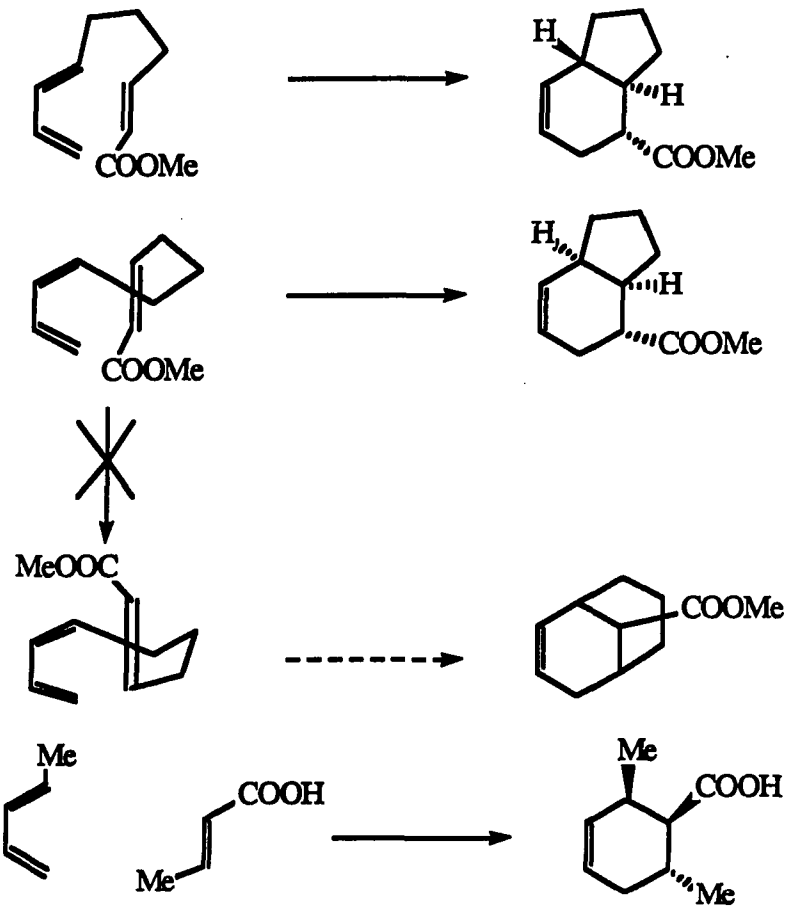


When substituted benzocyclobutenes[5] were heated, the o-quinodimethanes generated *in situ* possessed chain lengths of three (n= 1), four (n= 2) and five (n= 3) atoms. The intermediates with chain lengths of three and four underwent [4 + 2] cyclization in excellent



yields. The intermediate with a chain length of five underwent competing [4 + 2] and [4 + 4] cyclizations.

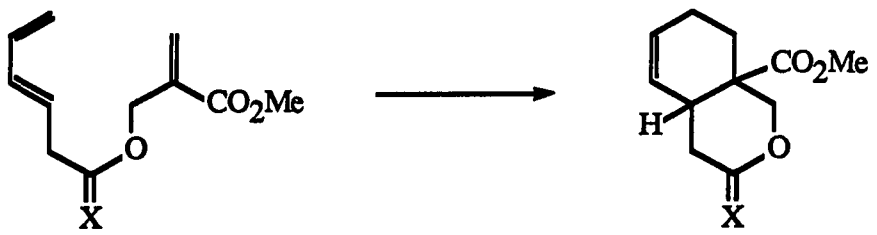
Another important aspect of the tether is the atoms that make up the tether. An all-carbon tether was utilized in the systematic investigation by House and Cronin[6] of the intramolecular Diels-Alder reaction of acrylic esters. In the case of the trans-diene unit, cyclization occurred to give the trans-annulated product. When the cis-diene was submitted



to the same conditions, the cis-annulated product was obtained. Interestingly, the reactions proceed in the opposite direction as the bimolecular counterpart as evidenced by

no formation of the bridged product. Molecular mechanics calculations[2e] indicate that even for tethers with as many as 6 atoms, the conformations leading to bridged products are much higher in energy that those for fused products. For all the chain lengths (3 to 6 atoms) studied, angle strain was the major reason for the difference in energy.

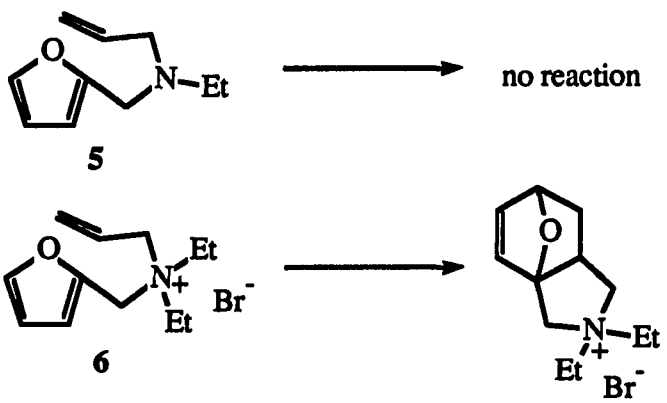
Heteroatoms also play a major role as part of a tether for the intramolecular Diels-Alder reaction. In a classic set of experiments, Boeckman and Demko[7] reported that while the



3. X= H_2
X= O

4. X= H_2

ether **3** (X= H, H) cyclized to form **4**, the corresponding ester (X= O) could not be induced to cyclize. Surprisingly, the amine **5** would not cyclize, whereas the ammonium salt **6** cyclized at 100°C[8].

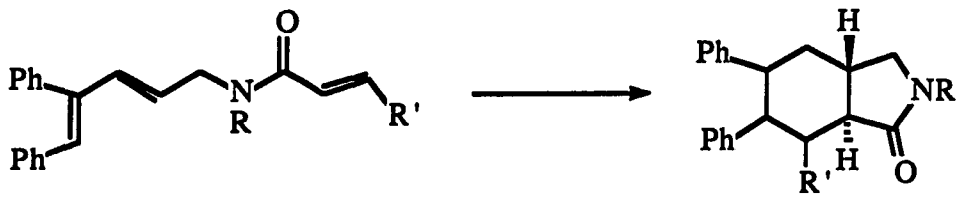


5

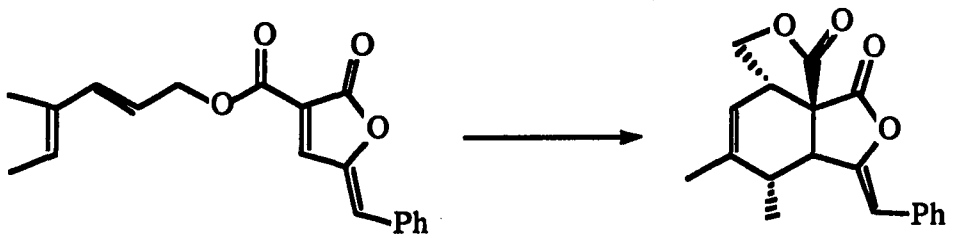
6

Amides have also been used as part of the tether.[9] Again the trans-fused products were formed selectively when the precursors were trans-dienes. It should be noted that as

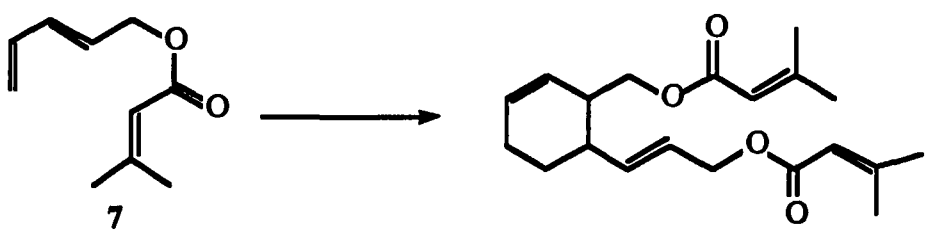
the size of the group attached to the nitrogen decreases, so does the rate of the reaction.[2b]



Unlike amides, esters as part of the tether are considered to hinder the reaction.[2e] This seems to be the rule, but there are a few exceptions. In these exceptions, the reactions employ strongly activated dienophiles as exemplified by Auerbach and Weinreb's[10] work.



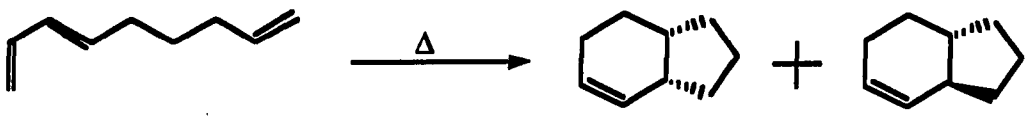
On the other hand, the ester **7** reacted in a bimolecular fashion rather than an



intramolecular fashion.[2e] This reduced reactivity may be attributed to the preference for the ester to exist in the transoid form and a relatively high energy barrier for interconversion of the two rotamers.[11]

In bimolecular Diels-Alder reactions, both the diene and the dienophile are activated in some way. Because the intramolecular Diels-Alder reaction holds these two components together, there are fewer degrees of rotational and translational freedom that the diene and

dienophile can obtain.[2a] Proximity alone can be a strong enough factor for cyclization to occur. Thermolysis of 1,3,8-nonatriene yielded [4 + 2] products.[12]

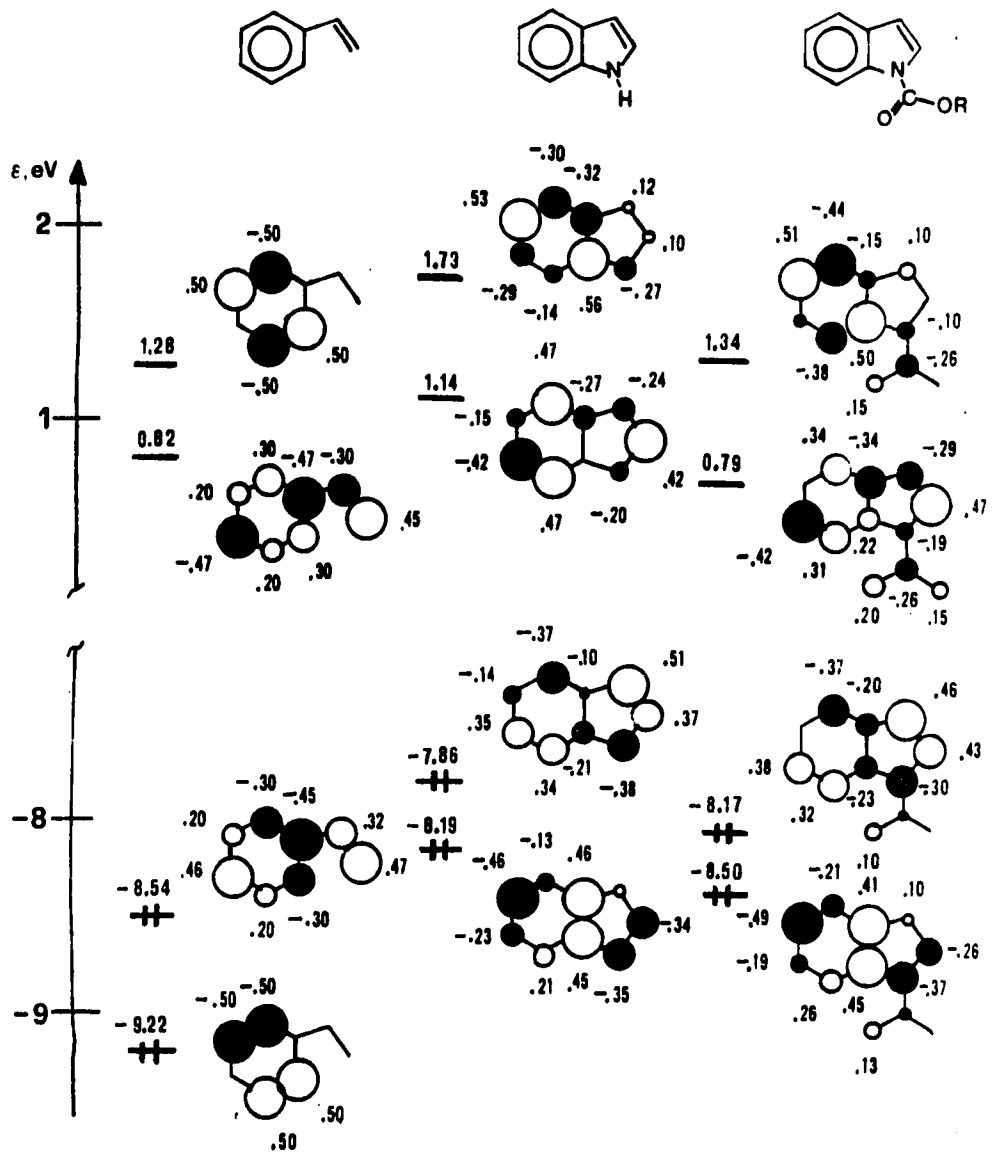


If unactivated olefins can undergo [4 + 2] cyclization in an intramolecular sense, could deactivated olefins participate by employing more stringent conditions? While the indole nucleus in unquestionably aromatic, the degree of aromaticity is uncertain. The C-2 - C-3 double bond of indoles (1.34Å) is shorter than a C - C bond in benzene (1.39Å), but longer than an isolated C - C double bond (1.33Å). Furans and pyrroles are also aromatic, but are considered to be less aromatic than benzene. There are many examples of furans and pyrroles acting as electron-rich dienes,[13] in inverse electron demand Diels-Alder reactions, and recently as a dienophile.[14]

It has been shown that the C-2 - C-3 double bond of the indole nucleus can react in 1,3-dipolar reactions as the dipolarophile.[15] However, examples of Diels-Alder cyclizations have been limited to very reactive dienes, dienophiles or inverse electron demand Diels-Alder reactions.

Frontier molecular orbital calculations[16] of indole and substituted indoles show a large coefficient at C-3, followed closely by the coefficients at C-2 and N-1. This helps to explain why the N-1 through C-3 is open to electrophilic attack, specifically at C-3. These calculations also show that an electron-withdrawing group at N-1 lowers the HOMO and LUMO energies, reduces the difference in coefficients magnitudes, as well as narrows the

gap between the energies. Caramella et al. calculated these energies and coefficients while

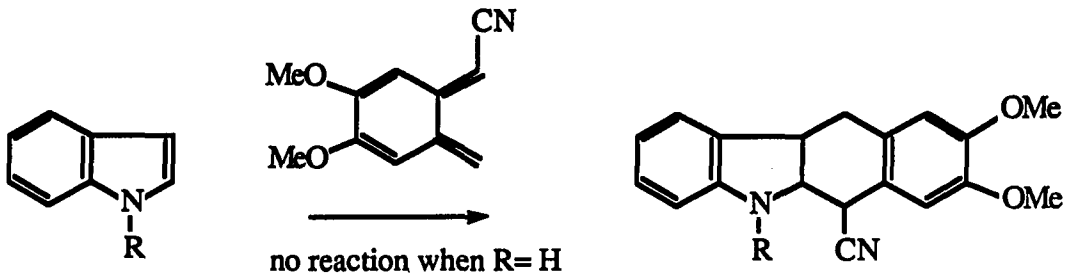


specifically looking at 1,3-dipolar additions to indole and substituted indoles. They came to the conclusion that the aromatic character of indoles manifests itself in reduced

1,3-dipolar reactivity and that the reaction does indeed proceed through $HOMO_{(indole)}$ $LUMO_{(dipole)}$ interactions.

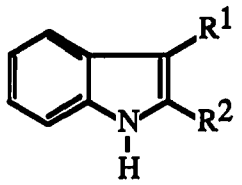
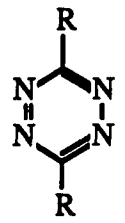
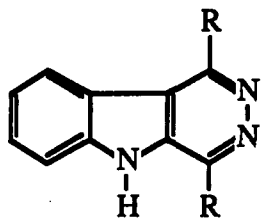
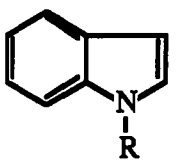
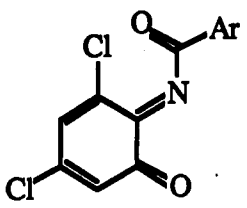
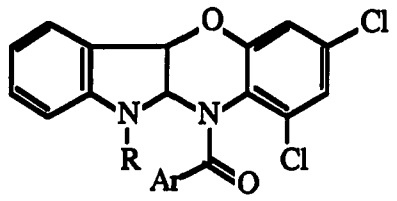
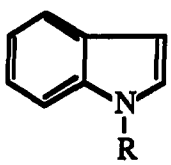
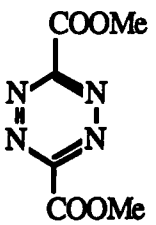
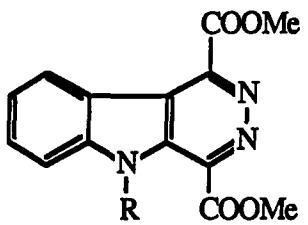
As early as 1950,[17] indole was recognized as a 2π system when it was discovered that ozone would add to and cleave the C-2 - C-3 bond of indole. Later it was found that indole would react with 2,4,6-trinitrophenyl azide[18] and other 1,3-dipolar components.[19]

Attempts at reaction of indole with a cyano-substituted ortho-xylylene[20] gave only xylylene dimer. However, the reaction of the cyano-substituted ortho-xylylene with indolyl magnesium bromide led to products that actually arose from an ionic process.



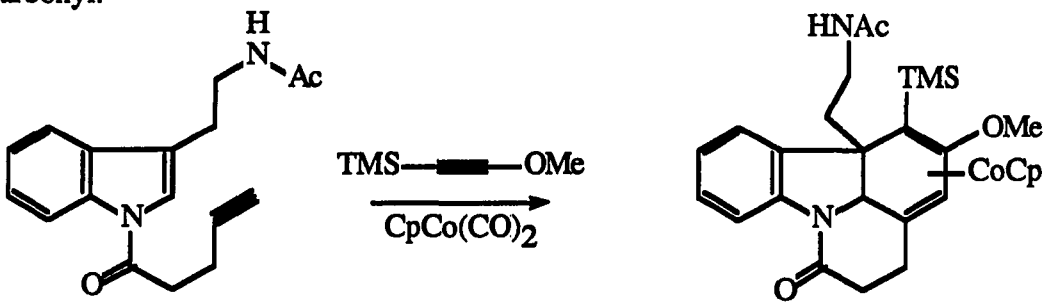
Diels-Alder products were later reported[21] with 2- or 3-methyl indoles acting as a 2π system under inverse electron demand conditions. A recent report[22] studied, in part, the effect of a substituent at N-1 on inverse demand [4 + 2] reactions. No direct Diels-Alder products were observed; only products after spontaneous aromatization were isolated. The authors determined that electron-withdrawing groups require higher temperatures, but gave higher yields of the aromatized products after cyclization and elimination of H_2 (see Table 1).

Table 1. Diels-Alder reaction under inverse electron demand conditions

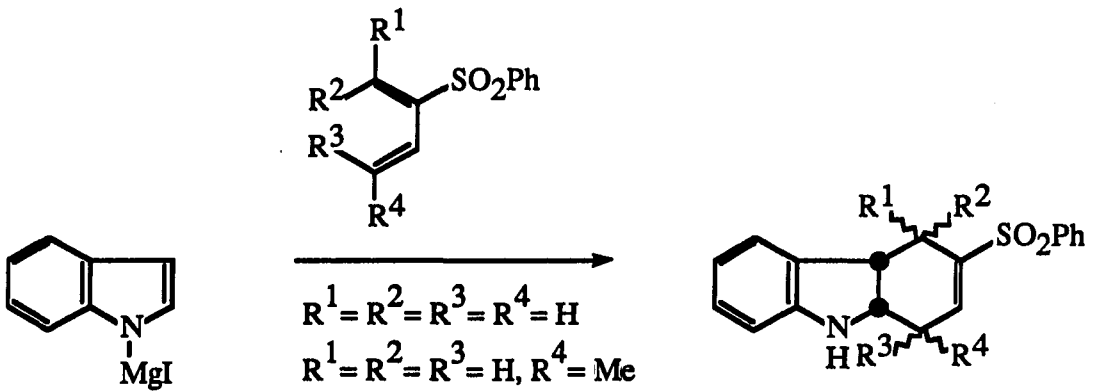
Dienophile	Diene	Product	Reference
 $R^1 = R^2 = H$ $R^1 = H, R^2 = Me$ $R^1 = Me, R^2 = H$	 R= 2-pyridyl or 4-pyridyl	 R= 2-pyridyl or 4-pyridyl	21a
 R= COMe, COPh, SO_2Ph		 R= COMe, COPh, SO_2Ph	21b
 R= H, Me, COMe, COPh		 R= H, Me, COMe, COPh	22

The C-2 - C-3 double bond was also reported to participate in [2 + 2 + 2] condensations with alkynes[23] mediated by cobalt. Thus, trimethylsilyl methoxy acetylene

cyclized with the acetylenic tryptamine derivative in the presence of cyclopentadienecobalt dicarbonyl.

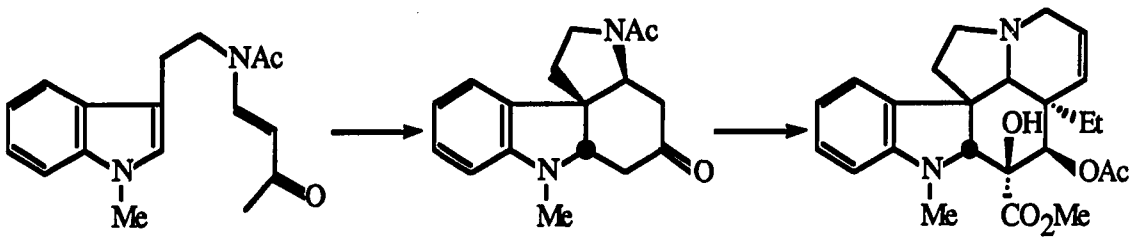


A step-wise mechanism was proposed by Bäckvall et al.[24] for the reaction of indolyl magnesium iodide with 2-phenylsulfonyl dienes. These dienes are unique because they possess one electron-deficient olefin and one electron-rich olefin. This dual nature proves to be useful in both normal and inverse demand Diels-Alder reactions. However, with the dienophile they had chosen, neither pathway was detected. Only an ionic pathway was

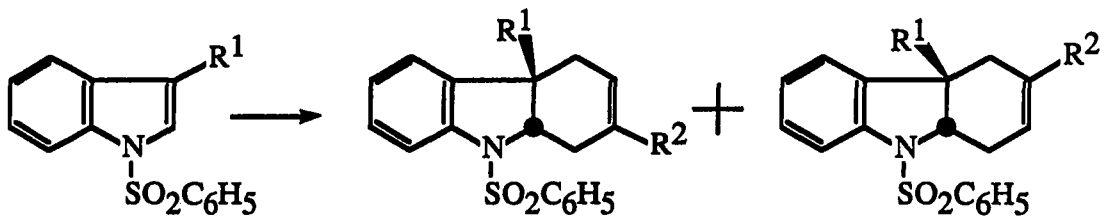


detected, as depicted by the example with $R^1 = R^4 = Me$, $R^2 = R^3 = H$, where loss of stereocontrol was experienced.

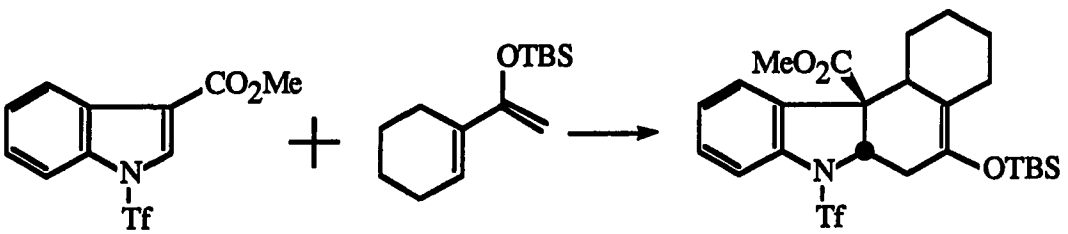
Büchi et al.[25] utilized an electrophilic attack on C-3 followed by a nucleophilic enol addition to C-2 to yield, by appearance, a Diels-Alder product for the synthesis of the aspidosperma alkaloid (±)-vindorosine.



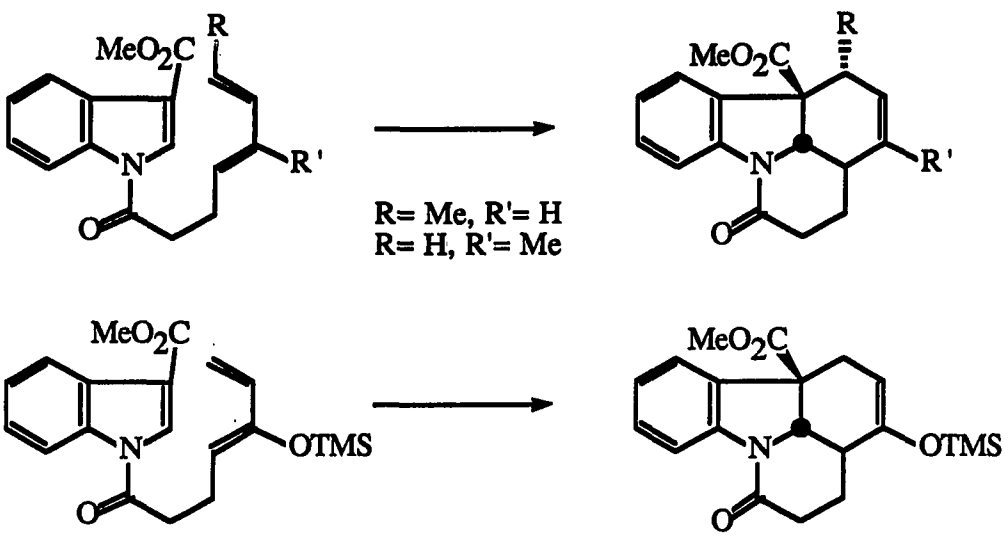
Only two groups have reported the use of the indole olefin as a dienophile under normal Diels-Alder conditions. Wenkert et al.[14] and Kraus et al.[26] simultaneously and independently published reports of this olefin participating in such a manner. Wenkert et al. reported intermolecular reaction with indoles possessing electron-withdrawing groups at



N-1 and C-3. Reaction of these indoles with either isoprene or butadiene under high temperatures and pressure gave cyclized products. Kraus et al. also found this to be the case for intermolecular reactions. This also appears to be the case for intramolecular

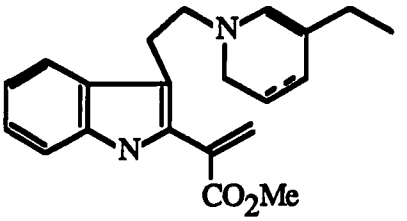


examples. However, the tethers in these examples serve a dual purpose. The tethers not only hold the diene and the dienophile together but also tie the N-1 positions up as an amide, a net electron-withdrawing group.



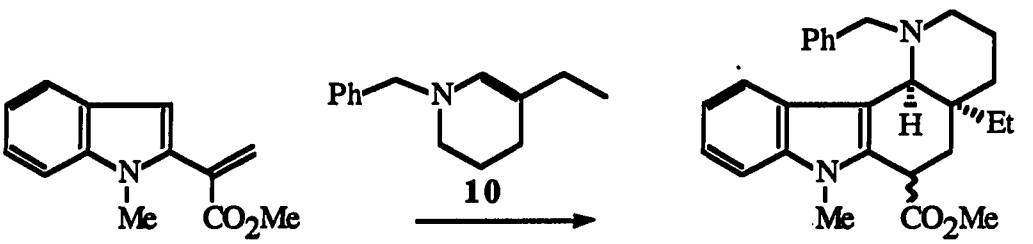
The 4π system is the other component of a Diels-Alder reaction. The C-2 - C-3 olefin of an indole could also be incorporated into this system. It has been shown through SCF-MO calculations of 3-vinyl indoles[27] that [4 + 2] cycloadditions with these dienes should proceed through $HOMO_{(diene)}$-$LUMO_{(dienophile)}$ interactions. These calculations also indicate that cycloadditions could also occur with $LUMO_{(diene)}$ control. It is also expected that 2-vinyl indoles should behave in a similar fashion.

Wenkert[28] postulated that the biosynthesis of the aspidosperma and ibogo alkaloids arose from tryptophan and loganin through a common intermediate such as the 2-vinyl indole **8**.



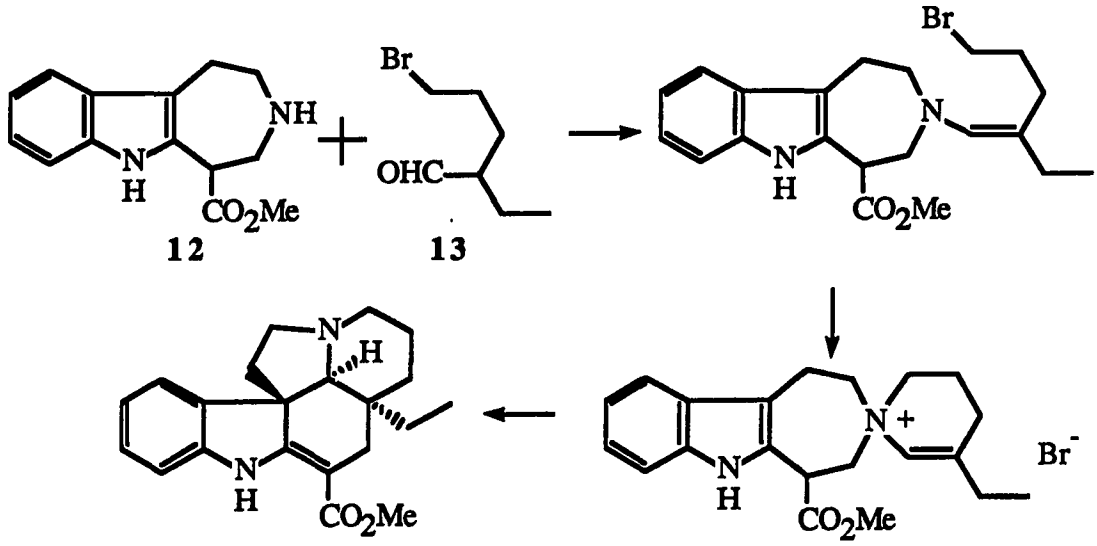
8

With this in mind, Zeigler and Spitzner[29] synthesized (±)-minovine. Thermolysis of the readily available 2-vinyl indole **9** and the enamine **10** gave, after regeneration of the indole nucleus, the tetracyclic amine **11**.



9 **11**

Kuehne et al.[30] adopted a similar method, but took Wenkert's proposal one step further. The tetrahydropyridine was the target of the authors' work. Combining **12** with the aldehyde **13** gave (±)-vincadifformine directly via this intermediate.



Other [4 + 2] reaction with 2-vinyl indoles have been sporadically reported which may be due to the instability of this system. Table 2 summarizes these reports. In almost every case the Diels-Alder reaction was also accompanied by rearrangement or aromatization.

Table 2. Diels-Alder reaction with 2-vinyl indoles

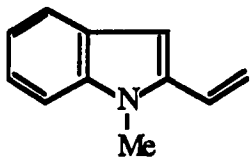
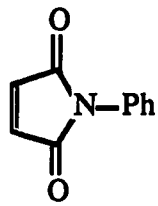
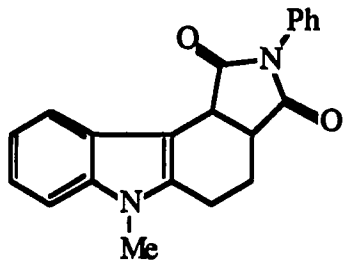
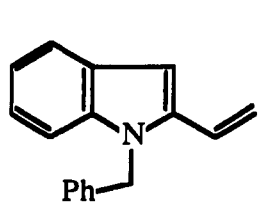
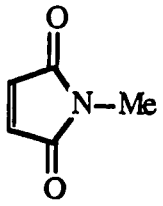
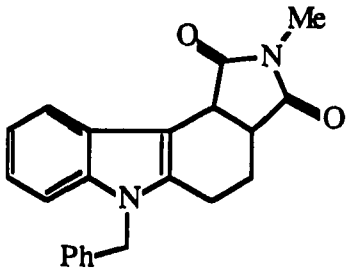
Diene	Dienophile	Product	Reference
			31a

Table 2 (cont.)







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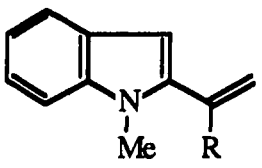
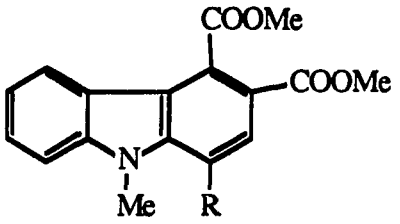


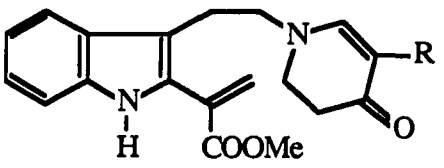
DMAD

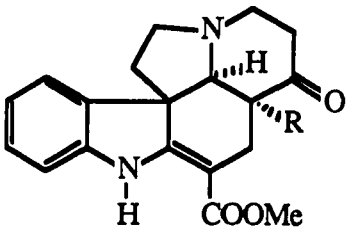


31c

R= H, Me, t-Bu, Ph

R= H, Me, *t*-Bu, Ph

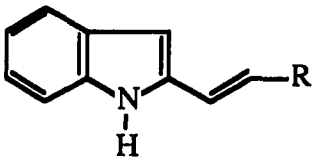




31d

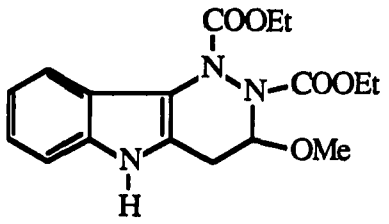
R= H, Et

R= H, Et



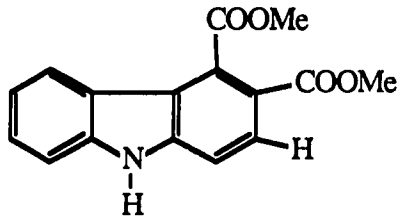
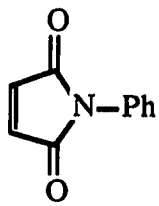
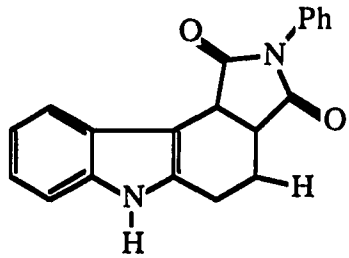
R= OMe

DEAD

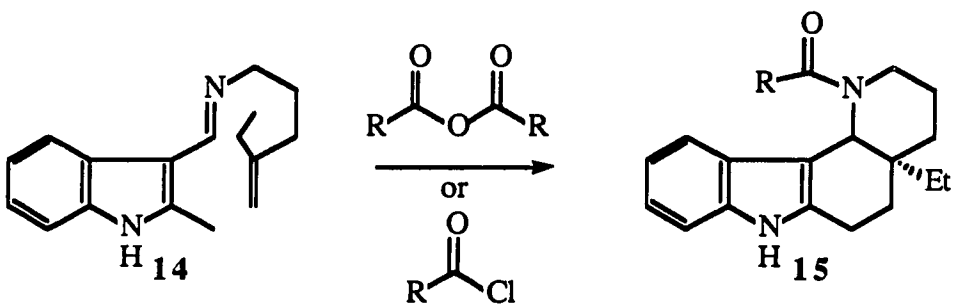


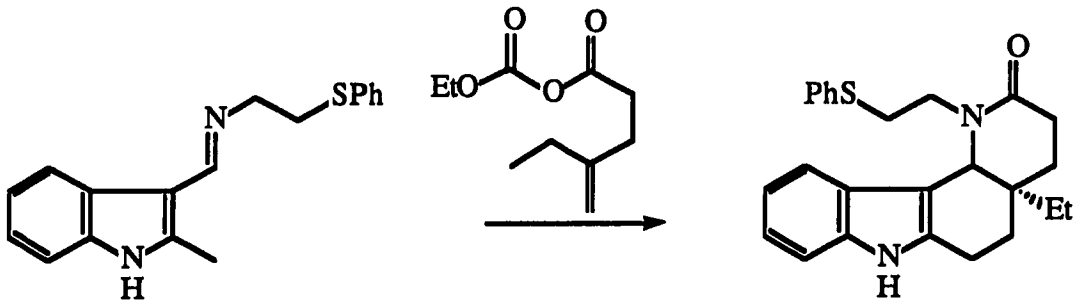
27

Table 2 (cont.)

R= H	DMAD		27
R= H			27

Interestingly, Magnus et al.[32] reported a strategy using an indole-2,3-quinodimethane as an intermediate toward the synthesis of the aspidosperma alkaloids. Treatment of the imine **14** with an electrophile (acetic anhydride or a chloroformate) yielded, via a quinodimethane, the tetracyclic material **15**.





The Diels-Alder reaction with respect to 3-vinyl indoles has been studied more extensively than the 2-vinyl indoles, probably due to the stability of the 3-vinyl indoles in contrast with their 2-vinyl counterparts. Lambert and Porter[33] reported the isolation of direct [4 + 2] products from the reaction of N-benzyl-3-vinyl indole with naphthoquinone, benzoquinone, maleic anhydride and N-phenyl maleimide. These products arose from the endo transition state (Table 3).

Table 3. Diels-Alder reaction with N-benzyl-3-vinyl indole

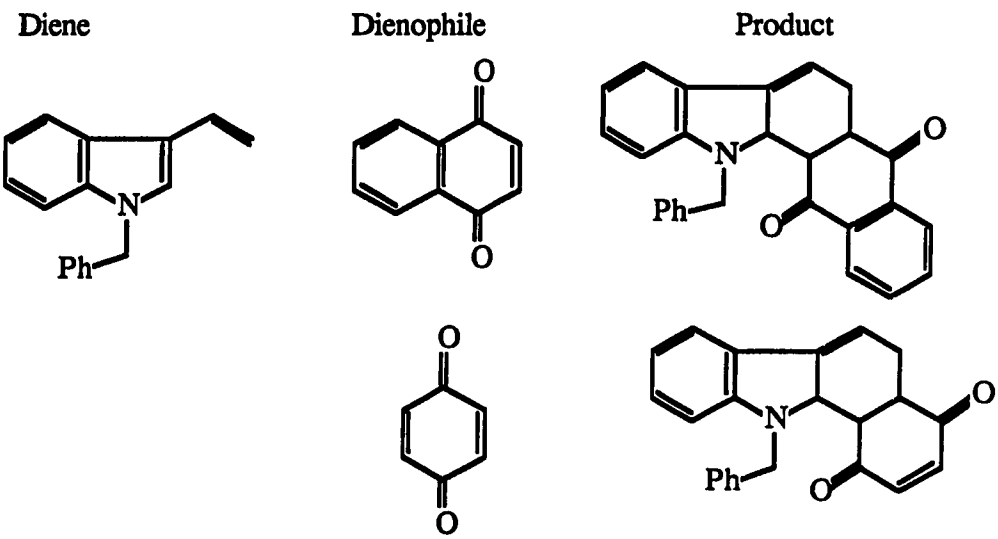
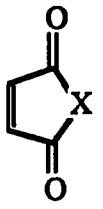
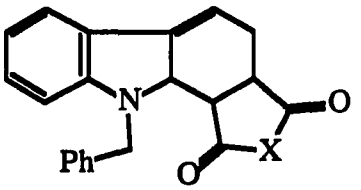


Table 3 (cont.)



X= O, NPh



X= O, NPh

With an electron-withdrawing group on the N-1 position of the indole moiety,[34] higher temperatures are required (i.e., refluxing xylene compared to room temperature). Under these conditions, a 1,3-H shift occurred to regenerate the indole nucleus, or in the case of DMAD, aromatization occurred. Other substituted 3-vinyl indoles[35] reacted with dienophiles to give similar results (Table 4).

Table 4. Diels-Alder reaction with substituted 3-vinyl indoles

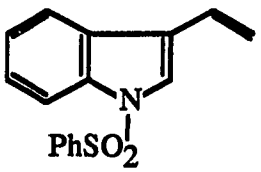
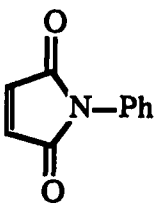
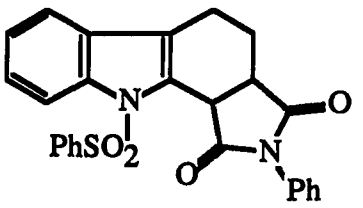
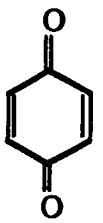
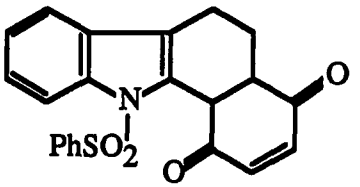
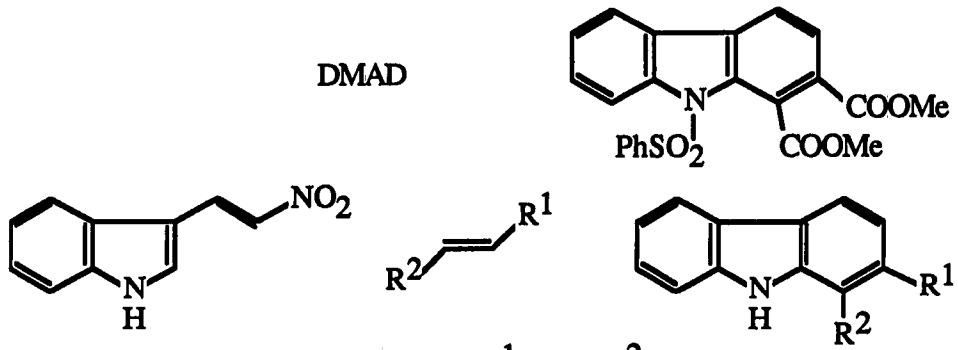
Diene	Dienophile	Product	Reference
			34
			34

Table 4 (cont.)

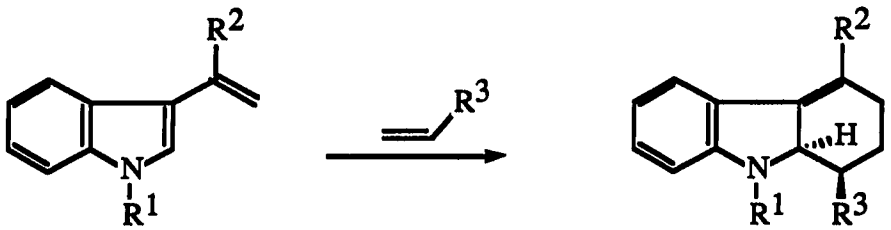


34

35

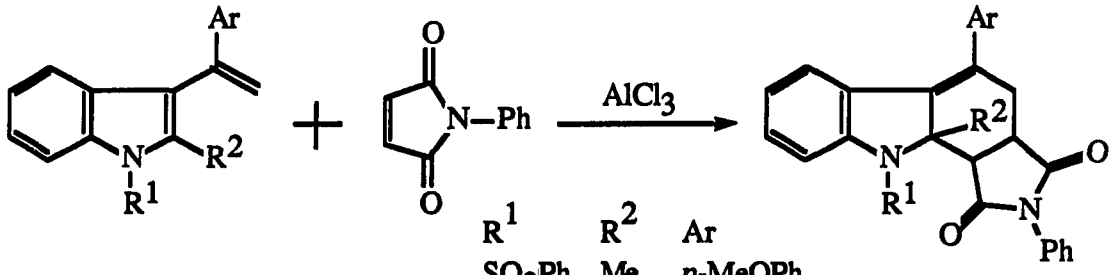
R^1= CN, R^2= H
R^1=COOEt, R^2= H
R^1= CHO, R^2= Ph

3-Indolylenimides and 3-indolylenamides[36] have been shown to undergo [4 + 2] cycloadditions on neat dienophiles with long reaction times.



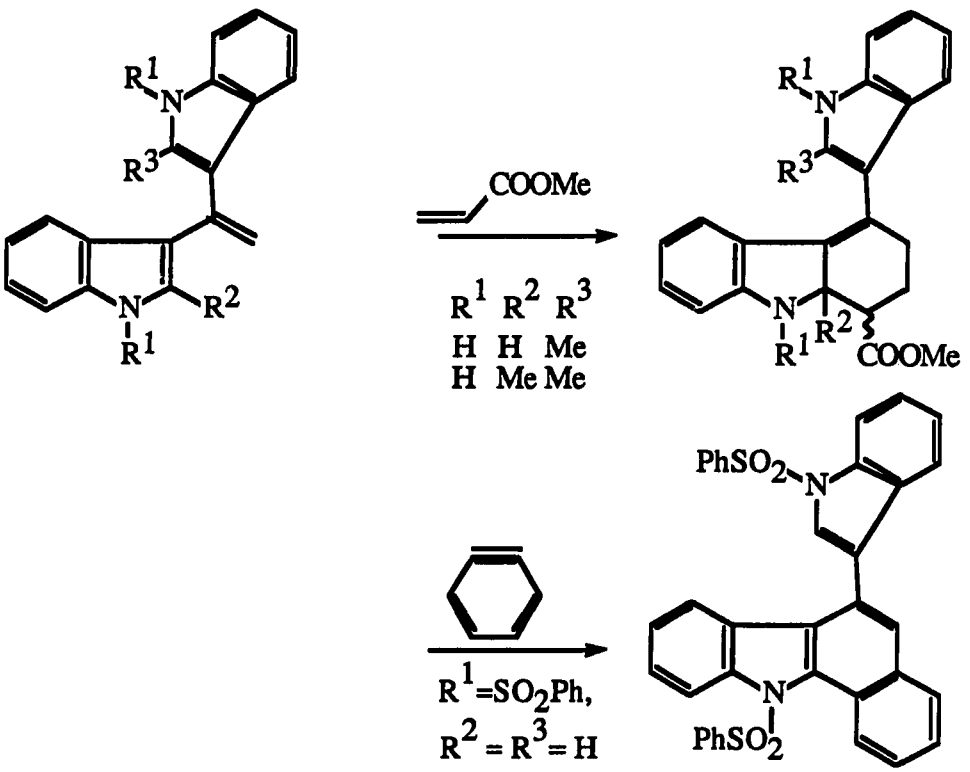
R^1= Ac, R^2= N(Ac)$_2$, R^3= COOMe
R^1= SO_2Ph, R^2= NHAc, R^3= CHO
R^1= SO_2Ph, R^2= NHAc, R^3= COOMe
R^1= SO_2Ph, R^2= NHAc, R^3= CN

Lewis acid catalyzed Diels-Alder reactions were also briefly studied.[37] However, yields were moderate to low.



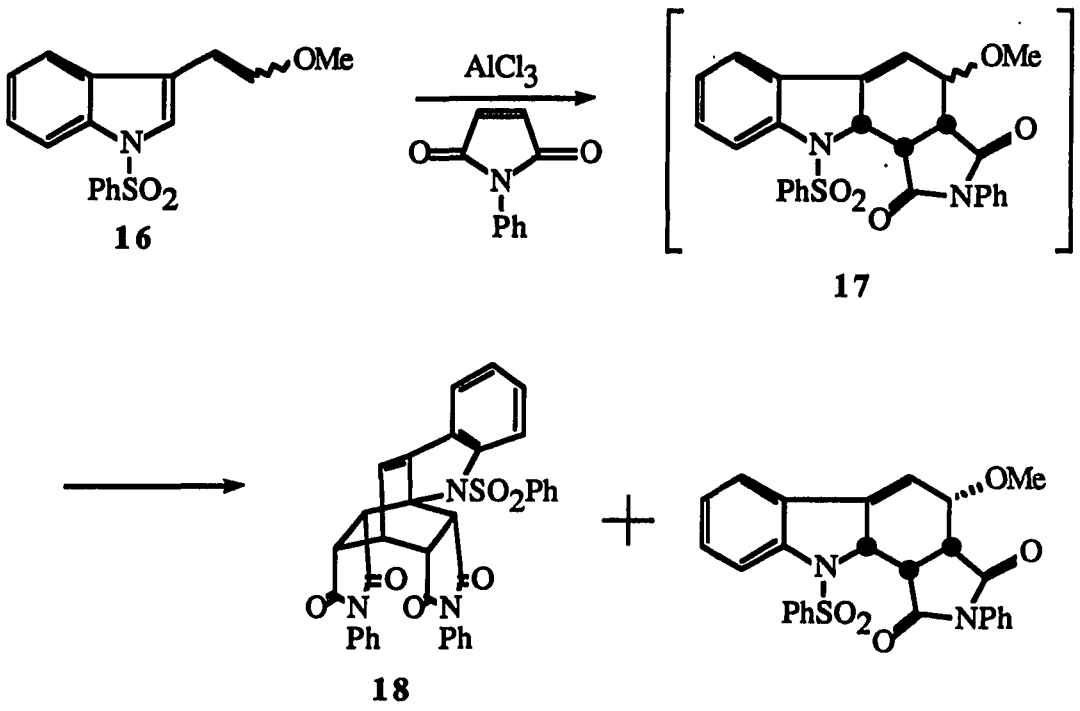
R^1	R^2	Ar
SO_2Ph	Me	*p*-MeOPh
SO_2Ph	H	Ph
Me	Me	Ph
SO_2Ph	Me	Ph
Me	H	Ph

Surprisingly, bisindolylethenes,[38] with one equivalent of dienophile, only undergo monocyclization. No bis-cyclized products were detected.



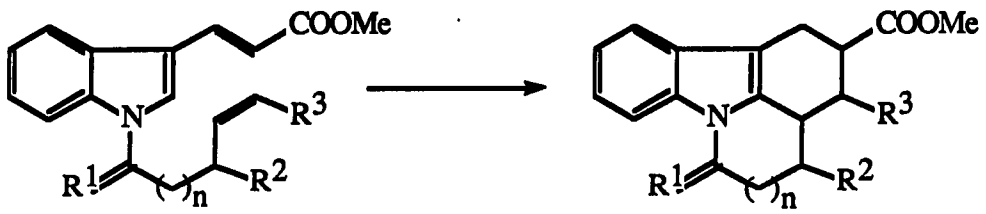
The only case of a double Diels-Alder reaction occurring was under Lewis acid conditions[39] with the enol ether **16** and N-phenyl maleimide as shown in Scheme 1. A [4 + 2] cyclization to yield the intermediate **17** which loses methanol and is followed by another [4 + 2] cyclization to give the product **18** and one of the diastereomers from the first Diels-Alder reaction.

Scheme 1.

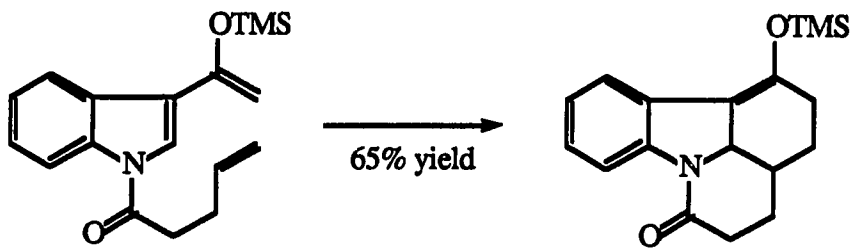


There have been only two laboratories to report the intramolecular Diels-Alder reaction with 3-vinyl indoles. In both reports, high temperatures were required for cyclization. In the work of Eberle et al.,[40] all of the cyclizations were accompanied by a 1,3-H shift to

regenerate the indole moiety. This was not the case with the chemistry described Kraus et al.[41] The product isolated was that of the [4 + 2] reaction without rearrangement.

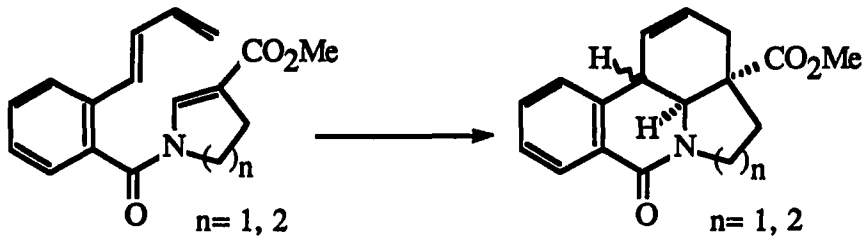


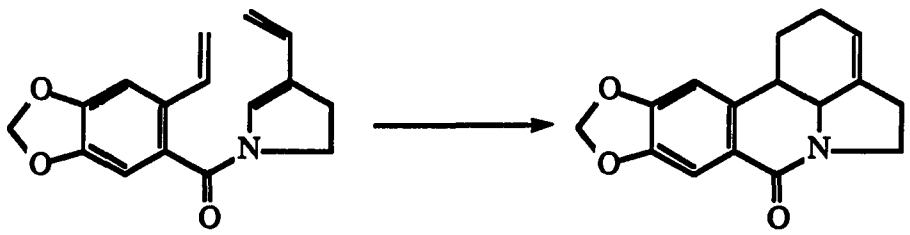
R^1	n	R^2	R^3	% yield
H_2	1	H	H	43
H_2	2	H	H	10
H_2	1	$-(CH_2)_2-$		46
H_2	1	$-(CH_2)_3-$		60
O	1	$-(CH_2)_3-$		13
O	1	H	H	30



Other interesting cases are acyclic ones. None of these cases contain an indole moiety, but all of them use an enamide in an intramolecular Diels-Alder reaction as either the 2π system or the 4π system. Morgans and Stork[9d,9e] reported two approaches to the galanthan ring system. The first approach was based on the enamide as the 2π component. When n=1, cyclization occurred in high yield to form a 1.2:1 mixture of α:β isomers. When n was increased to 2, cyclization gave a 1:2 mixture of α:β isomers in good yield.

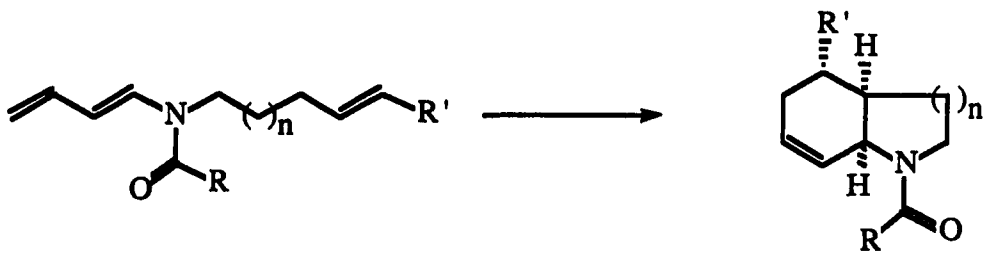
The other approach presented was based on the enamide as part of the 4π system. Hence, **19** was synthesized and underwent cyclization to yield **20.**

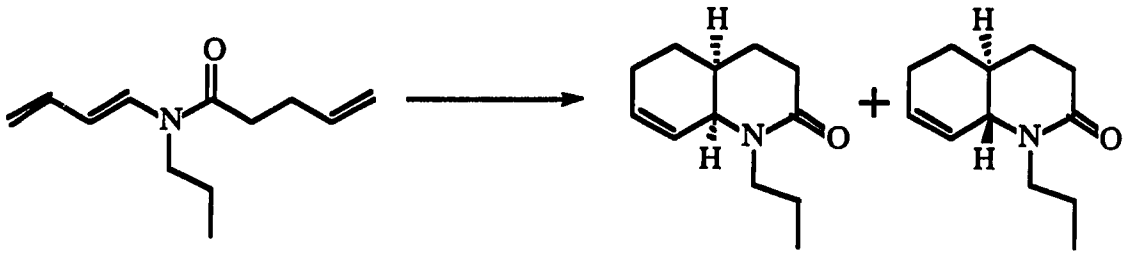




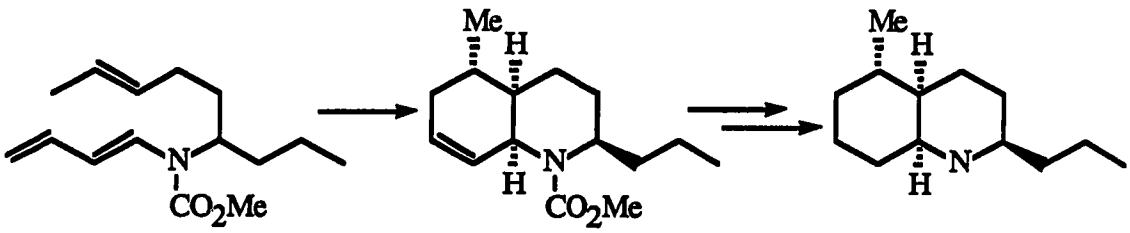
19 **20**

Two reports, stemming from the same laboratory,[9f,42] use as part of the 4π system an enamide in an approach to octahydroquinolines and in the synthesis of (±)-pumiliotoxin C. The amide as either part of the tether or removed from the tether cyclized to give the octahydroquinolines.





The second report described the synthesis of the cyclic product **21** from **22**. This cyclic product was converted into racemic pumiliotoxin C.

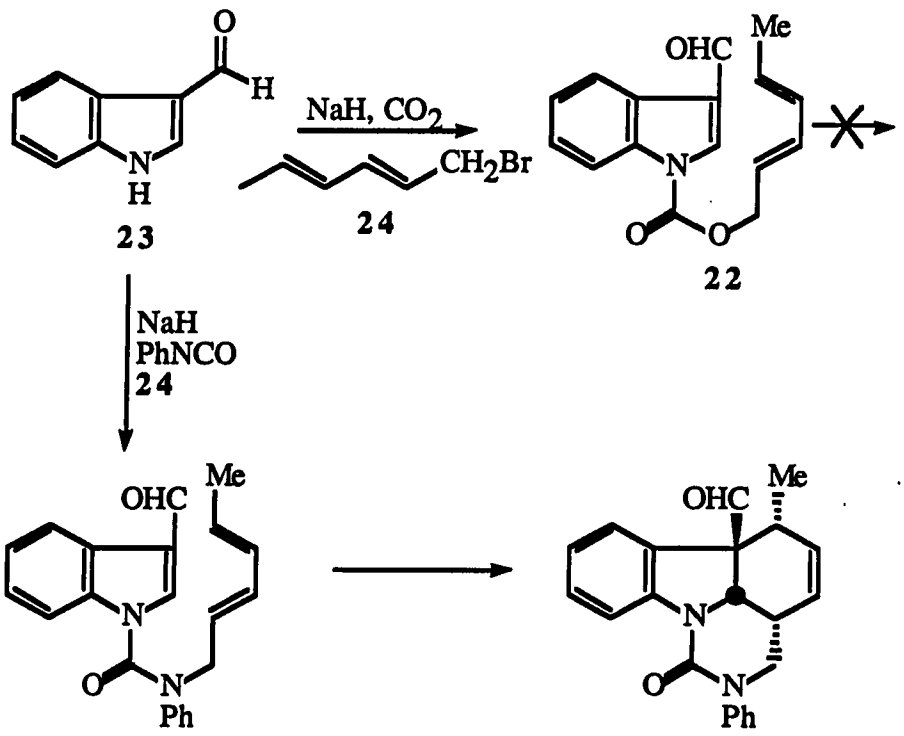


22 **21** pumiliotoxin-C

RESULTS AND DISCUSSION

In connection with the studies on intramolecular Diels-Alder reaction of indoles stemming from this laboratory, we required a tether that was sturdy enough to withstand thermolysis, oxidation, mild reduction and yet be amendable to cleavage later in the synthesis. It must also be a net electron-withdrawing group when attached to the N-1 position of the indole nucleus. The use of an amide as part of the tether was explored first with some promising results.[26,41] Carbamates and ureas were also perceived as desirable.

Carbamate **22** was initially studied. This carbamate was prepared by treating the sodium salt of indole-3-carboxaldehyde (**23**) with carbon dioxide gas followed by



1-bromo-2,4-hexadiene (**24**). Surprisingly, this carbamate failed to cyclize at temperatures as high as 290°C. Higher temperatures caused decomposition of the carbamate.

The urea **25** was synthesized by treating the sodium salt of **23** with phenyl isocyanate, followed by the bromide **24**. Thermolysis of this urea at 240°C gave a 93% yield of the tetracyclic compound **26** as a 6:1 mixture of exo:endo isomers. The major isomer was highly crystalline and the structure was determined to be exo by X-ray crystallography (Figure 1).

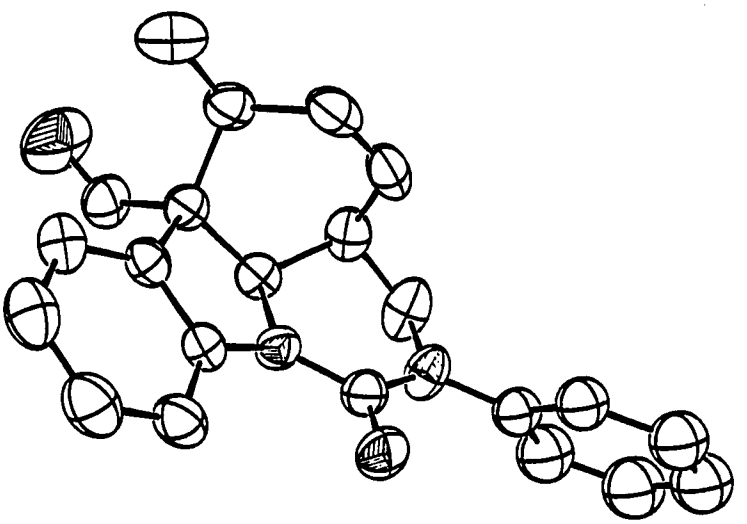
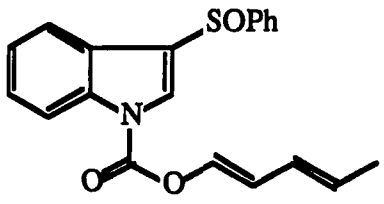


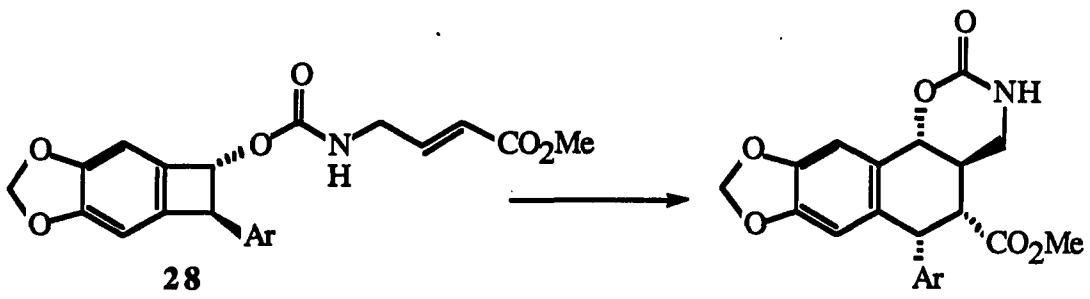
Figure 1. X-ray structure of compound **26**

As a means of determining whether the failure of the carbamate **22** to cyclize was a result of an unfavorable equilibrium, the carbamate sulfoxide **27** was synthesized in a similar manner. The indole-3-phenylsulfoxide was prepared from the corresponding sulfide with MCPBA. Submitting the sulfoxide **27** to thermolysis at 240°C also failed to produce a tetracyclic product; higher temperatures led to decomposition.



27

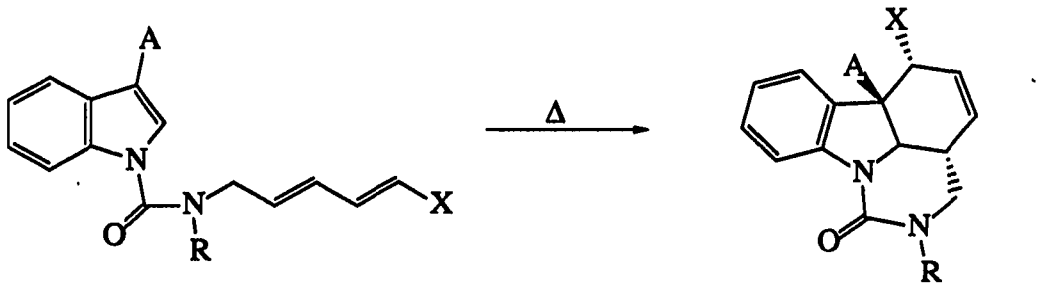
Boeckman and Demko[7] ascribed the failure of ester **4** to cyclize to the loss of ester resonance energy in the transition state. In order for the diene and the dienophile to align properly for cyclization, the ester must twist in such a way that the carbonyl π system and the lone pair orbitals of the adjacent oxygen atom are orthogonal. Alternatively, esters are believed to show a preference for the transoid form due to dipole repulsions and there may be a high barrier for the interconversion of the two rotamers.[11] While these are very plausible arguments for esters, it appears that they cannot be extended to carbamates. Macdonald and Durst [43] have demonstrated that carbamate **28** cyclized to **29** at 100°C via an *o*-quinodimethane intermediate.



28 **29**

Having no success with a carbamate as part of the tether, we next focused on the generality of the urea as the tether. These results are summarized in Table 5.

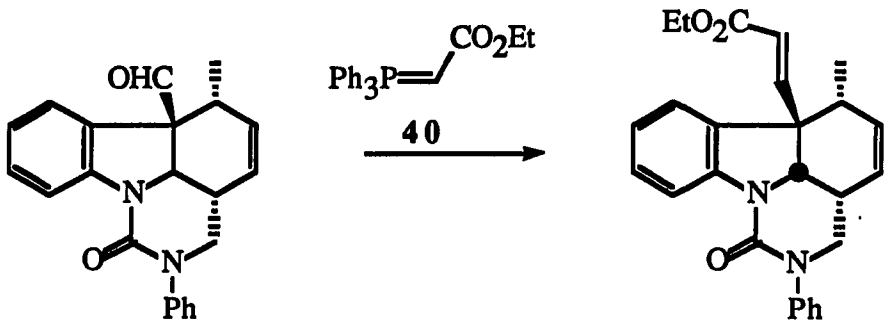
Table 5. Diels-Alder Reactions of Ureas



R	X	A	Compound Number	Temp(°C)	Time(h)	%Yield	Adduct Number
Ph	CH_3	CHO	**25**	240	12	93	**26**
Ph	CH_3	SOPh	**30**	240	6	68	**31**
Ph	CH_3	H	**32**	250	18	52	**33**
Ph	CH_3	$CHCHCO_2Et$	**34**	270	12	DEC	
Ph	CO_2Et	CHO	**35**	240	12	20 *	**36**
t-Bu	CH_3	CHO	**37**	240	12	NR	
2,6-diMeC_6H_5	CH_3	CHO	**38**	170	18	67	**39**

* Recrystalized from ethyl acetate

While an activating group on C-3 of the indole nucleus is not required, it clearly accelerates the reaction. Surprisingly, the indole with a propenoic ester moiety failed to cyclize. This may be due to unfavorable interactions in the transition state. However, this product of the cyclization was produced by a Wittig reaction on the corresponding aldehyde. Thus, aldehyde **26** reacted with the stabilized ylide **40** to give the α,β-unsaturated ester in quantitative yield.



26

As suggested earlier, the substitutent on the nitrogen of an amide can affect the course of an intramolecular Diels-Alder reaction.[2b] We, therefore, decided to test this phenomenon on the urea tether. The ureas **37** and **38** were made by employing *tert*-butyl isocyanate and 2,6-dimethylphenyl isocyanate, respectively. The *tert*-butyl urea failed to cyclize at 240°C and decomposed at higher temperatures. The 2,6-dimethylphenyl urea cyclized under much milder conditions (170°C vs 240°C) than other ureas. The use of a more functionalized diene was also successful as in the case when R was an ester, compound **35**.

Initial attempts to extend this methodology to acyclic and other heterocyclic aromatic compounds met with failure. However, even with these failures, the successful examples still warrant the urea as a useful tether for further examination.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. N,N-Dimethylformamide (DMF) was dried with calcium hydride, followed by vacuum distillation. Benzene was distilled from lithium aluminum hydride. Dichloromethane (CH_2Cl_2), 1,2-dichloroethane and acetonitrile were distilled from calcium hydride. Toluene was distilled from sodium. All reactions were conducted under a nitrogen atmosphere and all extracts were dried over anhydrous sodium sulfate. The apparatus for experiments requiring anhydrous conditions was flamed-dried under a stream of nitrogen or dried in a 150°C oven for 12h and cooled in a desiccator under nitrogen. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA) unless otherwise noted. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicolet NMC-1280 spectrometer and are reported in δ relative to $CDCl_3$ (77.06 ppm). High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low

resolution mass spectra were obtained on a Finnegan 4023 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was judged to be ≥ 90% by ^{1}H NMR spectral determinations and/ or elemental analysis.

General Procedure for the Reaction of Indoles, Isocyanates, and Dienes: To a suspension of hexanes-washed NaH (1.1 equivalent) in dry DMF (5 ml/ mmol of indole) at 0°C was added the requisite indole (1 equivalent, 1M in DMF). The reaction was stirred at 0°C for 15 min. The isocyanante (1.1 equivalent) was added and the reaction was stirred at 0°C for 15 min. The diene[44] (1.1 equivalent) was then added and the reaction was stirred for 2 additional h. The reaction was diluted with ether and washed with brine. The organic layer was dried and concentrated. The crude product was then chromatographed by silica gel flash chromatography. All reactions were run on 2-4 mmol scales.

N-(2,4-Hexadienyl)-N-phenyl-1-(3-formylindolyl)urea (25): tan oil, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, J=7 Hz, 3H), 4.54 (d, J=6 Hz, 2H), 5.63-5.82 (m, 2H), 5.94-6.28 (m, 2H), 7.00-7.10 (m, 2H), 7.13-7.42 (m, 6H), 7.97 (d, J=8 Hz, 1H), 8.19 (d, J=8 Hz, 1H), 9.70 (s, 1H); IR (CH_2Cl_2) 3030, 1687, 1662, 1387, 1375 cm^{-1}; MS m/e 81, 119, 145, 167, 180, 315, 344; HRMS m/e for $C_{22}H_{20}N_2O_2$ calcd 344.15248, measured 344.15285; R_f (3:2 H:EA) 0.42.

N-(2,4-Hexadienyl)-N-phenyl-1-(3-(phenylsulfinyl)indolyl)urea (30): tan oil, 62% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (d, J=7 Hz, 3H), 4.49 (d, J=6.5 Hz, 2H), 5.60-5.75 (m, 2H), 5.97-6.25 (m, 2H), 6.93-7.02 (m, 1H), 7.08-7.48 (m, 13H), 8.00 (d, J=8 Hz, 1H); IR ($CDCl_3$) 3005, 3020, 1700, 1685, 1592, 1490, 1445

cm^{-1}; MS m/e 81, 119, 193, 225, 241, 261, 315, 370, 424, 440; HRMS m/e for $C_{27}H_{24}N_2O_2S$ calcd 440.15586, measured 440.15527; R_f (3:2 H:EA) 0.25.

N-(2,4-Hexadienyl)-N-phenyl-1-indolylurea (32): tan oil, 79% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 (d, J=7 Hz, 3H), 4.51 (d, J=6 Hz, 2H), 5.58-5.86 (m, 2H), 6.24 (d, J=3 Hz, 1H), 6.77 (d, J=3 Hz, 1H), 6.98-7.06 (br d, J=8 Hz, 2H), 7.10-7.35 (m, 5H), 7.47 (d, J=8 Hz, 1H), 8.07 (d, J=8 Hz, 1H); IR (film) 3020, 1685, 1592, 1450, 1383, 985 cm^{-1}; MS m/e 81, 117, 182, 197, 292, 316; HRMS for $C_{21}H_{20}N_2O$ calcd 316.15757, measured 316.15727; R_f (3:1 H:EA) 0.42.

N-(2,4-Hexadienyl)-N-phenyl-1-(3-(3-ethoxy-3-oxo-1-propenyl)-indolyl)urea (34): tan oil, 76% yield; ^1H NMR ($CDCl_3$) δ 1.32 (t, J=7 Hz, 3H), 1.72 (d, J=7 Hz, 3H), 4.22 (q, J=7 Hz, 2H), 4.51 (d, J=4 Hz, 2H), 5.60-6.27 (m, 4H), 6.32 (d, J=15 Hz, 1H), 7.00-7.42 (m, 8H), 7.49 (d, J=15 Hz, 1H), 7.62 (d, J=8 Hz, 1H), 8.07 (d, J=8 Hz, 1H); IR ($CDCl_3$) 1695, 1680, 1520, 1295 cm^{-1}; R_f (3:1 H:EA) 0.48.

N-(6-Ethoxy-6-oxo-2,4-hexadienyl)-N-phenyl-1-(3-formylindolyl)-urea (35): oil, 76% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J=7 Hz, 3H), 4.19 (q, J=7 Hz, 2H), 4.63 (d, J=8 Hz, 1H), 8.18 (d, J=8 Hz, 1H), 9.70 (s, 1H); IR ($CDCl_3$) 1700, 1668, 1392, 1262, 1239 cm^{-1}; MS m/e 119, 167, 180, 194, 299, 373, 402; HRMS calcd 402.15796, measured 402.15766.

N-(2,4-Hexadienyl)-N-*tert*-butyl-1-(3-formylindolyl)urea (37): solid; mp 68-70°C; 64% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.76 (d, J=7 Hz, 3H), 4.78 (d, J=6 Hz, 2H), 5.64-6.26 (m, 4H), 7.30-7.42 (m, 3H), 7.73 (s, 1H),

8.29-8.33 (m, 1H), 10.00 (s, 1H); IR (CH_2Cl_2) 1650, 1645, 1520, 1373, 1155 cm^{-1}.

N-(2,4-Hexadienyl)-N-(2,6-dimethylphenyl)-1-(3-formylindolyl)urea (38): solid; mp 123°C; 35% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (d, J=7 Hz, 3H), 2.21 (s, 6H), 4.35 (d, J=7 Hz, 2H), 5.62-5.76 (m, 1H), 5.78-5.92 (m, 1H), 5.95-6.18 (m, 2H), 6.69-7.43 (m, 6H), 8.10 (d, J=8 Hz, 1H), 8.16 (d, J=8 Hz, 1H), 9.57 (s, 1H); IR ($CDCl_3$) 1685, 1667, 1392, 1232 cm^{-1}; MS m/e 81, 343, 372; R_f (3:2 H:EA) 0.40.

General Procedure for the Diels-Alder Reactions: A 0.1M solution of urea in dry degassed toluene was heated in a sealed glass tube at the temperature specified in Table 3 for the time specified in Table 3. The reaction was allowed to cool to ambient temperature and purified by silica gel flash chromatography using 1:1 to 5:1 H:EA. Isomers were separated by chromatography. Main isomer spectral data are given. All reactions were run on a 2-3 mmol scale.

(3aβ,6aβ,11aβ)-2,3,3a,6,6a,11a-Hexahydro-6a-formyl-6-methyl-2-phenyl- 1*H*-pyrimidino[3,2,1-jk]carbazol-1-one (26): solid, mp 171°C (from ethyl acetate); 93% yield; 6:1 exo:endo ratio; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J=7 Hz, 3H), 2.80-2.97 (m, 2H), 3.79 (dd, J=2.8, 12 Hz, 1H), 4.12 (dd, J=3.6, 12 Hz, 1H), 4.98 (d, J=4.4, 1H), 5.72-5.88 (m, 2H), 6.97-7.18 (m, 2H), 7.23-7.55 (m, 6H), 7.99 (d, J=8 Hz, 1H), 9.85 (s, 1H); IR ($CDCl_3$) 2715, 1722, 1650, 1480, 1430 cm^{-1}; MS m/e 81, 145, 193, 289, 315, 344; HRMS m/e for $C_{22}H_{20}N_2O_2$ calcd 344.15248, measured 344.15277; Analysis calcd: C, 76.72; H, 5.85; N, 8.13; found: C,76.63; H, 5.87; N, 8.16.

(3aβ)-2,3,3a,6-Tetrahydro-6-methyl-2-phenyl-1*H*-pyrimidino-

[3,2,1-jk]carbazol-1-one (31): tan oil; 68% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J=7 Hz, 3H), 3.56-3.76 (m, 1H), 3.80-4.08 (m, 3H), 5.75 (dt, J=10, 3 Hz, 1H), 5.98 (dt, J=10, 3 Hz, 1H), 7.48-7.53 (m, 7H), 7.62 (br d, J=8 Hz, 1H), 8.33 (br d, J=8 Hz, 1H); IR (film) 2970, 1685, 1467, 1406, 1318, 1292 cm^{-1}; MS m/e 106, 180, 193, 299, 314; HRMS m/e for $C_{21}H_{18}N_2O$ calcd 314.14192, measured 314.14176; R_f (3:2 H:EA) 0.59.

(3aβ,6aβ,11aβ)-2,3,3a,6,6a,11a-Hexahydro-6-methyl-2-phenyl-1-*H*-pyrimidino[3,2,1-jk]carbazol-1-one (33): tan oil; 52% yield; one isomer; ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.53 (d, J=7 Hz, 3H), 2.35-2.58 (m, 2H), 3.23-3.33 (m, 1H), 3.52-3.62 (m, 1H), 3.96-4.10 (m, 2H), 5.76 (dt, J=7, 3 Hz, 1H), 5.92 (dt, J=7, 3 Hz, 1H), 6.97 (t, J=8 Hz, 1H), 7.14-7.55 (m, 7H), 7.94 (d, J=8 Hz, 1H); IR (film) 3030, 2920, 1650, 1590, 1475, 1280 cm^{-1}; MS m/e 81, 117, 182, 162, 316; HRMS m/e for $C_{21}H_{20}N_2O$ calcd 316.15757, measured 316.15785; R_f (4:1 H:EA) 0.37.

(3aβ,6aβ,11aβ)-2,3,3a,6,6a,11a-Hexahydro-6a-formyl-6-(ethoxy-carbonyl)-2-phenyl-1*H*-pyrimidino[3,2,1-jk]carbazol-1-one (36): solid; mp 157-158°C (from ethyl acetate); one isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, J=7 Hz, 3H), 2.84-3.92 (m, 1H), 3.85 (dd, J=3.2, 12 Hz, 1H), 4.03-4.16 (m, 2H), 4.91 (d, J=4.5 Hz, 1H), 5.91 (br d, J=10 Hz, 1H), 6.30 (dt, J=3, 10 Hz, 1H), 6.97 (t, J=8 Hz, 1H), 7.14 (d, J=8 Hz, 1H), 7.24-7.54 (m, 6H), 7.96 (d, J=8 Hz, 1H), 10.04 (s, 1H); IR ($CDCl_3$) 1724, 1670, 1475, 1417 cm^{-1}; MS m/e 119, 139, 180, 299, 373, 402; HRMS m/e for $C_{24}H_{22}N_2O_4$ calcd 402.15796, measured 402.15790; Analysis calcd for: C, 71.63; H, 5.51; N, 6.85; found: C, 71.03; H, 5.56; N, 6.96.

(3aβ,6aβ,11aβ)-2,3,3a,6,6a,11a-Hexahydro-6a-formyl-6-methyl-2-(2,6-dimethylphenyl)-1*H*-pyrimidino[3,2,1-jk]carbazol-1-one (39): oil; 67% yield; 5:1 ratio of isomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (d, J=7 Hz, 3H), 2.20 (s, 3H), 2.32 (s, 3H), 2.56-2.69 (m, 1H), 2.80-2.92 (m, 1H), 3.42-3.73 (m, 2H), 4.42 (d, J=10 Hz, 1H), 5.72-5.94 (m, 2H), 6.95-7.40 (m, 5H), 7.56 (d, J=8 Hz, 1H), 7.98 (d, J=8 Hz, 1H), 9.80 (s, 1H); R_f (1:1 H:EA) 0.33.

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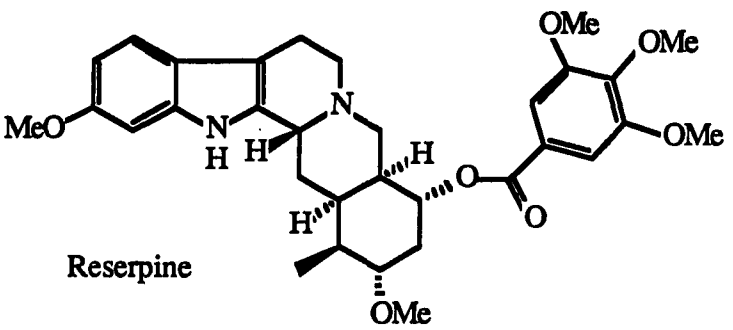
PART II: AN ATTEMPTED SYNTHESIS OF STRYCHNINE

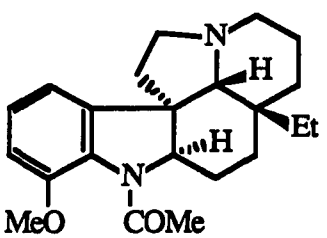
HISTORICAL

The indole alkaloids are a diverse group of compounds possessing a wide range of medicinally significant and complex structures. This class of compounds is the largest group of compounds whose members possess biological activity in many areas. Compounds in this class of alkaloids are antihypertensive agents, diuretics, respiratory stimulants, central nervous stimulants, anticancer agents, carcinogens and so on.

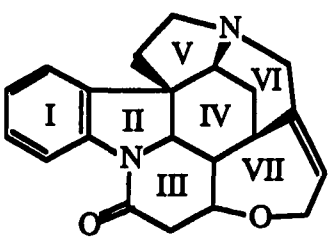
Some of these alkaloids retain the complete indole moiety such as reserpine. While others possess the indole moiety in a reduced state like aspidospermine and strychnine.



Reserpine



Aspidospermine



Strychnine

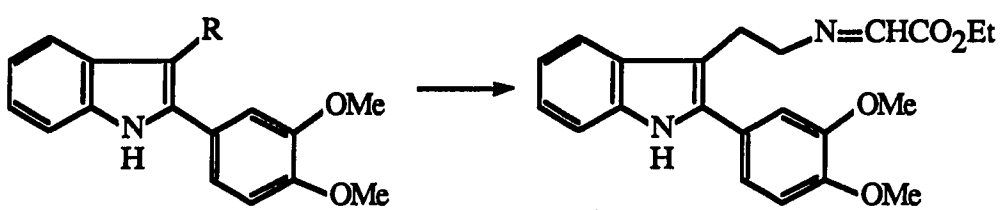
With the initial results produced in this laboratory, it was decided to attempt a total synthesis of strychnine. Strychnine, a well known fearsome poison, was used as early as the 16th century as a means of controlling rodents and other undesirables. Today it is

being used as a probe in studying neurotranmission.[1] Strychnine acts through binding at postsynaptic sites (glycine sites) in the spinal cord and the brain stem. The conventional numbering system of the strychnine rings is as shown.

There is only one reported synthesis of strychnine to date. However, this is not due to lack of effort.[2] Recently several reports have been published dealing with approaches and or advanced intermediates toward the synthesis of strychnine.

Woodward et al.[3] reported a synthesis of strychnine over 35 years ago. This marvelous piece of work still stands out today as a major synthetic achievement. The strategy behind this synthesis was strongly influenced by biogenetic considerations. Many of the advanced intermediates could be obtained from and have been compared to those from natural sources.

Chosen as a starting point was 2-veratrylindole **1** (R=H), which is readily available from acetoveratrone. A tryptamine side chain moiety was then added by a Mannich condensation with formaldehyde and dimethylamine (R=$CH_2N(CH_3)_2$). Extension of the chain on C-3 of the indole nucleus was accomplished in three steps by first treatment of the amine with methyl iodide. The methiodide was then displaced by sodium cyanide and the

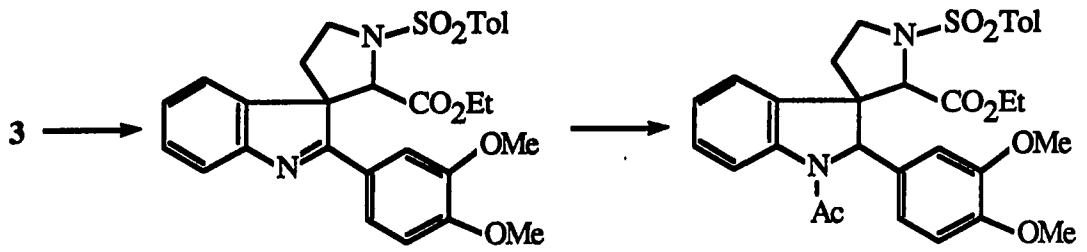


1 R= H
R= CH_2NMe_2
2 R= $CH_2CH_2NH_2$

3

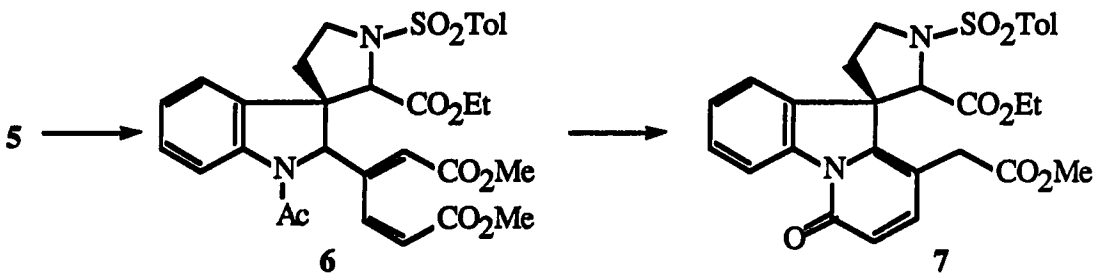
resulting nitrile was reduced with lithium aluminum hydride to yield the

2-veratryltryptamine **2** (R=$CH_2CH_2NH_2$). The Schiff base **3** was produced from the tryptamine and ethyl glyoxylate. Formation of ring V was realized only after treatment of the Schiff base with pyridine and toluenesulfonyl chloride to give the intermediate **4**.



4 **5**

These conditions were necessary, because the resulting amine had to be trapped to prevent the reverse reaction (the regeneration of the Schiff base) from occurring. Reduction of the indolenine with sodium borohydride, followed by acetylation, gave the N-acetyl indoline **5**. The stereochemistry at the new center was not of significance, because it was lost later in the synthesis. Oxidation of the dimethoxyaryl group with ozone provided the diester **6** in a 29% yield. Masking this muconic ester in this manner proves to be very clever for the formation of ring III. Once the nitrogen of the indole residue was released, it could react with only one of the esters. Thus, formation of the 6-membered lactam proceeded without

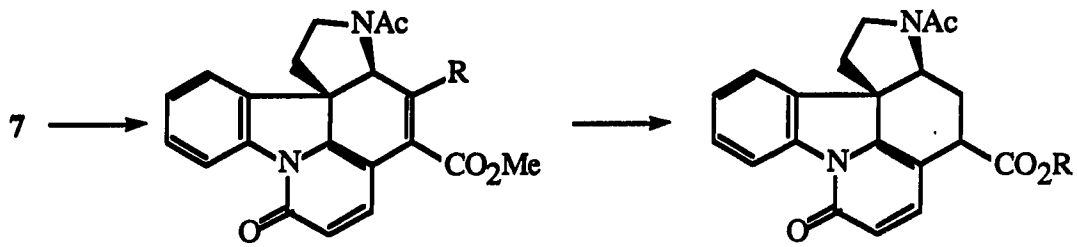


6 **7**

formation of the 5-membered lactam. Deconjugation of the α,β-unsaturated ester leaves the

stable pyridone **7**. This pyridone ring played an important role late in the synthesis and allowed the assembly of rings IV and VI to proceed unhindered.

Initial attempts at a Dieckmann condensation did not afford the desired formation of ring IV. Replacement of the tosyl group with an acetyl protecting group, followed by a Dieckmann condensation afforded ring IV, as compound **8** (R= OH). Reductive removal of the ketone proved to be tricky. Attempts to form and cleave the thioketal failed, probably due to the enolic nature of the β-keto ester. This difficulty was overcome by a four step sequence. First tosylation with pyridine and toluenesulfonyl chloride afforded the enol tosylate **9** (R= OTs). Michael addition of sodium benzylmercaptide and β-elimination

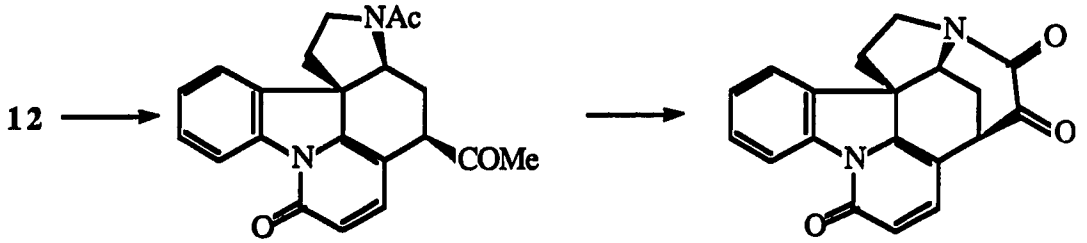


8 R= OH
9 R= OTs
10 R= SBz
R= H

11 R= Me
12 R= H

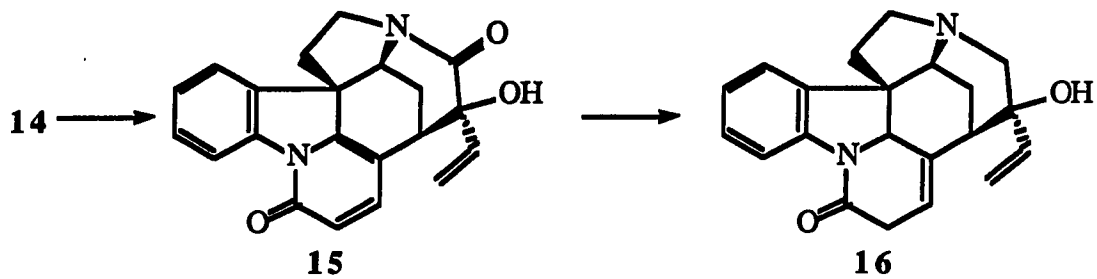
of the tosylate yielded the thioenol ether **10** (R= SCH_2Ph). Removal of the thioether with Raney nickel (R= H) and catalytic hydrogenation provided the ester **11**. Saponification of the ester provided the acid **12** which is also available by the degradation of strychnine.

The next stage of the synthesis was the closure of ring VI. Conversion of the acid into the methyl ketone **13** by treatment with pyridine and acetic anhydride, followed by selenium dioxide oxidation, gave the hexacyclic ketoamide **14**. Addition of a two carbon unit (sodium acetylide followed by reduction with Lindlar catalysis) yielded the alcohol **15**.

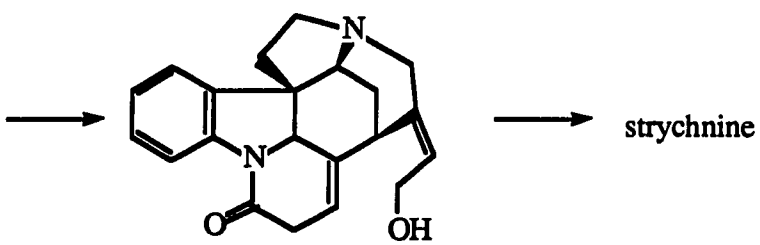


13 14

Reduction of the lactam and the pryidone ring with lithium aluminum hydride gave the β,γ-unsaturated amide, compound **16**. Acidic rearrangement provided the allylic alcohol, isostrychnine. The final ring was assembled by treatment of this alcohol with base under known conditions to give strychnine.



15 16

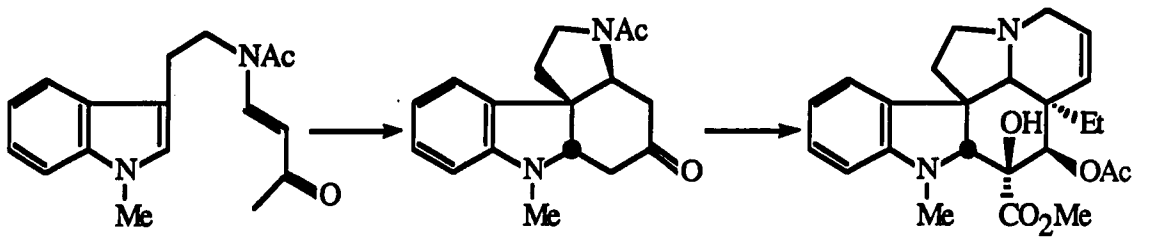


isostrychnine

Reports of other synthetic approaches toward strychnine remained dormant until recently; even reports toward the strychnos alkaloids were sporadic until the last decade.

Büchi et al.[4] reported the total synthesis of (±)-vindorosine, an aspidosperma alkaloid. The ketoamide **17** was made in two steps from 1-methyltryptamine and

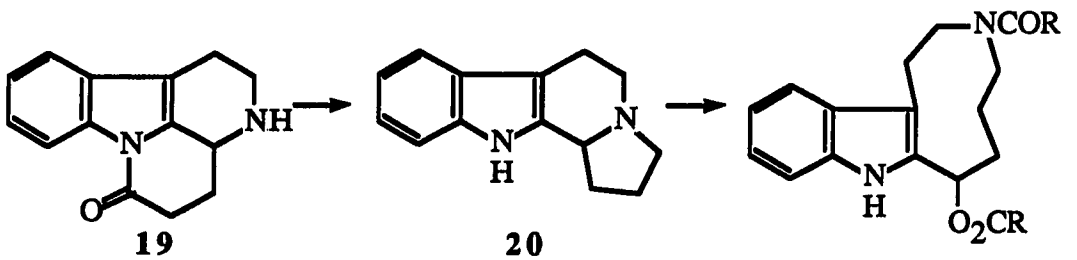
3-oxo-1-chloro-1-butene. The ketoamide, upon treatment with boron trifluoride etherate in refluxing benzene, gave the tetracyclic intermediate **18**. This appears to be the result of a



17 **18** vindorosine

[4 + 2] cycloaddition, but the authors comment that indoline **18** was formed directly from its precursor by electrophilic C-3 substitution, followed by nucleophilic enol addition to C-2 of the resulting indolenine. This was determined to be the case through further experimentation.

The first general approach to the strychnos alkaloids was developed by Harley-Mason.[5] This route was based on the lithium aluminum hydride reduction of the lactam **19** which yielded the pyrrolidinecarbazole **20**. Treatment of this carbazole with

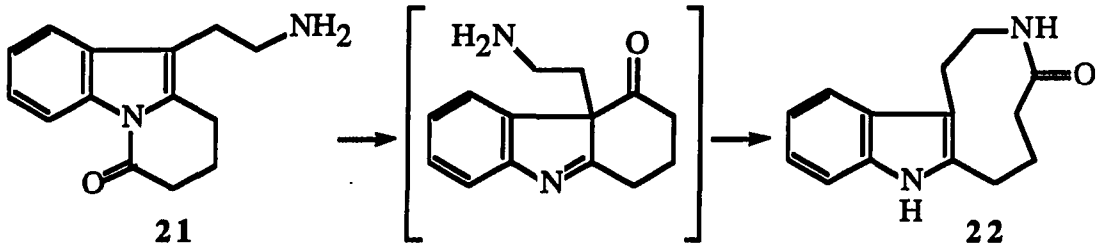


19 **20**

various anhydrides brought about N-C bond fission which resulted in the 9-membered indoles and eventually several strychnos alkaloids.

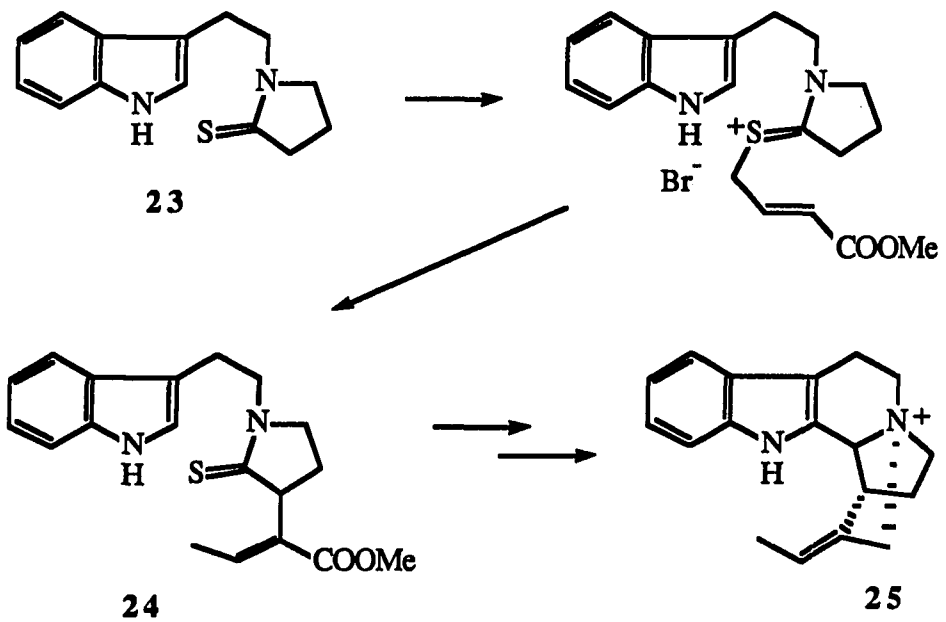
A photoisomerization[6] was the key step in the formation of a common intermediate for the strychnos, aspidosperma, schizozygone and eburnamine alkaloids. The lactam **21**

was irradiated to furnish the rearranged lactam **22**, which is similar to the Harley-Mason intermediates. This intermediate was utilized for the total syntheses of tabifoline, tubifolidine, condyfoline, 1,2-dehydroaspidospermidine, 1-acetylaspidospermidine and quebrachamine and for the formal synthesis of strempeliopine.



21 **22**

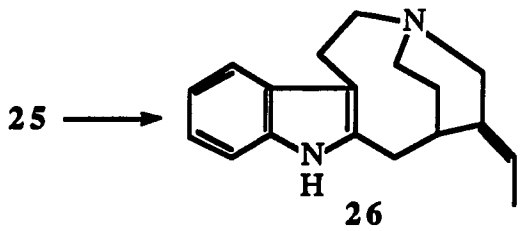
Takano et al.[7] used a thio-Claisen rearrangement and a reductive ring opening for the synthesis of the strychnos skeleton. The thioamide **23** was treated with methyl 4-bromocrotonate and after a Claisen rearrangement followed by conjugation of the olefin



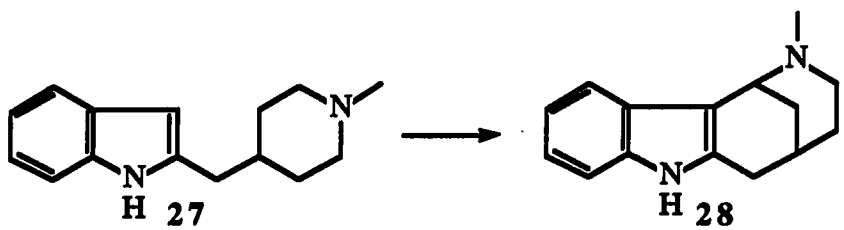
23 **24** **25**

gave the α,β-unsaturated ester **24**. After several steps, the ammonium salt **25** was

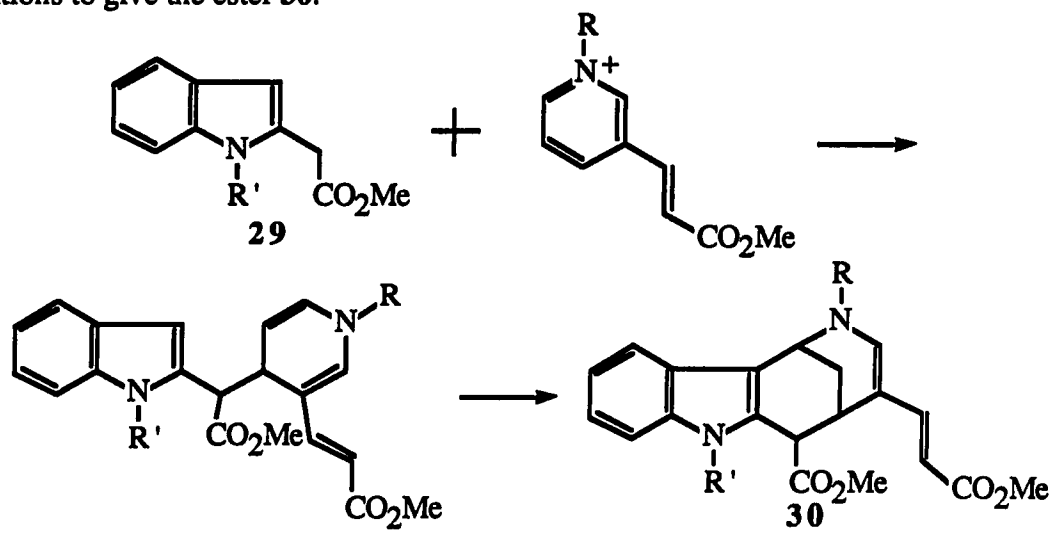
produced which underwent reduction with sodium in ammonia to yield the tetracyclic amine **26**.



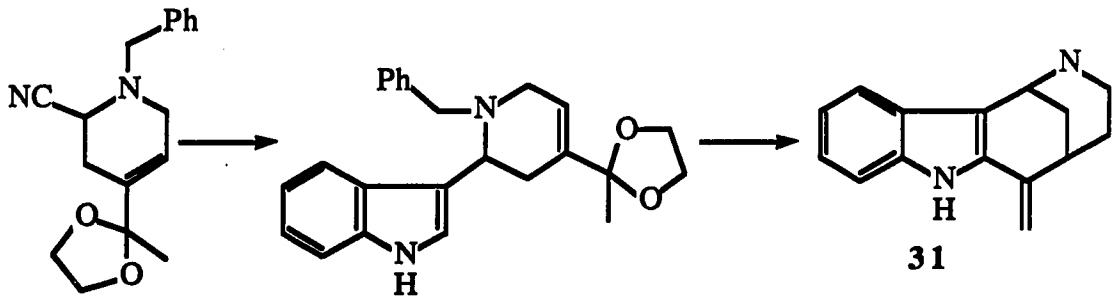
Bosch et al.[8] reported several approaches to the strychnos skeleton. Oxidation of the 2-substituted indole **27** with mercuric acetate provided the tetracyclic indole **28**.



Also utilized in this laboratory was the addition of a pyridinium salt to the anion of the indole ester **29**. The resulting dihydropyridine was subsequently cyclized under acidic conditions to give the ester **30**.

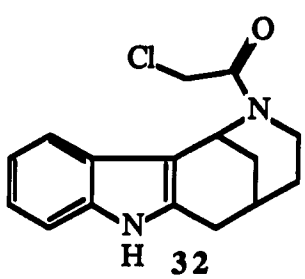


Displacement of a nitrile by indole, either under acidic conditions or with the Grignard reagent derived from indole, was employed to assemble the strychnos skeleton. Once the indole moiety was attached to the piperidine ring, a second cyclization could take place to achieve the tetracyclic compound **31**.



31

Bosch et al. in an attempt to extend the chemistry used in their aspidosperma alkaloid synthesis to the strychnos alkaloids initially met with failure. The photocyclization of the chloroacetamide **32** and the Pummerer rearrangement of the sulfoxide **33** both yielded unexpected products. Finally, generation of the thionium salt from the thioacetal **34** with dimethyl(methylthio)sulfonium fluoroborate (DMTSF) produced the pentacyclic strychnos skeleton.



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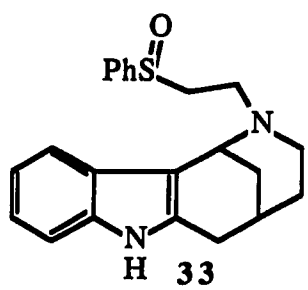

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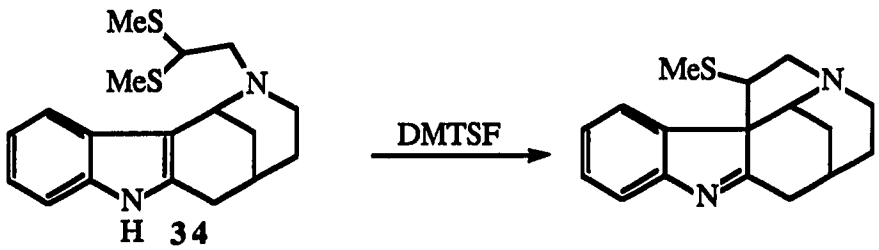
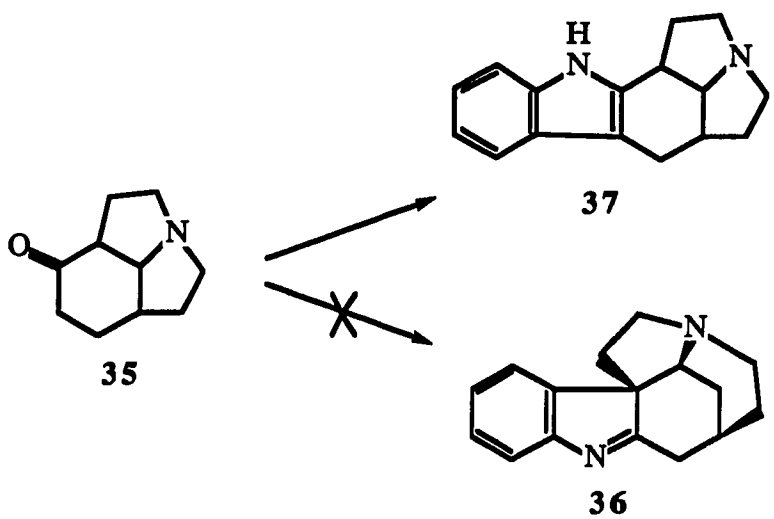
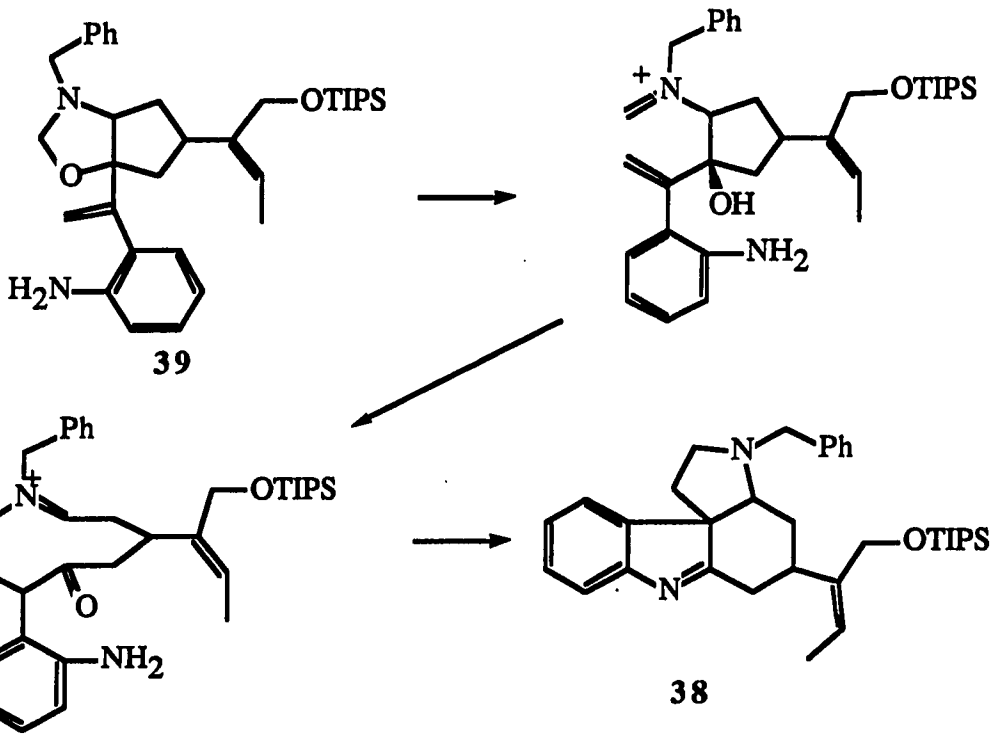


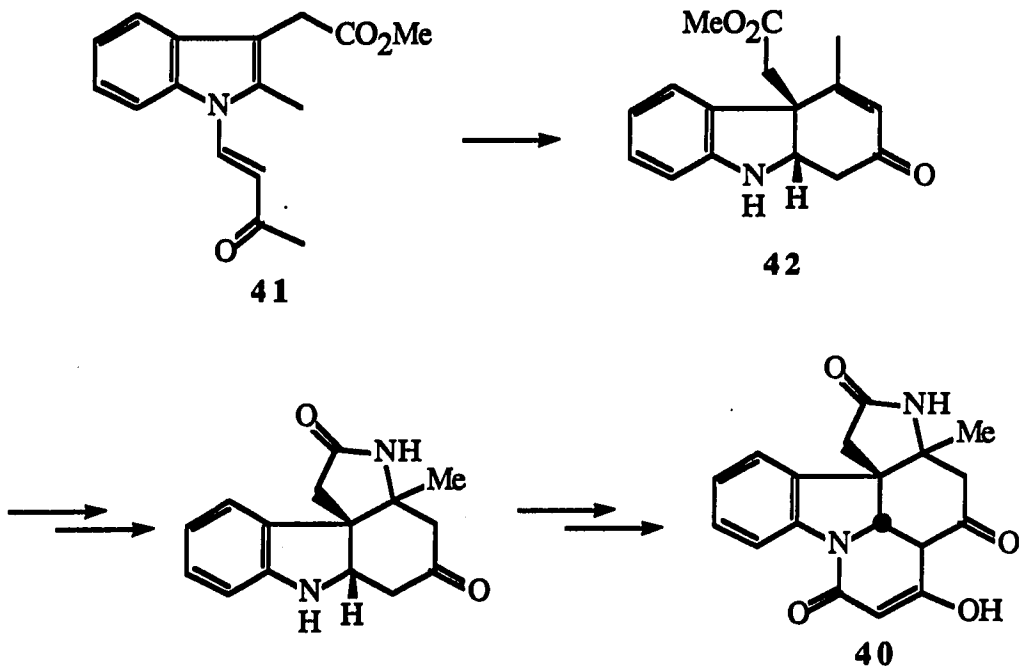
A Fisher indole synthesis was the key step in yet another approach stemming from this laboratory. The azabicyclic[3.3.1]nonane **35** was assembled and submitted to a Fisher indole synthesis. The product of the reaction was not the desired pentacyclic **36**, but the regioisomer **37**.



Overman and Angle[9] also experienced difficulties in trying to extend their methodology for the aspidosperma alkaloids to the strychnos alkaloids. The tetracyclic amine **38** was formed by a tandem cationic aza-Cope rearrangement/Mannich condensation from the protected amine **39**. However, their initial efforts to convert this advanced intermediate into a pentacyclic system failed.

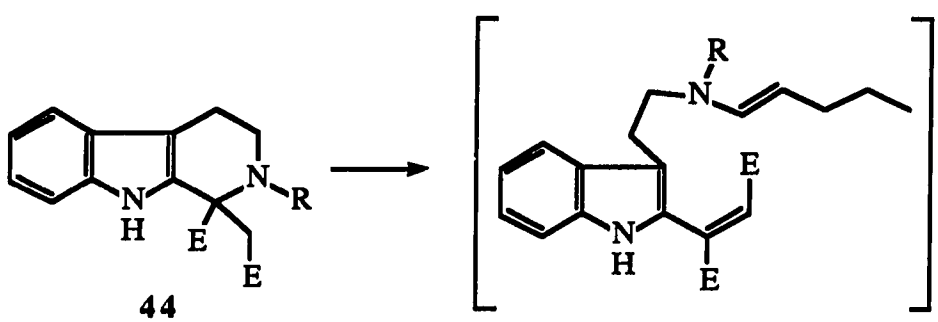


Teuber et al.[10] described the efficient synthesis of the pentacyclic intermediate **40**. Rearrangement of the 2-substituted indole **41** led to the unsaturated ketone **42**. Noteworthy is the limitation of this approach. The rearrangement will only proceed if the C-2 position of the indole nucleus is substituted. In this case a methyl group was substituted at this position which yielded an angular methyl group in the advanced intermediate **40**. This methyl group will be difficult to remove. However, the simplicity of this approach (the intermediate **40** is available in just five steps from the starting material) makes it attractive for unnatural analogs.

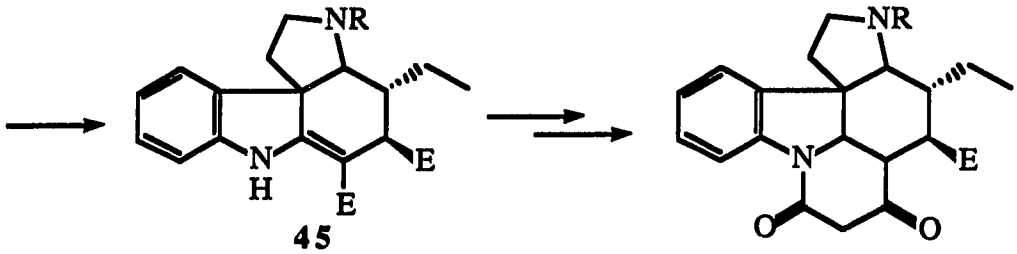


41 42 40

Vercauteren et al.[11] recently reported a pentacyclic intermediate containing rings I to V of the strychnine skeleton. The key step used the Kuehne-type cycloaddition by *in situ* generation of enamine **43**. Thermolysis of the precursor **44** to this intermediate with acetic acid and butyraldehyde gave the highly functionalized tetracyclic ester **45**. Further elaboration led to the pentacyclic intermediate. This intermediate, however, possesses an ethyl group on ring III which will be difficult to remove for the completion of this synthesis. The authors made no indication if acetaldehyde would work in this reaction.

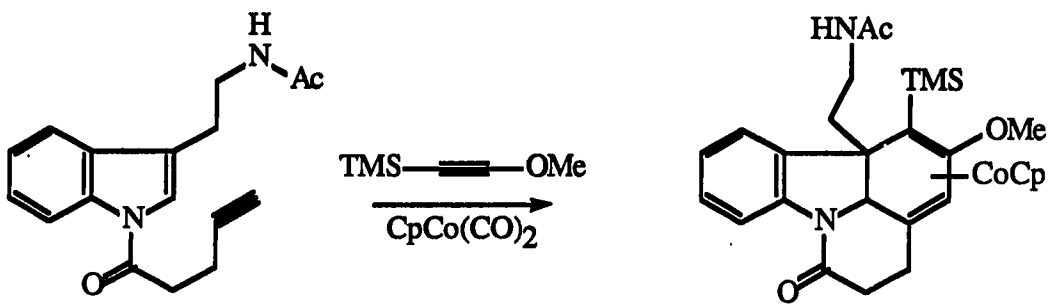


44 43

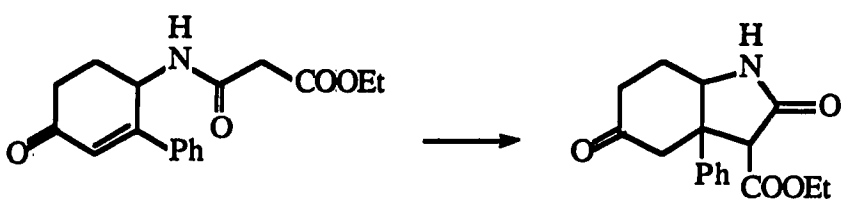


45

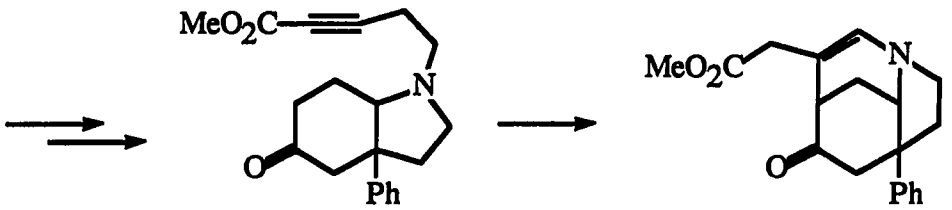
A cobalt mediated [2 +2 +2] cycloaddition is the basis for Grotjahn and Vollhardt's[12] approach. The reaction of trimethylsilyl methoxy acetylene with the tryptamine derivative in the presence of cyclopentadienylcobalt dicarbonyl produced the tetracyclic intermediate **46**.



Recently reported[13] was an approach to strychnine using a series of Michael additions to obtain the tricyclic unit **47**. The amide ester **48** was synthesized from 2-aminoacetophenone and under basic conditions formed the ketoamide **50**.



48 50



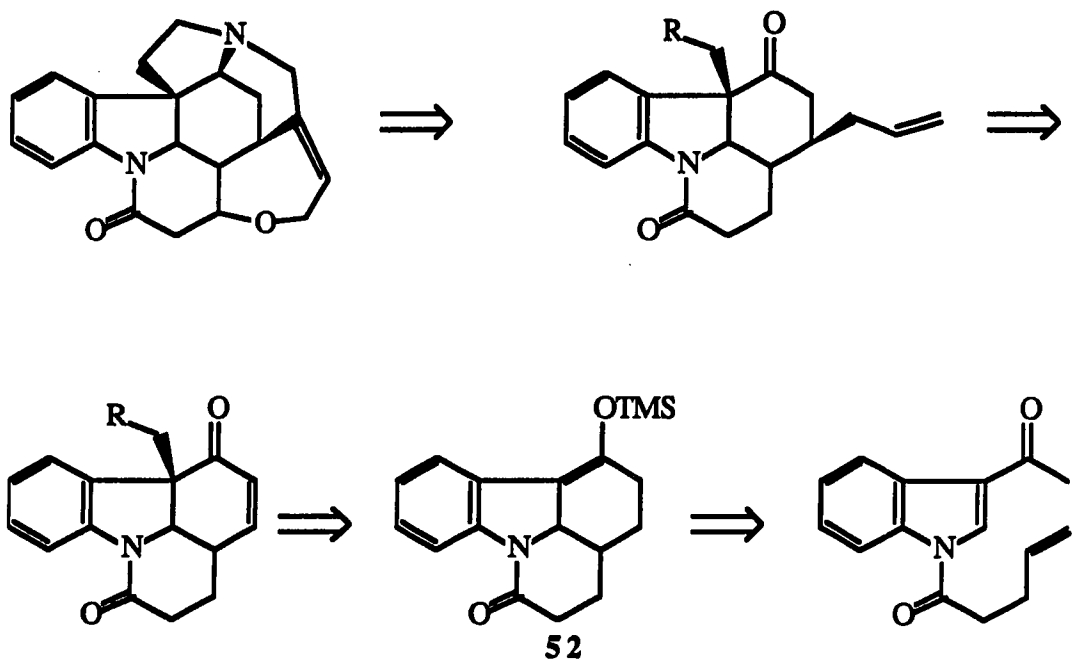
51 **47**

After several functional group manipulations, the amine **51** was set to undergo the next Michael addition and the tricyclic ester **47** was produced.

RESULTS AND DISCUSSION

We have studied the use of intramolecular Diels-Alder reactions to gain access into the indole alkaloids and have reported the quick assembly of tetracyclic intermediates.[14] To demonstrate the utility of this intramolecular Diels-Alder reaction, it was decided that strychnine would pose a challenging target.

The retrosynthetic analysis features three key carbon-carbon bond forming reactions: the intramolecular Diels-Alder, the alkylation of the enol silyl ether and a conjugate addition. This latter reaction poses the most challenging stereochemical problem. The completion of these three tasks will yield a highly functionalized tetracyclic intermediate.

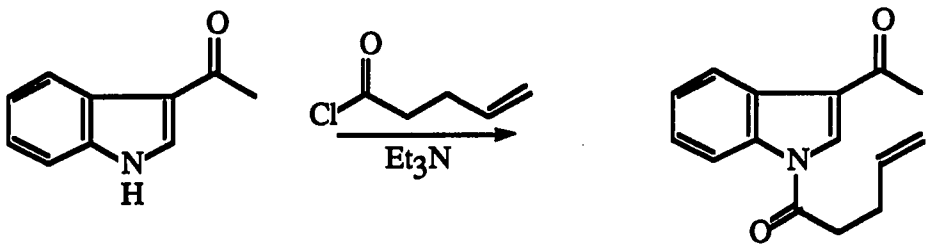


52

The Diels-Alder reaction on vinyl indoles has good precedent. Several examples using 2-vinyl indoles have been reported, most notably being the reaction developed by

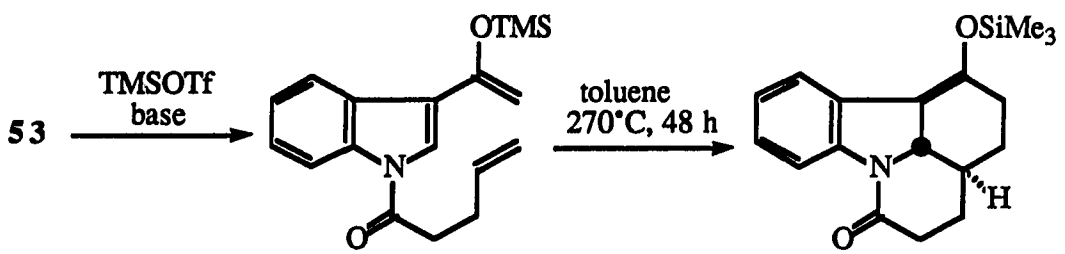
Kuehne et al.[15] for the synthesis of the aspidosperma alkaloids. Surprisingly, only a few reactions with 3-vinyl indoles have been reported.[16]

Our first goal was to synthetize the enol silyl ether **52**, which would be the result of an intramolecular Diels-Alder reaction. The N-acylation of 3-acetylindole with 4-pentenoyl chloride afforded the amide **53** in 79% yield. A slight excess of the indole had to be used



53

since O-acylation of the resulting amide was a competing reaction with excess acid chloride. Generation of the diene was attempted with lithium diisopropylamide and chlorotrimethylsilane at -78°C. This led to a mixture of products. Success was achieved by treatment of the amide with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and diisopropylethylamine. The unpurified material was sufficiently pure to be taken on to the



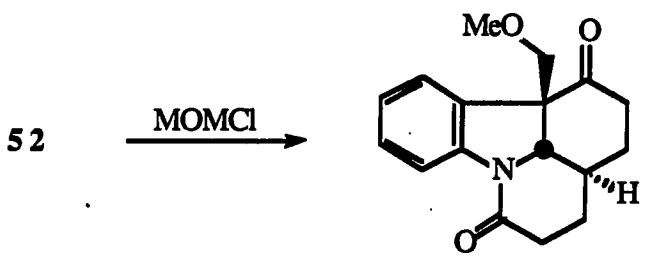
54 **52**

thermolysis step. Thermolysis of the triene **54** at 270°C for 48 h gave the resulting enol silyl ether which was stable to flash column chromatography. The methine protons in the

tetracyclic intermediate are trans as evidenced by a coupling constant of 10 Hz in the proton NMR spectrum. This enol silyl ether could be hydrolyzed to the corresponding ketone.

Recently Gramain et al.[17] achieved the successful C-alkylation of a similar ketone by generation of the enolate with KH. However, we desired to utilize the enol silyl ether **52**, thus making our route more direct and avoiding the need for selectivity in enolate formation. This was the second of our goals.

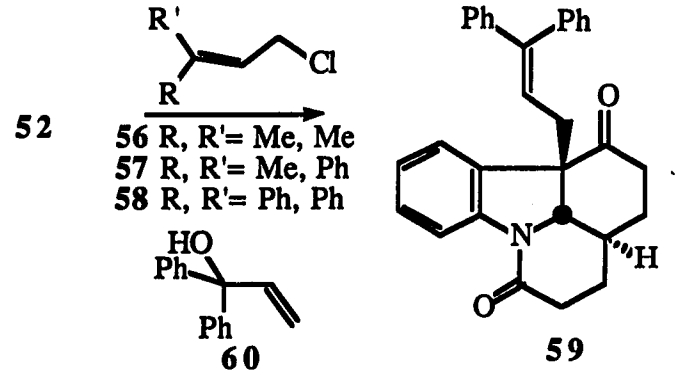
Alkylation of enol silyl ethers is a well documented reaction, affording products under either Lewis acid[18] or fluoride-mediated conditions.[19] The reaction of **52** with allyl bromide and tetra-*n*-butylammonium fluoride afforded only the O-alkylated product. This product could not be isomerized via a Claisen rearrangement. The use of Lewis acids with several halides led to poor yields with one exception. Ether **55** could be generated in 88%



55

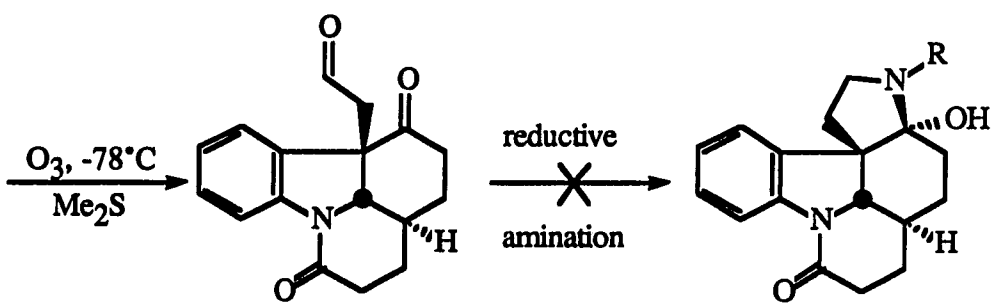
yield by using chloromethyl methyl ether. Unfortunately, efforts to extend this to more useful halides failed.

It appears that a halide which would result in a more stable carbocation is desired. Thus, the allylic chlorides **56**, **57** and **58** were considered. Of these, only 1-chloro-3,3-diphenyl-2-propene (**58**) reacted with stannic chloride to provide the desired material **59** in an excellent yield. The alcohol **60**, the precursor to **58**, also afforded an excellent yield of **59** with titanium tetrachloride.



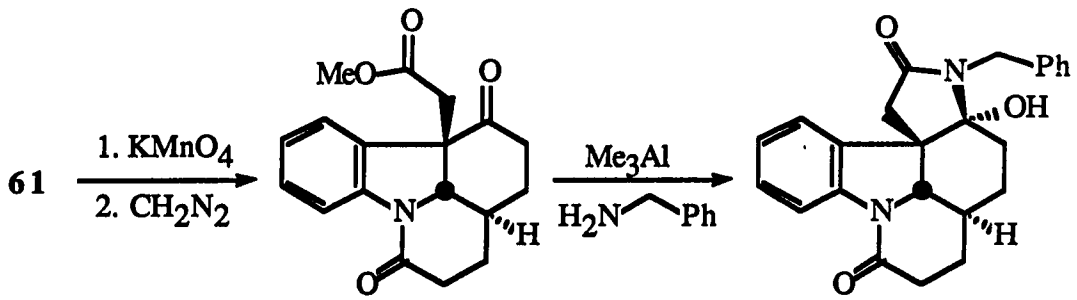
With two of the three key carbon-carbon forming steps completed, we needed to determine which path to follow. We had two choices: further functional group manipulations to address the final key step or examine the appendage of ring V. It was decided to attempt to introduce the fifth ring.

Ozonolysis of the ketoamide **59** yielded the aldehyde **61** cleanly. Reductive amination with benzylamine and sodium cyanoborohydride, in an attempt to form the hydroxyamine, produced several products. This result led us to yet another fork in this route towards strychnine. The aldehyde could either be oxidized to the acid or selectively reduced to the alcohol.



Oxidation of the aldehyde with permanganate[20] produced the acid which was

converted to the ester **62** with diazomethane. Reaction of this ester with the reagent formed from trimethylaluminum and benzylamine[21] afforded the crystalline hydroxylactam **63** in 42% yield. Efforts to extend this result to the reagent made from trimethylaluminum and ammonia gas failed.



62 **63**

Support for this hydroxylactam subunit came from infrared absorptions at 3360 and 1700 cm^{-1}, the presence of a carbon resonance at 93 ppm (N-C-O) and the absence of a resonance in the ketone region of the ^{13}C NMR. Support for the cis- II-IV ring juncture came from difference NOE spectroscopy, wherein irradiation of the endo methylene proton adjacent to the carbonyl of the five-membered lactam provided a 12.9% enhancement of the methine proton at the II-IV ring juncture. The 10.3 Hz coupling constant for the methine proton at 3.40 ppm strongly supports a trans- III-IV ring juncture. Also in support of this trans-ring juncture was the lack of NOE enhancement when the methine proton (3.40 ppm) was irradiated and the lack of an island in the 2-D mapped NOESY between these two ring juncture protons (see figures 1a-c).

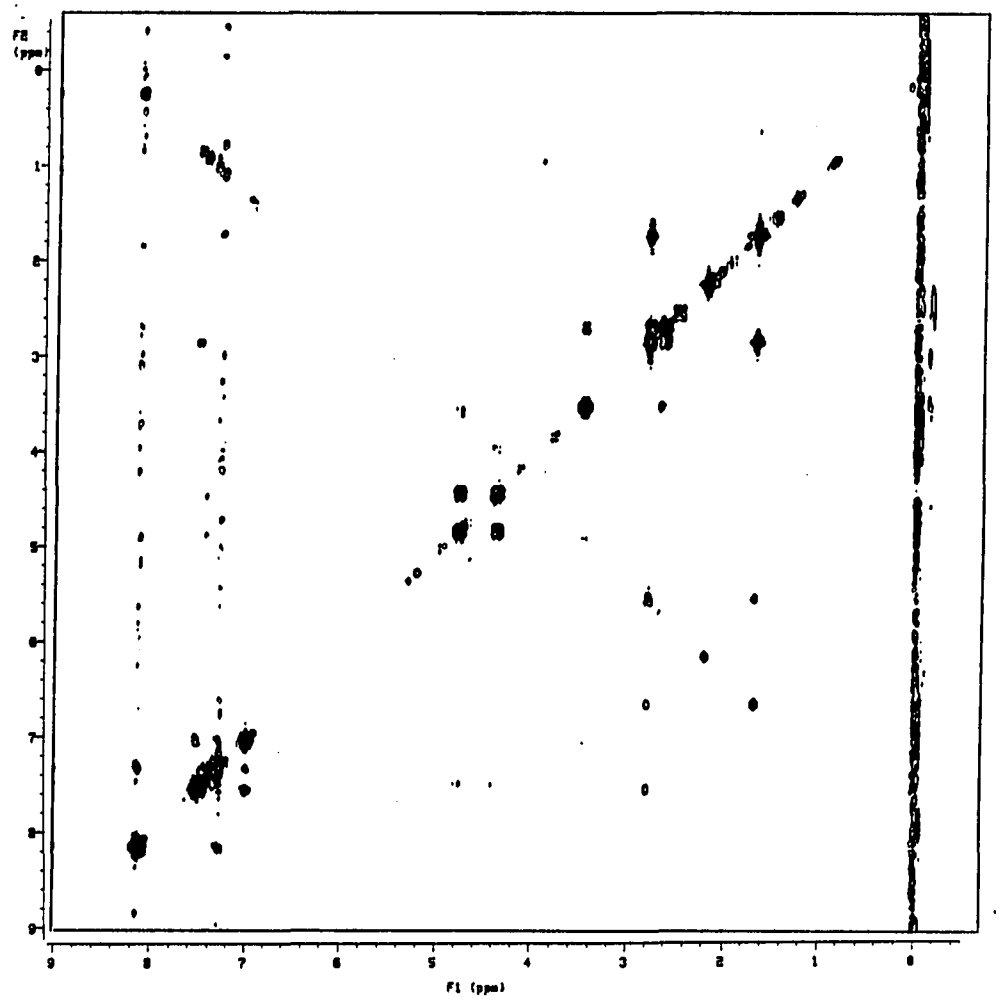


Figure 1a. 2D NOESY map of compound **63**

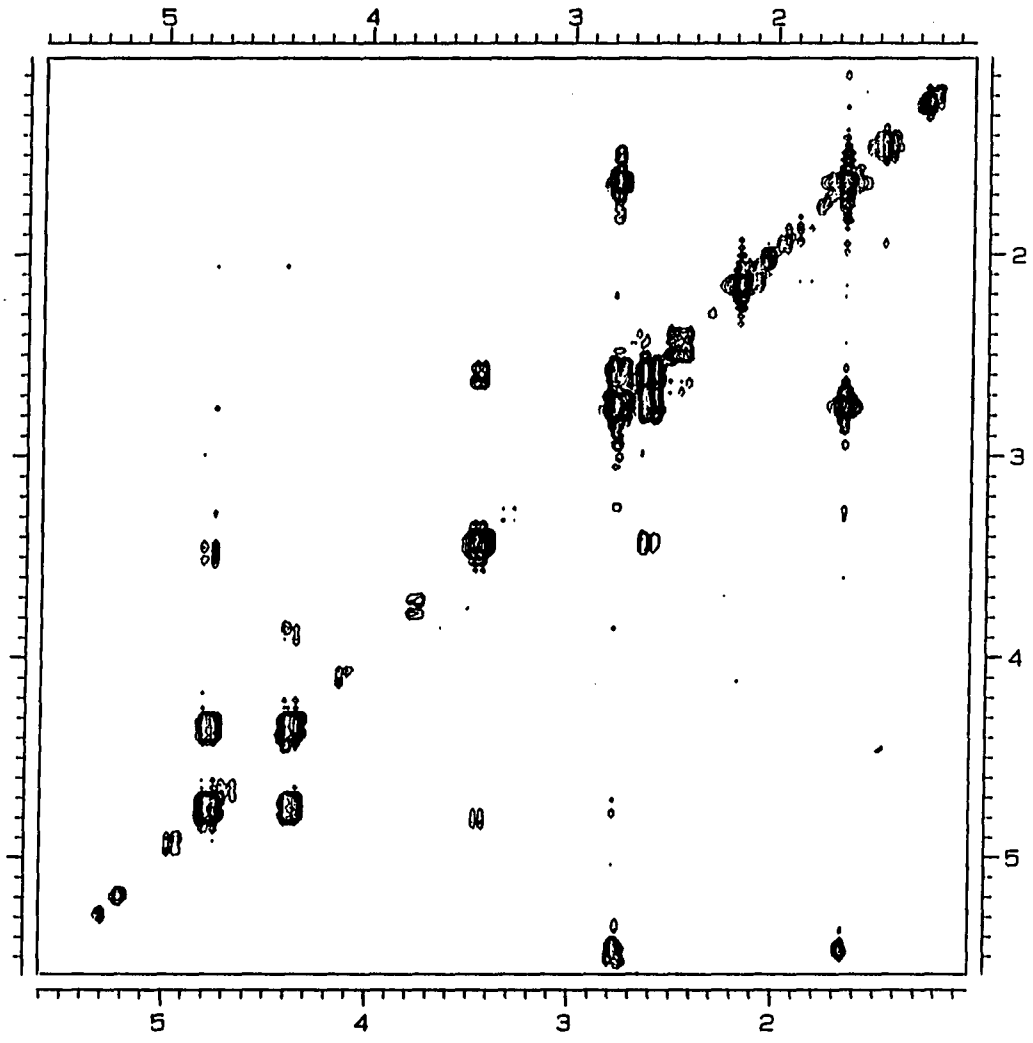


Figure 1b. 2D NOESY map of compound **63**; both the x and y axes are expanded from 0.9 to 5.6 ppm

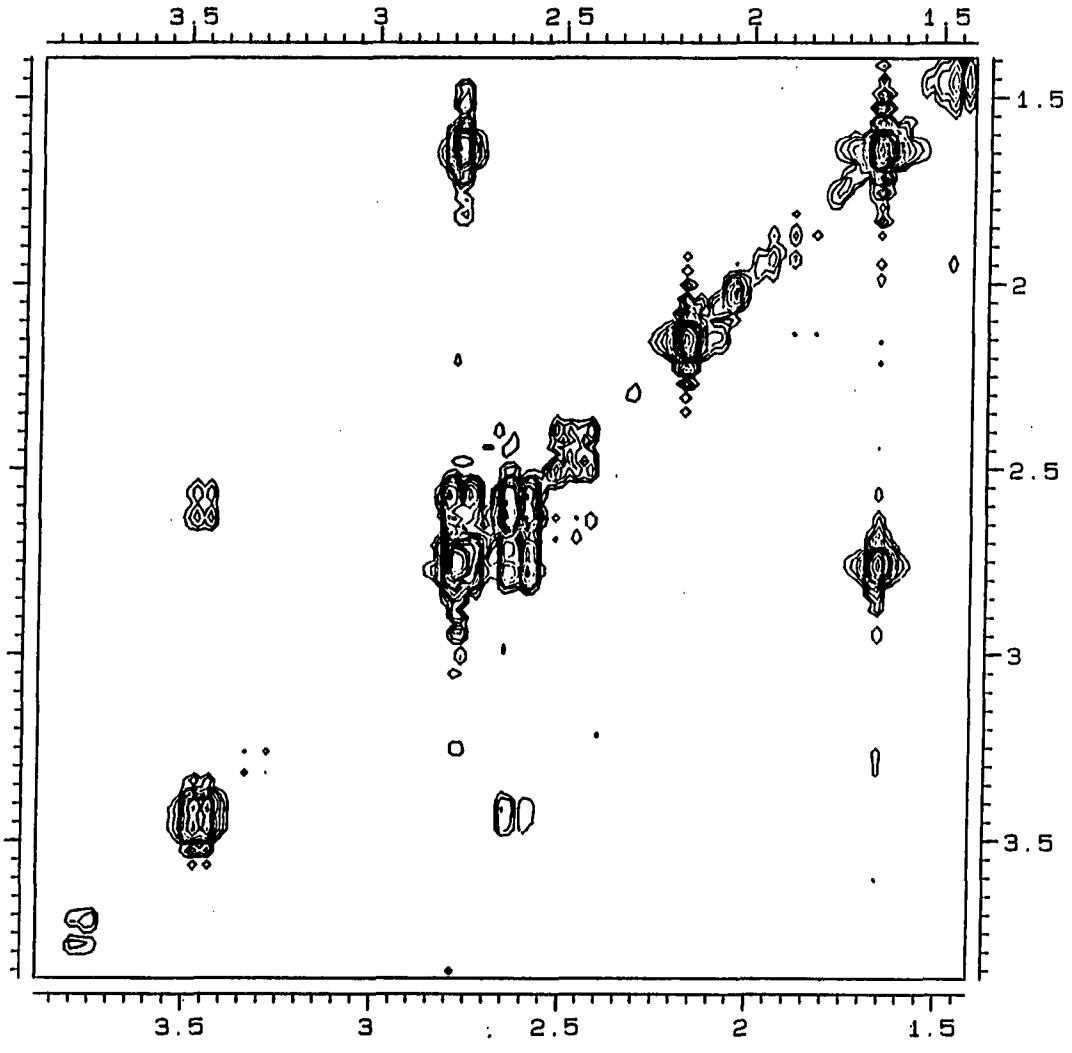
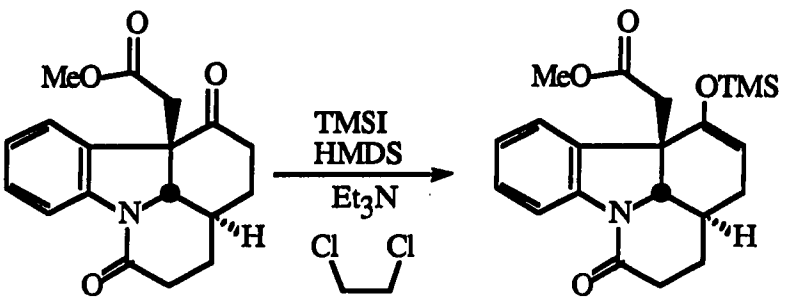


Figure 1c. 2D NOESY map of compound **63**; both the x and y axes are expanded from 1.4 to 3.9 ppm

Introduction of an allyl group as the last key carbon-carbon forming step could take place at several different stages in this synthesis. The most logical point to complete this task would be when the ketone functionality in ring IV is still in tact. Formation of an α,β-unsaturated ketone in the presence of an ester and an amide could be tricky. The use of a strong base (i.e., LDA, LTMP or LHMDS) and chlorotrimethylsilane was not even considered due to the results with the ketoamide **53**. The use of TMSOTf and diisopropylethylamine returned starting material. When iodotrimethylsilane was utilized with triethylamine and hexamethyldisilazane in 1,2-dichloroethane,[22] the desired enol silyl ether **64** was isolated in quantitative yield after flash column chromatography.

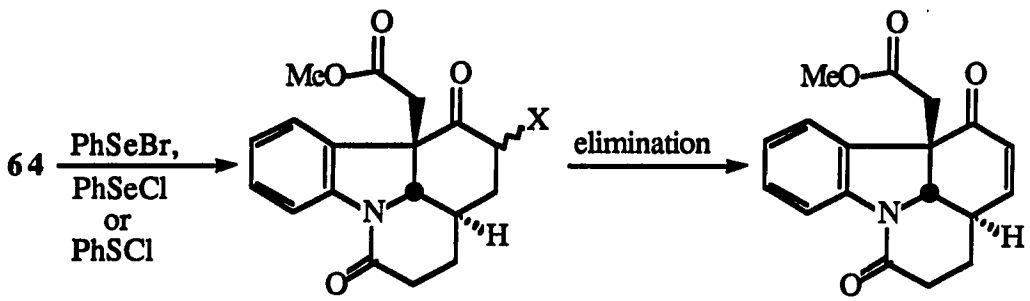


64

This enol silyl ether was treated with several electrophilic reagents in an attempt to set the stage for the final key carbon-carbon bond forming step. Initial attempts to add a phenylselenenyl moiety by the reaction of **64** with phenylselenenyl bromide produced the α-bromoketone **65**. While this bromide was not the desired material, it also was not a total surprise. Phenylselenenyl halides have been shown to act as halogenating agents for activated benzene derivatives.[23] Elimination of this bromide was unsuccessful. Introduction of the phenylselenenyl group was realized with phenylselenenyl chloride. Oxidation of the selenide **66** with hydrogen peroxide[24] gave a good yield of a compound

that was not the desired material. The proton NMR spectrum did not possess the olefinic protons of an α,β-unsaturated ketone. The low resolution mass spectrum of this material indicated this product was the result of overoxidation.

Formation of the phenylsulfoxide **67** proceeded uneventfully from the enol silyl ether. The enol silyl ether reacted with benzenesulfenyl chloride to produce a 1:1 mixture of sulfides **68** which were oxidized to the sulfoxides. Thermolysis of this mixture of sulfoxides gave the unsaturated ketone **69**, but also returned 50% of the starting material. Further investigation showed that the returned starting material was only one diastereomer, the compound with the phenylsulfoxide moiety in the equatorial position. Attempts to force elimination of this equatorial sulfoxide failed.

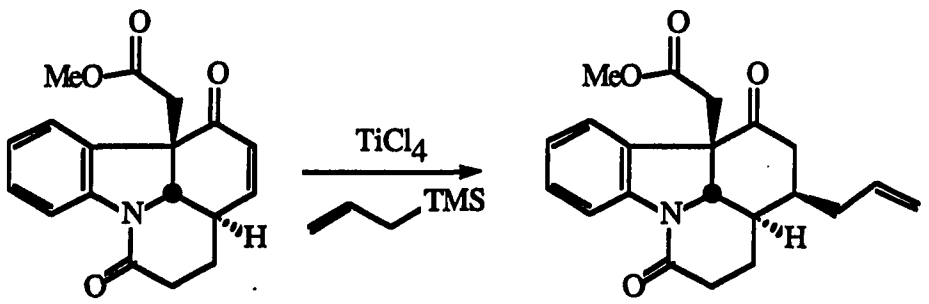


65 X= Br
66 X= SePh
67 X= SOPh
68 X= SPh

69

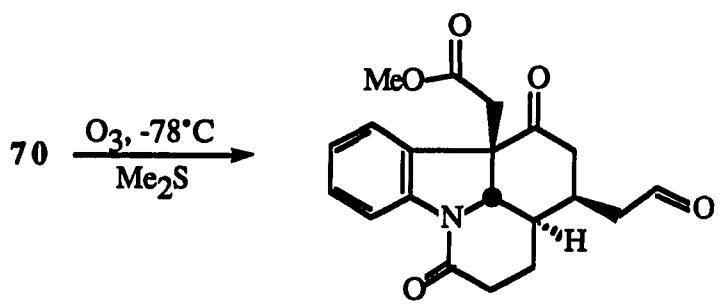
These results led us to try palladium acetate.[25] Initial efforts with palladium acetate with benzoquinone as a reoxidant of the palladium was hindered by difficulty in purification and long reaction times. Optimized conditions were developed using a full equivalent of palladium acetate in acetonitrile at 50°C for 48 h. Higher temperatures (refluxing acetonitrile) gave decomposition products. Optimal conditions, however, only produced a 1:1 mixture of saturated and unsaturated ketones.

With the unsaturated ketone **69** in hand, the introduction of an allyl group could be undertaken. Treatment of the unsaturated ketone with titanium tetrachloride and allyltrimethylsilane[26,18] gave the allylated ketone **70** as a 20:1 mixture in favor of the desired diastereomer. These diastereomers were readily separated by flash column chromatography.



70

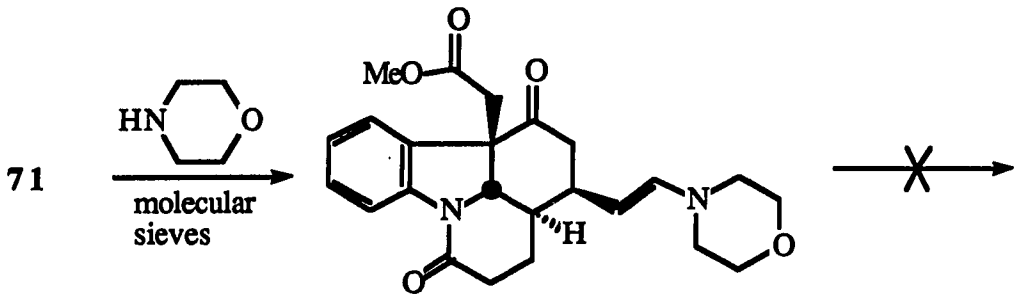
In the attempts to further functionalize this newly added allyl group to allow for the appendage of ring VII later in the synthesis, the olefin was cleaved with ozone to the aldehyde **71.**



71

The formation of the enol silyl ether of this aldehyde with TMSOTf failed and with iodotrimethylsilane gave a mixture of products. However, the morpholine enamine **72**

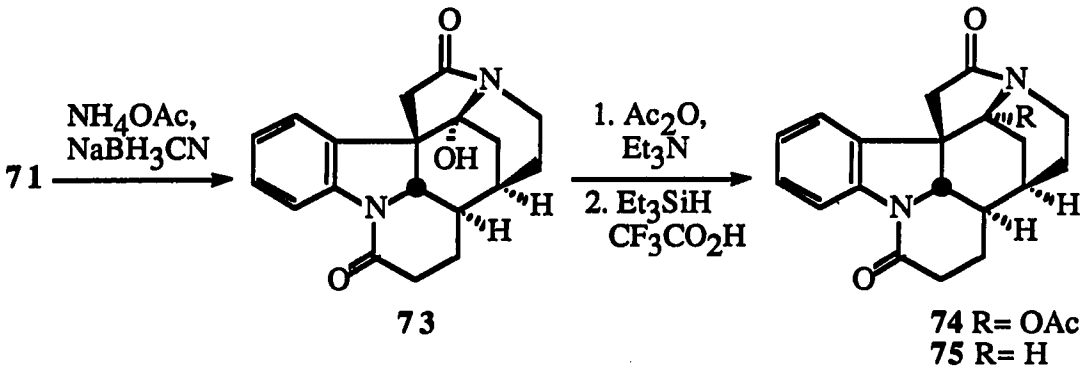
formed cleanly and in quantitative yield. All efforts to react this enamine with allyl bromide, ethyl bromoacetate,[27] acetoxyacetyl chloride and triethylamine,[28] osmium tetroxide or dimethyldioxirane[29] only returned the starting aldehyde.



72

A Mannich condensation with ammonium chloride and paraformaldehyde was tried with the aldehyde **71**. While this did not return the starting material, it also did not produce the desired product. This was evident from the low resolution mass spectrum. While this spectrum did not possess a peak corresponding to the molecular weight ion, it did possess a peak at the molecular weight ion plus 26.

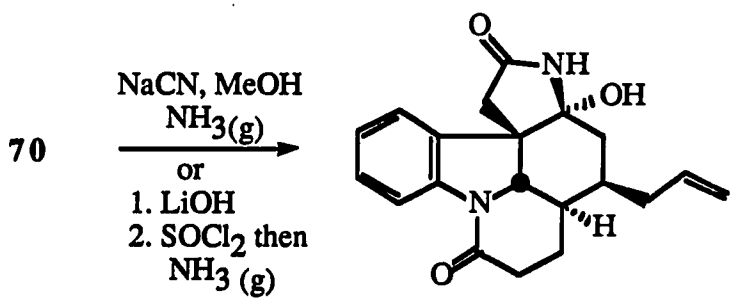
In a final attempt to utilize this aldehyde, we turned to a reductive amination. The reaction of the aldehyde with ammonium acetate and sodium cyanoborohydride gave the hexacyclic amide **73** in 18% yield after three days. While this was a promising result, this intermediate does not possess the proper functionality to append the final ring for the strychnine skeleton. This intermediate did provide us with the opportunity to address the question of the reduction of the bridgehead alcohol. To accomplish this the alcohol was converted to its acetate **74**. The acetate was then treated with trifluoroacetic acid and triethylsilane to yield the amide **75**.



73

74 R= OAc
75 R= H

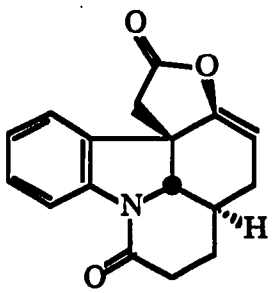
Since the reductive amination appended two rings simultaneously, could turning the ester into an amide provide similar results and allow for functionality to remain in ring VI? As mentioned earlier, the reagent from trimethylaluminum and ammonia gas did not work with the ester **62**. Sodium cyanide with ammonia[30] in a sealed tube was an alternative method to from an amide. Employing these conditions, produced the pentacyclic amide **76** in moderate yield. The following two step procedure provides this amide in much improved yields. Saponification of the ester with lithium hydroxide afforded the acid.



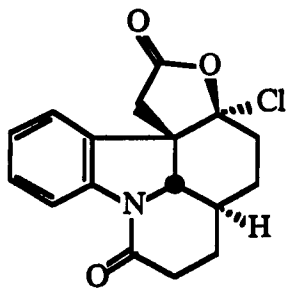
76

Formation of mixed anhydrides followed by displacement with ammonia did not provide the desired amide. Conversion of the acid to the acid chloride proved interesting. Since our initial efforts were not successful, we utilized the ester **62** as our model system until the optimal conditions were discovered. Reaction of the acid derived from the ester **62** with oxalyl chloride failed to give the acid chloride. Thionyl chloride in refluxing

1,2-dichloroethane, followed by addition of ammonia, provided a mixture of the enol lactone **77** and the chlorolactone **78**. Finally, thionyl chloride in refluxing dichloromethane, followed by ammonia provided the lactam. These conditions were then employed with the ester **70**.

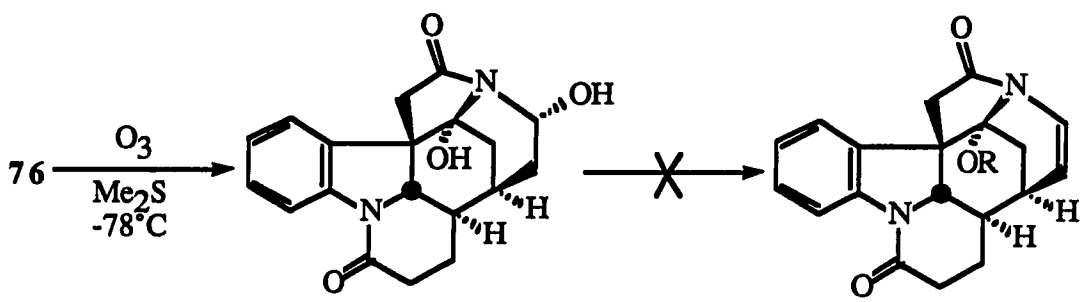


77



78

Ozonolysis of the olefin afforded the hexacyclic alcohol **79**. Attempts to convert this to the enamide led only to degradation of the starting material. Conversion of the alcohols into appropriate leaving groups should have given the enamide and a protected bridgehead alcohol. It was expected that the bridgehead group would not interfere with this reaction, because that would lead to a bridgehead olefin. Bridgehead olefins are known to be very unstable. However, it is difficult to speculate what happened in our attempts to alter the functionality of **79**, because no characterizable products were isolated.

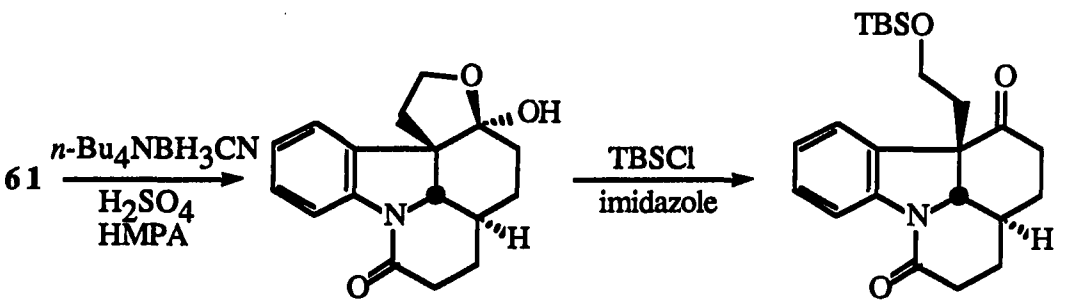


79

In looking at the work that was accomplished, we decided that maybe the oxidation of the aldehyde **61** was not in our best interest. The chemistry was suffering from low to moderate yields for certain steps and leading to dead ends. Also this route required the reduction of a five-membered lactam over a six-membered lactam, a task that is possible, but may prove to be difficult in a complex molecule.

Reductive carbamation was recently reported[31] on simple aldehydes. This would provide the amine in a protected form and not require the oxidation of the aldehyde. Efforts to apply this to our aldehyde failed.

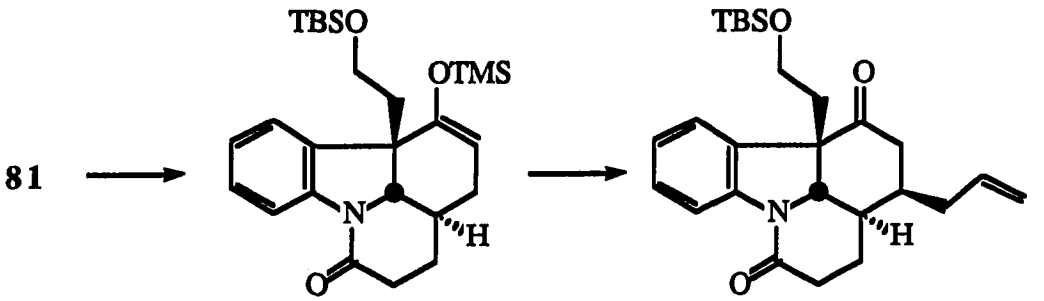
Selective reduction of an aldehyde over a ketone at an early stage in the synthesis could only prove to be beneficial. Sodium borohydride and sodium triacetoxy borohydride[32] gave mixtures of the diol and the desired material. Selective reduction was finally realized with the combination of tetra-*n*-butylammonium cyanoborohydride and sulfuric acid in HMPA.[33] This gave the hemiketal **80** in excellent yield. Protection of the alcohol as a *tert*-butyldimethylsilyl ether[34] proceeded cleanly to provided the silyl ether **81**.



80 **81**

From this point, this reductive route parallels the oxidative route through to the introduction of the allyl group. Formation of the enol silyl ether by the same conditions,

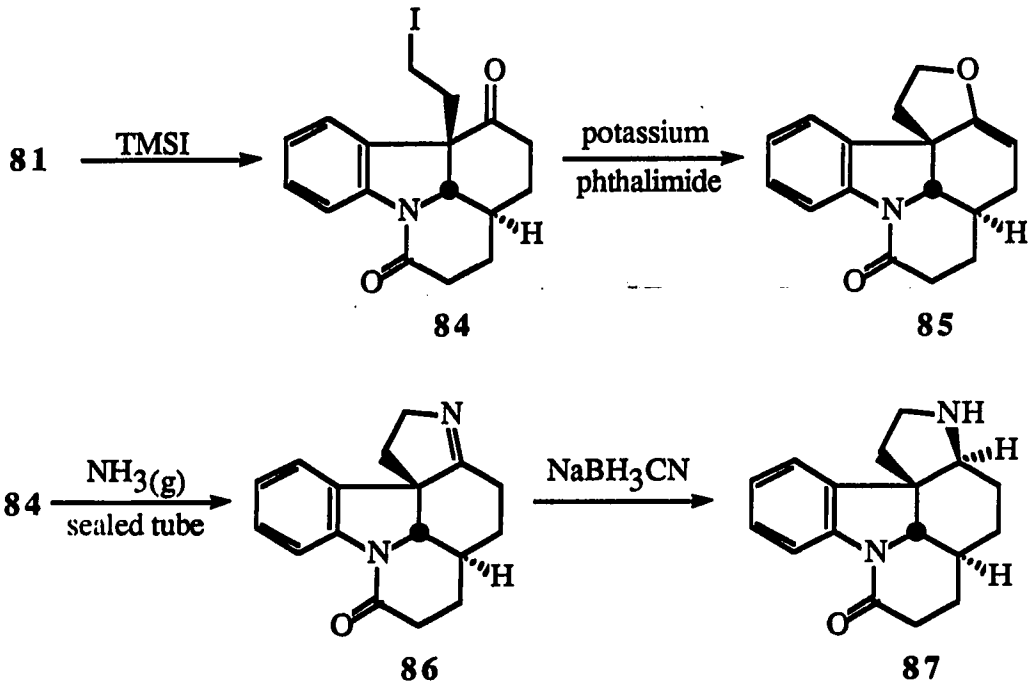
followed by palladium acetate oxidation, provided the unsaturated ketone. The allyl group was put in place under identical conditions to provide the allyl ketone as the only isolated diastereomer!



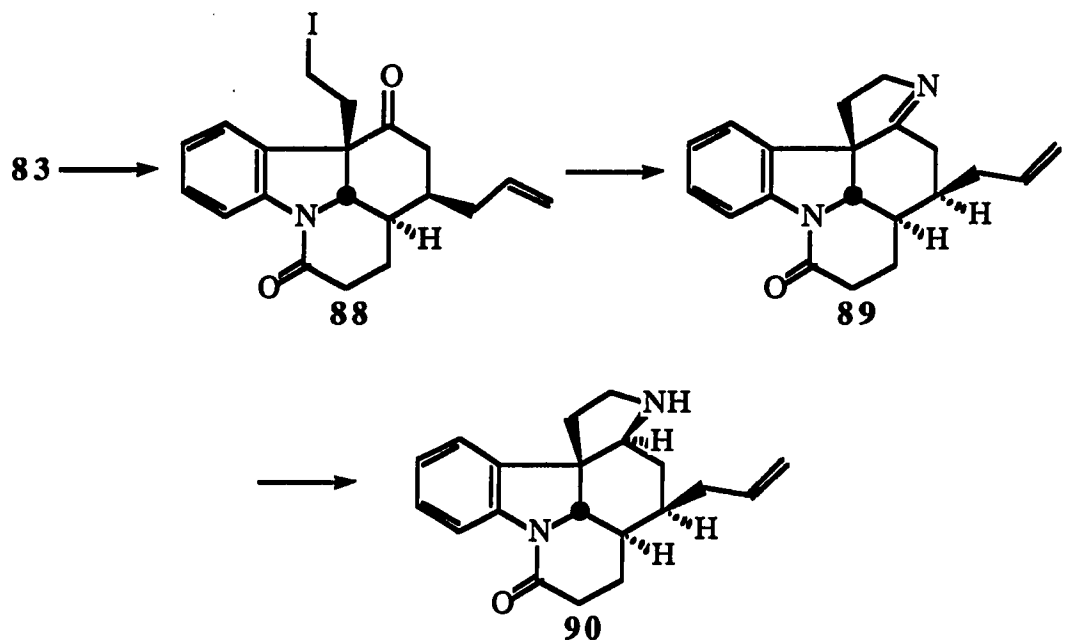
One advantage of this route was that it provided its own model for advanced intermediates. Most of the following reactions have been tried initially on the silyl ether **80** and then extended to the allylated ketone **83.**

With this TBS ether in hand, we required a method to replace the ether with an amine. Oxidative deprotection of the silyl ether with trityl salts[35] returned the hemiketal **80**. Efforts to convert the hemiketal into a ketone with a primary alcohol protected as a suitable leaving group (as a tosylate) proved to be fruitless.

Conversion of the silyl ether **81** to a primary iodide **84** was successful utilizing iodotrimethylsilane.[36] Addition of potassium phthalimide to the primary iodide gave the enol ether **85**. Dissolving this iodide in dichloromethane in a sealable tube, cooling the solution to -78°C, bubbling ammonia gas through the solution, sealing the tube and allowing the mixture to stand at room temperature for 12 h provided the imine **86** in an excellent yield. Reduction of the imine with sodium cyanoborohydride gave the amine **87**.



This sequence was then repeated with the allyl ketone **83** to produce the iodide **88**, the imine **89** and the amine **90**.



At this point it became necessary to verify the stereochemistry of this amine **90**. This was done by 2D NOESY and decoupling experiments. The most important aspects of this information are the NOESY interactions between the doublet at 3.71 ppm with the methylene of the allyl group, and with the methylene of the five-membered amine ring and no interaction with the amine methine proton at 3.63 ppm. Also of importance is the interaction of the aromatic proton and the methine at 3.63 ppm (figures 2a-c).

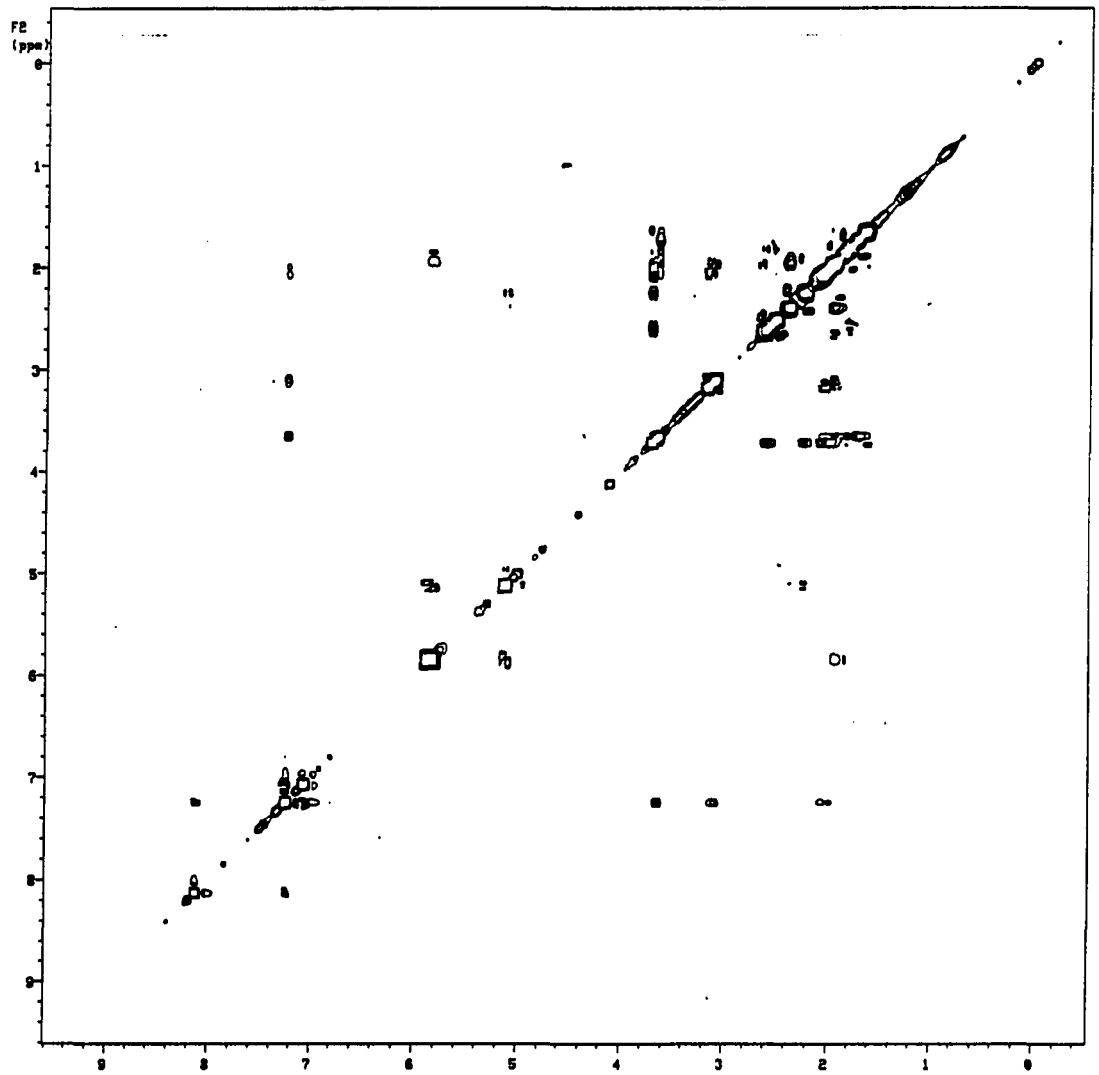


Figure 2a. 2D NOESY map of compound **90**

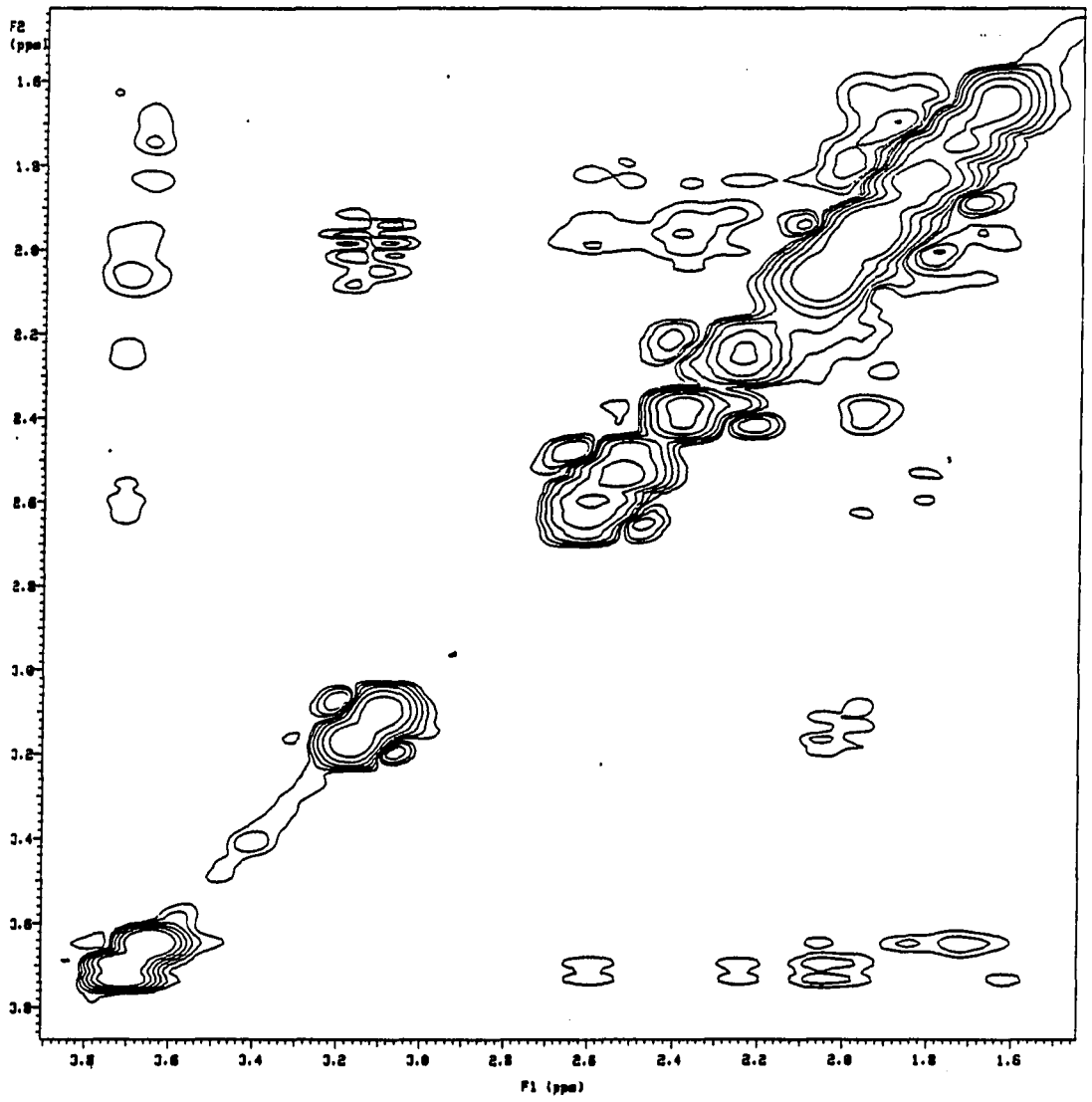


Figure 2b. 2D NOESY map of compound **90**; both x and y axes are expanded from 1.45 to 3.90 ppm

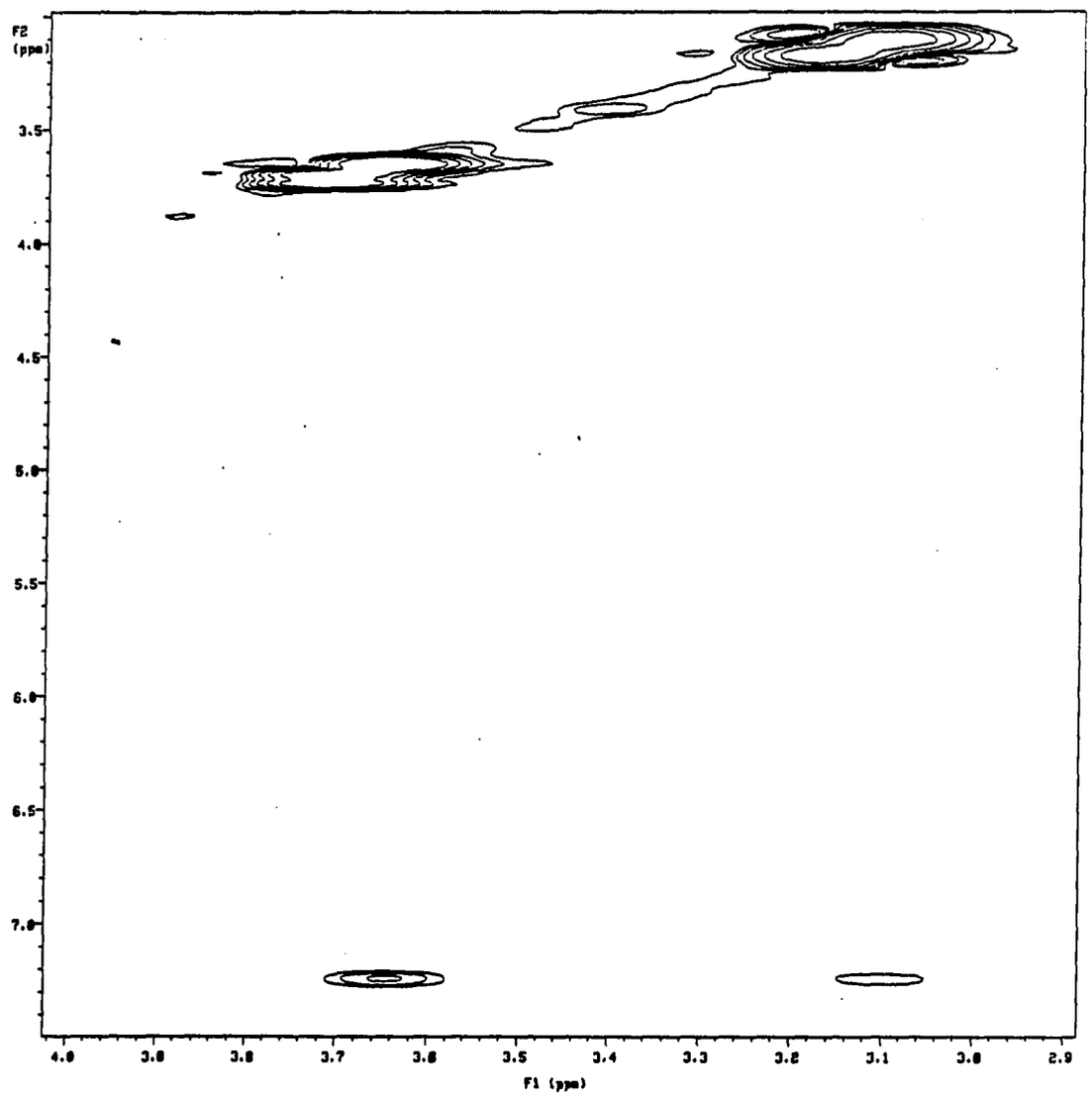
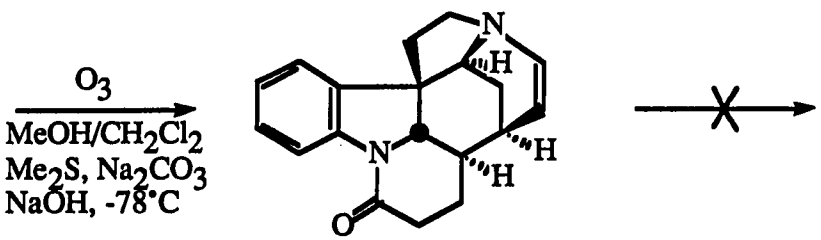


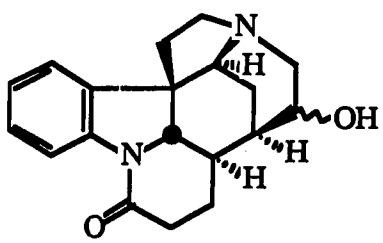
Figure 2c. 2D NOESY map of compound **90**; the x axis is expanded from 2.95 to 3.95 ppm and the y axis is expanded from 3.0 to 7.5 ppm

Formation of ring VI could be accomplished by ozonolysis of the olefin to furnish either a hydroxy amine or an enamine. Protecting the amine as the ammonium salt with trifluoroacetic acid followed by treatment with ozone gave the enamine **91** directly. Unfortunately, this reaction was not very reproducible. Attempts to utilize the enamine by many different methods failed.



91

The reaction of the enamine with 9-BBN, followed by an oxidative workup, gave decomposition. Oxidation with osmium tetroxide gave low yields of the alcohol **92** as a

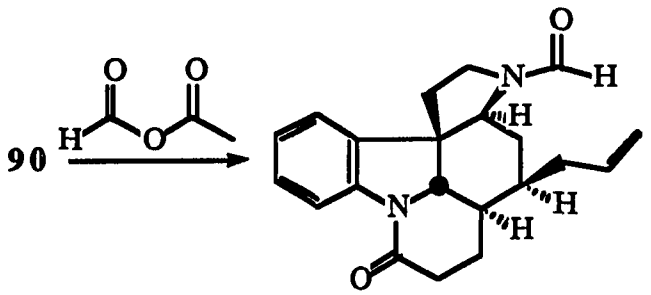


92

1:1 mixture of diastereomers. Reaction with chloroacetyl chloride or acetoxyacetyl chloride failed to give the desired enaminoketone.

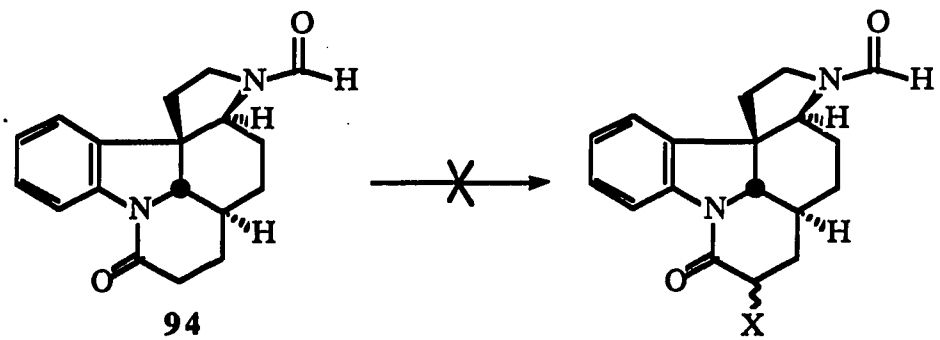
Again, we had to reassess our efforts. If we were to add one carbon to compound **92** the resulting compound would possess all the carbons of the strychnine skeleton. Formation of the formamide **93** by treatment of the amine **90** with acetic formic anhydride proceeded quantitatively. This formamide possesses all the carbon atoms with the proper

functionality to complete this synthesis.



93

At this point we needed to address the formation of an α,β-unsaturated amide from an amide. The use of strong bases (LDA and LTMP) with electrophiles (diphenyl disulfide, phenylsulfinyl chloride, phenylselenenyl bromide) on simple amides have been reported.[37] Utilizing these conditions on the amide **94**, however, did not produce the expected sulfide **95** or selenide **96**. These conditions only returned the starting material.



94

95 X= SPh
96 X= SePh

The formation of the α,β-unsaturated amide did not appear as straight forward as we had thought. This is also evident in work of Woodward et al., where a similar compound was postulated as an intermediate in the conversion of isostrychnine into strychnine. There

was no direct observation of an α,β-unsaturated amide in this conversion.

We have, however, synthesized several hexacyclic compounds with the proper stereochemical orientation for the completion of this project. Both the enamine **92** and the formamide **93** were synthesized in 12 steps from readily available materials. Either of these two compounds are viable intermediates for the completion of this synthesis of strychnine. Work will continue along this route.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. N,N-Dimethylformamide (DMF) was dried with calcium hydride, followed by vacuum distillation. Benzene was distilled from lithium aluminum hydride. Dichloromethane (CH_2Cl_2), 1,2-dichloroethane and acetonitrile were distilled from calcium hydride. Toluene was distilled from sodium. All reactions were conducted under nitrogen atmosphere and all extracts were dried over anhydrous sodium sulfate. The apparatus for experiments requiring anhydrous conditions was flamed-dried under a stream of nitrogen or dried in a 150°C oven for 12h and cooled in a desiccator under nitrogen. Flash chromatography was performed on EM Science Kieselgel 60 (mesh 230-400). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with a thickness of 0.25 mm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA), unless otherwise noted. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300 MHz) were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet); addition of br indicates a broadened pattern. Carbon-13 NMR spectra (75.46 MHz) were obtained on a Nicolet NMC-1280 spectrometer and are reported in δ relative to $CDCl_3$ (77.06 ppm). High resolution mass spectra were obtained on a Kratos model MS-50 spectrometer. Low resolution mass

spectra were obtained on a Finnegan 4023 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories. The purity of all title compounds was judged to be ≥ 90% by ^1H NMR spectral determinations and/ or elemental analysis.

2-(N-(1-Oxo-4-pentenyl)-3-indolyl)ethanone (53): To a stirred suspension of 3-acetylindole (3.18 g, 20 mmol) and triethylamine (4.03 g, 40 mmol) in CH_2Cl_2 (100 ml) at 0°C was added a solution of 4-pentenoyl chloride (2.24 g, 19 mmol) in 25 ml of CH_2Cl_2 over 1 h. The solution was stirred at 0°C for 8 h and then washed twice with ice-cold 2N HCl, once with 2N Na_2CO_3, and once with brine. The organic layer was then dried, concentrated in vacuo, and purified by silica gel flash chromatography (30% ethyl acetate in hexanes) to afford a 79% yield of product: m.p. 94°C; R_f 0.25 (3:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.32-8.46 (m, 2H), 8.12 (s, 1H), 7.35-7.48 (m, 2H), 5.87-6.02 (m, 1H), 5.08-5.24 (m, 2H), 3.07-3.16 (m, 2H), 2.55-2.70 (m, 2H), 2.58 (s, 3H); IR (CH_2Cl_2) 1718, 1662, 1190, 1115 cm^{-1}; MS m/e calc'd for $C_{15}H_{15}NO_2$: 241.1103, found 241.1103; 241, 159, 144, 55.

6-((Trimethylsilyl)oxy)-1-oxo-2,3,3a,4,5,7a-hexahydropyrido-[3,2,1-jk]carbazole (52): To a solution of the N-acylated indole (2.00 g, 8.3 mmol) and diisopropylethylamine (1.78 g, 13.78 mmol) in 40 ml CH_2Cl_2 at 0°C was added trimethylsilyl trifluoromethanesulfonate (TMSOTf) (2.21 g, 9.95 mmol) over 5 min. The solution was stirred at 0°C for 4 h and then allowed to warm to ambient temperature overnight. The solution was diluted with 250 ml of dry hexanes and was stirred for 5 min. The mixture was filtered, and the filtrate was concentrated in vacuo. Hexanes were again added, and the mixture was filtered and concentrated. This procedure was repeated until a

clear oil was obtained. This clear oil was taken on immediately to the next reaction.

The oil was dissolved in 30 ml of dry toluene. To this solution was added hexamethyldisilazane (0.5 ml). The solution was degassed with nitrogen. The tube (Lab Glass Co. LG9375-104) was closed and heated at 270°C for 48 h. The tube was cooled. The toluene was removed in vacuo. The residue was purified by silica gel flash chromatography (35% ethyl acetate in hexanes) to afford 1.30 g of product (65% yield): m.p. 98-100°C; R_f 0.19 (7:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J=7.8 Hz, 1H), 7.51 (d, J=7.4 Hz, 1H), 7.15 (t, J=7.7 Hz, 1H), 7.04 (t, J=7.5 Hz, 1H), 4.26 (dt, J=3.2, 9.7 Hz, 1H), 2.52-2.80 (m, 2H), 2.40-2.48 (m, 2H), 1.50-2.10 (m, 4H), 0.28 (s, 9H); MS m/e calc'd for $C_{18}H_{23}NO_2Si$: 313.14981, found 313.14907; 313, 312, 285, 239, 224, 184, 168, 73; Analysis calc'd for $C_{18}H_{23}NO_2Si$: C, 68.97; H, 7.39; found: C, 68.52; H, 7.39.

1,6-Dioxo-6a-(3,3-diphenyl-2-propenyl)-2,3,3a,4,5,6,6a,7a-octahydropryrido[3,2,1-jk]carbazole (59): To a solution of **52** (1.01g 3.23 mmol) and alcohol **60**[38] (1.43g, 6.8 mmol) in CH_2Cl_2 (30 ml) at -78°C was added $TiCl_4$ (1.82 g, 9.6 mmol) over 3 min. The solution was stirred at -78°C for 6 h. It was quenched at -78°C with H_2O (30 ml). Methylene chloride was added and the layers separated. The organic layer was washed twice with brine, dried, and concentrated in vacuo. The crude product was purified by silica gel flash chromatography (40% ethyl acetate in hexanes) to afford an 80% yield of **59**: m.p. 174-175°C; R_f 0.29 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J=8.0 Hz, 1H), 7.49 (dd, J=1.0, 8.0 Hz, 1H), 6.95-7.45 (m, 12H), 5.70 (dd, J=7.3, 7.9 Hz, 1H), 3.83 (d, J=10.1 Hz, 1H), 2.25-2.85 (m, 6H), 2.00-2.10

(m, 1H), 1.80-1.95 (m, 2H), 1.35-1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.67, 169.52, 146.19, 141.66, 141.15, 139.17, 129.86, 129.60, 128.87, 128.36, 128.10, 127.42, 127.08, 125.59, 124.00, 122.04, 115.60, 67.60, 59.16, 40.89, 37.80, 37.64, 31.23, 25.47, 23.93; IR ($CDCl_3$) 1720, 1660, 1595, 1490, 1480, 1400 cm^{-1}; MS m/e calc'd for $C_{30}H_{27}NO_2$: 433.20419, found 433.20377; 240, 193, 178, 156, 130, 115, 91, 55.

1,6-Dioxo-6a-(2-oxoethyl)-2,3,3a,4,5,6,6a,7a-octahydropyrido-[3,2,1-jk]carbazole (61): To a solution of **59** (0.80 g, 1.85 mmol) in CH_2Cl_2 (50 ml) at -78°C was introduced ozone until the solution turned light blue. The ozone stream was removed and nitrogen was bubbled through the solution until the light blue color disappeared. Triphenylphosphine (0.53 g, 2.04 mmol) was added, and the solution was allowed to slowly warm to ambient temperature. The solution was concentrated in vacuo. The residue was purifid by silica gel flash chromatography (2:3 hexanes-ethyl acetate) to afford 0.38 g (74% yield) of aldehyde **61**: m.p. 208-210°C; R_f 0.24 (2:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.23-7.33 (m, 2H), 7.06 (dt, J=0.7, 7.4 Hz, 1H), 3.77 (d, J=10.5 Hz, 1H), 3.57 (d, J=19.0 Hz, 1H), 2.87 (d, J=19.0 Hz, 1H), 2.45-2.78 (m, 3H), 1.85-2.40 (m, 4H), 1.50-1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.76, 199.44, 172.53, 140.74, 129.49, 129.41, 124.25, 123.57, 116.24, 68.96, 56.60, 54.31, 39.31, 38.47, 31.39, 24.88, 24.78; IR ($CDCl_3$) 1720, 1700, 1670, 1590, 1485, 1385 cm^{-1}; MS m/e calc'd for $C_{17}H_{17}NO_3$: 283.12085, found 283.12048; 254, 240, 226, 198, 184, 170, 130; Analysis calc'd for : C, 72.06; H,

6.05; found: C, 71.90; H, 6.14.

Methyl-1,6-dioxo-2,3,3a,4,5,6,6a,7a-octahydropyrido[3,2,1-jk]-carbazole-6a-acetate (62): To a solution of aldehyde **61** (0.30 g, 1.06 mmol) in *tert*-butyl alcohol (10 ml) was added 4 ml of a 1.25M KH_2PO_4 solution, followed by 6 ml of a 1M solution of $KMnO_4$. This was stirred 15 min, and 10 ml saturated Na_2SO_3 solution was added. The pH of the mixture was adjusted to between 1 and 3 with 2M HCl. This was extracted with CH_2Cl_2 (10 x 20 ml), and the organic extracts were concentrated. To the residue was added Et_2O (30 ml), and the solution was extracted with 2M NaOH (3 x 20 ml). The aqueous layer was acidified (to pH 1) and extracted with CH_2Cl_2 (10 x 10 ml). The organic layer was dried and concentrated to give 0.27 g (85% yield) of the desired acid. The acid was treated with excess diazomethane in CH_2Cl_2 to provide the methyl ester: m.p. 193-194°C; R_f 0.35 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.0 Hz, 1H), 7.23-7.32 (m, 2H), 7.06 (dt, J=1.0, 8.0 Hz, 1H), 3.95 (d, J=11.0 Hz, 1H), 3.68 (s, 3H), 3.38 (d, J=18.0 Hz, 1H), 2.57 (d, J=18.0 Hz, 1H), 2.50-2.80 (m, 4H), 2.22-2.40 (m, 1H), 1.85-2.20 (m, 3H), 1.65-1.83 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 208.12, 172.39, 171.55, 140.58, 129.40, 129.31, 124.04, 123.57, 116.12, 68.78, 55.33, 51.85, 45.73, 39.31, 38.30, 31.32, 24.87; IR (CH_2Cl_2) 1725, 1705, 1670, 1590, 1475 cm^{-1}; MS m/e calc'd for $C_{18}H_{19}NO_4$: 313.13141, found 313.13078; 313, 285, 269, 256, 240, 226, 212, 198, 184, 170.

1,6-Dioxo-6a-(3-aza-2-oxo-4-phenylbutyl)-2,3,3a,4,5,6,6a,7a-octa-hydropyrido[3,2,1-jk]carbazole (63): To a solution of trimethylaluminum (0.53 ml

of a 2M solution in hexanes, 1.1 mmol) in benzene (5 ml) at -5 to -10°C was added benzylamine (0.11 g, 1.0 mmol). This was stirred for 30 min, the cold bath was removed, and the solution was allowed to stir 45 min at 25°C. To this mixture was added the ester **62** (0.29 g, 0.93 mmol) in benzene (10 ml), and the solution was heated at reflux for 24 h. After the solution was cooled to 25°C, 10 ml of 1M HCl was added slowly. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The organic extracts were combined, washed with brine, dried and concentrated. Purification by flash column chromatography yielded 0.15 g (42%) of the desired material: m.p. 135-137°C; R_f 0.14 (1:1 H:EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.0 Hz, 1H), 7.58 (d, J=7.6 Hz, 1H), 7.15-7.45 (m, 6H), 6.99 (dt, J=0.7, 7.5 Hz, 1H), 4.63 (d, J=15.0 Hz, 1H), 4.46 (d, J=15.0 Hz, 1H), 3.66 (s, 1H), 3.40 (d, J=10.3 Hz, 1H), 2.76 (d, J=16.6 Hz, 1H), 2.58 (d, J=16.7 Hz, 1H), 2.35-2.70 (m, 2H), 2.05-2.20 (m, 1H), 1.75-2.00 (m, 3H), 1.50-1.65 (m, 1H), 1.35-1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.06, 173.05, 141.86, 137.98, 130.34, 128.96, 128.54, 127.97, 127.56, 125.30, 124.30, 116.05, 92.87, 69.80, 52.20, 46.22, 42.73, 36.98, 32.18, 31.22, 25.00, 24.13; IR (CH_2Cl_2) 3360, 3050, 1700, 1675, 1595, 1475, 1460 cm^{-1}; MS m/e calc'd for $C_{24}H_{24}N_2O_3$: 388.17870, found 388.17819; 370, 240, 211, 198, 149, 130, 91.

Methyl-6-(trimethylsilyloxy)-2,3,3a,4,6a,7a-hexahydropyrido-[3,2,1-jk]carbazole-6a-acetate (64): To a solution of the ketone **62** (0.58 g, 1.85 mmol) in 1,2 dichloroethane (10 ml) at 0°C were added hexamethyldisilazane (0.78 ml, 3.71 mmol) and triethylamine (0.52 ml, 3.71 mmol). After 5 min, iodotrimethylsilane (0.42 ml, 2.96 mmol) was added. This mixture was allowed to stir for 4 h at 0°C and then

allowed to stir overnight, warming to ambient temperature. The reaction mixture was recooled to 0°C, poured into ice-cold saturated $NaHCO_3$ and extracted with ether (3 x 10 ml). The combined organic extracts were then washed once with ice-cold brine (15 ml), dried and concentrated. The resulting oil was then purified by flash column chromatography using 18 g of silica gel in a 30 mm column with a flow rate of 2.5 inches/min to yield 0.64 g (97%) of the desired material: m.p. 100-101°C; R_f 0.44 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=8.1 Hz, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.24 (dt, J=7.8, 1.2 Hz, 1H), 7.03 (dt, J=7.3, 1.0 Hz, 1H), 4.94 (dd, J=6.9, 1.9 Hz, 1H), 4.35 (d, J=10.8 Hz, 1H), 3.58 (s, 3H), 2.91 (d, J=14.6 Hz, 1H), 2.65-2.75 (m, 1H), 2.55 (d, J=14.6 Hz, 1H), 2.45-2.55 (m, 1H), 2.16-2.19 (m, 1H), 1.90-2.15 (m, 2H), 1.50-1.70 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.30, 170.47, 149.90, 140.14, 133.12, 128.30, 124.88, 123.32, 115.63, 102.14, 65.92, 51.08, 49.40, 44.22, 35.96, 31.22, 26.71, 24.20, -0.05, -0.10; IR ($CDCl_3$) 2950, 1730, 1660, 1590, 1480, 1460, 1400, 1200, 870 cm^{-1}; MS m/e calc'd for $C_{21}H_{27}O_4Si$: 385.1709, found 385.1703; 312, 296, 256, 222, 149, 137.

Methyl-1,6-dioxo-2,3,3a,6,6a,7a-hexahydropyrido[3,2,1-jk]-carbazole-6a-acetate (69): To a solution of the enol silyl ether **64** (0.58g, 1.62 mmol) in acetonitrile (16 ml) was added $Pd(OAc)_2$ (0.40g, 1.79 mmol) as a solid. This was stirred for 48 h at 50°C. The resulting mixture was filtered through a pad of celite, concentrated and purified to yield 0.24 g of the desired α,β-unsaturated ketone and 0.20 g of the saturated ketone which was recycled: m.p. 150-151°C; R_f 0.21 (2:3 H:EA); ^1H

NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J=8.3 Hz, 1H), 7.48 (dd, J=7.9, 1.2 Hz, 1H), 7.31 (dt, J=7.7, 1.3 Hz, 1H), 7.11 (dt, J=7.5, 1.0 Hz, 1H), 6.79 (dd, J=10.0, 1.9 Hz, 1H), 6.28 (dd, J=10.0, 3.0 Hz, 1H), 4.35 (d, J=9.5 Hz, 1H), 3.64 (s, 3H), 3.29 (d, J=17.1 Hz, 1H), 2.75-2.90 (m, 1H), 2.62 (d, J=17.1 Hz, 1H), 2.59 (dd, J=14.0, 1.0 Hz, 1H), 2.20-2.40 (m, 2H), 2.00 (dt, J=11.0, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.54, 173.30, 170.81, 146.14, 141.02, 130.86, 129.60, 128.75, 124.66, 124.26, 116.23, 66.15, 53.53, 51.83, 45.31, 35.94, 31.45, 23.83; IR ($CDCl_3$) 1730, 1670, 1590, 1470, 1460, 1380, 1200 cm^{-1}; MS m/e calc'd for $C_{18}H_{17}O_4N$: 311.1158, found 311.1149; 256, 238, 222, 189, 168, 130.

Methyl-1,6-dioxo-4-(2-propenyl)-2,3,3a,4,5,6,6a,7a-octahydro-pyrido[3,2,1-jk]carbazole-6a-acetate (70): To a solution of the enone **69** (0.68 g, 2.19 mmol) in CH_2Cl_2 (35 ml) at -78°C, was added $TiCl_4$ (0.48 ml, 4.37 mmol). This was stirred 5 min and allyltrimethylsilane (0.87 ml, 5.47 mmol) was added. This mixture was stirred at -78°C for 2 h. The -78°C bath was removed and replaced with an ice bath. The mixture was allowed to stir at 0°C for 2 h, recooled to -78°C and 30 ml of water was added. The -78°C bath was removed and the mixture allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2 and separated. The organic layer was washed with brine, dried, concentrated and purified to yield 0.49 g of the desired material and 0.24 g of the starting material (98% based on recovered starting material): m.p. 170-171°C; R_f 0.29 (3:2 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=7.9 Hz, 1H), 7.25-7.35 (m, 2H), 7.06 (d, J=4.1 Hz, 1H), 5.65-5.85 (m, 1H), 5.09-5.16 (m, 2H), 4.40 (d, J=10.5 Hz, 1H), 3.63 (s, 3H), 3.08 (d, J=16.6 Hz, 1H), 2.67-2.80 (m, 2H),

2.50-2.62 (m, 1H), 2.47 (d, J=16.6 Hz, 1H), 2.35-2.50 (m, 3H), 2.05-2.15 (m, 2H), 1.87-2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.41, 173.26, 170.86, 140.69, 135.91, 130.47, 129.54, 124.05, 122.74, 117.21, 116.34, 66.05, 56.93, 51.60, 42.99, 42.10, 41.33, 34.82, 31.59, 31.00, 21.46; IR ($CDCl_3$) 1735, 1705, 1675, 1590, 1470, 1460, 1380, 1200 cm^{-1}; MS m/e calc'd for $C_{21}H_{23}NO_4$: 353.16271, found 353.16226; 280, 256, 198, 184, 130; Analysis calc'd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; found: C, 71.14; H, 6.75.

Methyl-1,6-dioxo-4-(2-oxoethyl)-2,3,3a,4,5,6,6a,7a-octahydro-pyrido[3,2,1-jk]carbazole-6a-acetate (71): Ozone was bubbled through a solution of the olefin **70** (0.10 g, 0.32 mmol) in CH_2Cl_2 (5 ml) at -78°C until the solution turned light blue. The ozone stream was then replaced with a stream of nitrogen. Nitrogen was bubbled through the solution until the solution was colorless. Triphenylphosphine (0.092 g, 0.35 mmol) was added and the cold bath removed. The mixture was allowed to warm to ambient temperature and the solvent removed. The desired material was purified by flash column chromatography to yield 0.0843 g (74% yield): R_f 0.42 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.10 (d, J=8.1 Hz, 1H), 7.31 (dt, J=1.7, 7.6 Hz, 1H), 7.06 (dt, J=0.7, 7.2 Hz, 1H), 7.01 (dd, J=1.3, 7.6 Hz, 1H), 4.27 (d, J=10.3 Hz, 1H), 3.67 (s, 3H), 3.17 (d, J=17.6 Hz, 1H), 3.13-3.25 (m, 1H), 2.75-2.95 (m, 2H), 2.50-2.75 (m, 4H), 2.42 (d, J=17.6 Hz, 1H), 1.75-2.05 (m, 3H).

Methyl-1,6-dioxo-4-(2-morpholinoethenyl)-2,3,3a,4,5,6,6a,7a-octa-hydropyrido[3,2,1-jk]carbazole-6a-acetate (72): To a solution of the aldehyde **71** (0.0442 g, 0.124 mmol) in benzene (1 ml) with activated molecular sieves was added

morpholine (0.022 ml, 0.25 mmol). This was allowed to stir at room temperature overnight. The mixture was filtered and concentrated to give the enamine (0.052 g) in quantitative yield. This product was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.2 Hz, 1H), 7.25-7.34 (m, 1H), 7.07-7.01 (m, 2H), 5.85 (d, J=13.6 Hz, 1H), 4.94 (dd, J=10.1, 13.4 Hz, 1H), 4.34 (d, J=10.3 Hz, 1H), 4.05-4.40 (m, 1H), 3.64-3.80 (m, 4H), 3.60 (s, 3H), 3.11 (d, J=17.0 Hz, 1H), 2.78-3.00 (m, 5H), 2.47-2.75 (m, 4H), 2.44 (d, J=17.1 Hz, 1H), 1.75-2.10 (m, 2H).

2,9-Dioxo-13a-hydroxy-2,3,10,11,11a,11b,13,13a,14,15-deca-hydro-12*H*-1,12-ethano-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (73): To a solution of the aldehyde **71** (0.0843 g, 0.238 mmol) in methanol (4 ml) were added ammonium acetate (0.18 g, 2.38 mmol) and sodium cyanoborohydride (0.0105 g, 0.166 mmol). This mixture was allowed to stir at ambient temperature for 72 h. The solvent was removed and the residue was taken up in CH_2Cl_2 (10 ml). The organic layer was washed with brine (10 ml) dried and concentrated. Flash column chromatography gave 0.014 g of the desired material (18% yield): R_f 0.19 (EA); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=7.5 Hz, 1H), 7.78 (dd, J=1.0, 7.5 Hz, 1H), 7.30 (dt, J=1.0, 7.5 Hz, 1H), 7.09 (dt, J=1.0, 7.5 Hz, 1H), 4.02-4.10 (m, 1H), 3.46 (d, J=10.3 Hz, 1H), 3.12 (d, J=15.6 Hz, 1H), 2.98-3.10 (m, 1H), 2.55-2.67 (m, 2H), 2.48 (d, J=15.6 Hz, 1H), 2.25-2.32 (m, 1H), 2.18 (dd, J=3.0, 11.4 Hz, 1H), 1.96 (dd, J=3.0, 11.4 Hz, 1H), 1.50-1.85 (m, 5H); IR ($CDCl_3$) 3400(br), 1705, 1680, 1595, 1475, 1460 cm^{-1}; MS m/e calc'd for $C_{19}H_{20}N_2O_3$: 324.14739, found 324.14694; 238, 199, 184, 157, 130.

2,9-Dioxo-13a-acetoxy-2,3,10,11,11a,11b,13,13a,14,15-deca-

hydro-12*H*-1,12-ethano-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (74): To a solution of the alcohol **73** (0.014 g, 0.043 mmol) in CH_2Cl_2 (1 ml) were added 4-(N,N-dimethylamino)-pyridine (DMAP) (0.011 g, 0.086 mmol), acetic anhydride (0.020 ml, 0.22 mmol) and triethylamine (2 drops). The mixture was allowed to stir overnight and diluted with CH_2Cl_2 (10 ml). The organic layer was washed with brine (2 x 10 ml), dried and concentrated. The mixture was purified by preparative thin layer chromatography to yield 6.4 mg of the desired material (40% yield): R_f 0.35 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=8.2 Hz, 1H), 7.69 (dd, J=0.9, 7.8 Hz, 1H), 7.33 (dt, J=1.3, 7.8 Hz, 1H), 7.11 (dt, J=0.9, 7.4 Hz, 1H), 4.09 (dd, J=7.1, 13.8 Hz, 1H), 3.47 (dt, J=5.4, 13.0 Hz, 1H), 3.39 (d, J=10.8 Hz, 1H), 3.07 (dd, J=4.4, 13.6 Hz, 1H), 2.99 (d, J=15.6 Hz, 1H), 2.45-2.71 (m, 3H), 2.41 (d, J=15.6 Hz, 1H), 2.30-2.45 (m, 1H), 2.23 (s, 3H), 1.50-1.90 (m, 5H); IR ($CDCl_3$) 1745, 1705, 1675, 1600, 1475, 1460, 1395, 1290, 1230 cm^{-1}; MS m/e calc'd for $C_{21}H_{22}N_2O_4$: 366.15796, found 366.15860; 324, 307, 238, 200, 184, 130, 96.

2,9-Dioxo-2,3,10,11,11a,11b,13,13a,14,15-decahydro-12*H*-1,12-ethano-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (75): To a solution of the acetate **74** (6.4 mg, 0.017 mmol) in CH_2Cl_2 (1 ml) at 0°C was added triethylsilane (3.1 μl, 0.019 mmol). Trifluoroacetic acid (0.013 ml, 0.17 mmol) was slowly added. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. The solution was diluted with CH_2Cl_2 (10 ml), washed with saturated $NaHCO_3$ and brine, dried and concentrated. The desired material (5.2 mg, quantitative yield) was isolated by

preparative thin layer chromatography: R_f 0.12 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=8.1 Hz, 1H), 7.78 (dd, J=0.9, 7.6 Hz, 1H), 7.30 (dt, J=1.0, 7.8 Hz, 1H), 7.09 (dt, J=0.8, 7.5 Hz, 1H), 4.08 (dd, J=6.6, 13.8 Hz, 1H), 3.36 (d, J=10.7 Hz, 1H), 3.12 (d, J=15.6 Hz, 1H), 3.03 (dt, J=5.5, 13.0 Hz, 1H), 2.45-2.72 (m, 3H), 2.39 (d, J=15.6 Hz, 1H), 2.27 (br dt, J=3.4, 10.6 Hz, 1H), 2.15 (dd, J=4.0, 13.8 Hz, 1H), 1.95 (dd, J=2.6, 13.8 Hz, 1H), 1.50-1.85 (m, 5H); IR ($CDCl_3$) 1700, 1675, 1475, 1460, 1390 cm^{-1}.

12-(2-Propenyl)-13a-hydroxy-2,9-dioxo-1,2,3,10,11,11a,11b,12, 13,13a-decahydro-9*H*-pyrido[1,2,3-lm]pyrrolo{2,3-d]carbazole (76): To a solution of the ester **70** (0.21 g, 0.59 mmol) in MeOH: THF: H_2O (3.6: 3.6: 1) was added lithium hydroxide (0.027 g, 0.65 mmol) as a solid. This mixture was allowed to stir for 4 h at room temperature. The solvent was removed in vacuo and the residue was taken up in 2M HCl (10 ml) and methylene chloride (10 ml). The layers were separated and the aqueous layer was extracted with methylene chloride (5 x 10 ml). The organic layers were combined, dried and concentrated. This residue was taken up in 10 ml of methylene chloride. To this solution was added thionyl chloride (0.77 ml, 1.15 mmol). This mixture was refluxed for 4 h. The solvent was removed in vacuo and benzene was added and removed in vacuo. The residue was dissolved in methylene chloride and transferred to a dry sealable tube. The tube was cooled to -78°C and $NH_{3(g)}$ was bubbled through the solution until the volume had doubled. The tube was sealed and allowed to stand overnight at room temperature. The tube was cooled to -78°C and opened. This was allowed to slowly warm to room temperature. After standing at room temperature for 1 h, nitrogen was bubbled through the solution for 5 min. The solution was then diluted with methylene chloride and brine. The layers were separated and the aqueous layer was extracted with

methylene chloride (3 x 10 ml). The combined extracts were dried and concentrated. Purification by flash column chromatography gave 0.18 g (85% yield) of the desired material: R_f 0.11 (1:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J=8.0 Hz, 1H), 7.44 (d, J=7.5 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.07 (d, J=7.5 Hz, 1H), 6.28 (br s, 1H), 5.15-5.33 (m, 1H), 5.06-5.18 (m, 2H), 3.97 (d, J=12.0 Hz, 1H), 2.73 (d, J=16.7 Hz, 1H), 2.59 (d, J=16.5 Hz, 1H), 2.32-2.60 (m, 3H), 1.70-2.30 (m, 7H); MS (CI (NH_3)) m/e 338 (M+1+NH_3-H_2O), 321 (M+1-H_2O), 298 (M+1-41), 279 (M-H_2O-41).

2,9-Dioxo-13a,15-dihydroxy-2,3,10,11,11a,11b,13,13a,14,15-decahydro-12*H*-1,12-ethano-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (79): Through a solution of the olefin **76** (0.18 g, 0.53 mmol) in CH_2Cl_2 (15 ml) at -78°C was bubbled ozone until the solution turned light blue. Nitrogen was then bubbled through the solution until the solution cleared and dimethylsulfide (0.043 ml, 0.59 mmol) was added. The cold bath was removed and the reaction mixture was allowed to warm to ambient temperature. The solvent was removed and the desired material was purified by flash column chromatography to yield 0.12 g (67% yield): R_f 0.14 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J=7.6 Hz, 1H), 7.76 (dd, J=1.4, 7.9 Hz, 1H), 7.30 (dt, J=1.4, 7.8 Hz, 1H), 7.10 (dt, J=1.0, 7.6 Hz, 1H), 5.83 (d, J=6.1 Hz, 1H), 3.26 (d, J=10.3 Hz, 1H), 3.16 (d, J=16.0 Hz, 1H), 2.77 (dd, J=3.8, 13.3 Hz, 1H), 2.50-2.68 (m, 3H), 2.39 (d, J=16.0 Hz, 1H), 2.22-2.32 (m, 2H), 1.92-2.08 (m, 2H), 1.75-1.90 (m, 2H); IR ($CDCl_3$) 3390 br, 1700, 1675, 1480, 1460, 1390 cm^{-1}; MS m/e calc'd for $C_{19}H_{20}N_2O_4$: 340.14231, found 340.14155; 322, 294, 279, 237, 222, 198, 130.

1,6-Dioxo-2,3,3a,4,5,6,6a,7a-octahydropyrido[3,2,1-jk]carbazole-

6a-ethanol (80): To a suspension of the aldehyde **61** (1.43 g, 5.01 mmol) in HMPA (17 ml) and concentrated H_2SO_4 (0.62 ml, 11.66 mmol) was added the tetra-*n*-butylammonium cyanoborohydride as a solid. This was stirred 20 min, poured into water (40 ml) and extracted with ether (10 x 10 ml). Purification by flash column chromatography yielded 1.22 g (85%) of the desired material: m.p. 197-198°C; R_f 0.29 (2:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J=7.5 Hz, 1H), 7.76 (d, J=7.3 Hz, 1H), 7.26 (dt, J=1.4, 7.8 Hz, 1H), 7.07 (dt, J=1.2, 7.6 Hz, 1H), 4.16 (dt, J=2.0, 7.9 Hz, 1H), 3.98 (q, J=8.4 Hz, 1H), 3.35 (d, J=10.0 Hz, 1H), 2.60-2.75 (m, 1H), 2.35-2.55 (m, 2H), 2.15-2.25 (m, 1H), 1.90-2.10 (m, 2H), 1.25-1.65 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.72, 142.14, 131.19, 128.43, 125.86, 124.15, 115.74, 104.60, 68.15, 64.12, 55.47, 41.11, 38.38, 34.31, 31.56, 25.41, 25.14; IR ($CDCl_3$) 3600 br, 2940, 1675, 1475, 1460, 1390 cm^{-1}; MS m/e calc'd for $C_{17}H_{19}NO_3$: 285.13647, found 285.13649; 285, 267, 226, 198, 184, 168, 156, 130.

1,6-Dioxo-6a-(2-(*tert*-butyltrimethylsilyloxy)ethyl)-2,3,3a,4,5,6,6a, 7a-octahydropyrido[3,2,1-jk]carbazole (81): To a solution of the hemiketal **80** (4.42 g, 15.51 mmol) in DMF (30 ml) at room temperature were added imidazole (2.11 g, 31.02 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (3.51 g, 23.26 mmol). The resulting mixture was allowed to stir overnight at room temperature, poured into water (60 ml) and extracted with ether (5 x 20 ml). The combined organic extracts were washed with brine, dried, concentrated and purified by flash column chromatography to yield 5.25g (85%) of the desired material: m.p. 105°C; R_f 0.45 (1:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J=0.6, 7.8 Hz, 1H), 7.44 (dd, J=1.2, 7.6 Hz, 1H), 7.27 (dt, J=1.2,

7.7 Hz, 1H), 7.08 (dt, J=1.0, 7.5 Hz, 1H), 4.36 (d, J=10.5 Hz, 1H), 3.62 (t, J=5.9 Hz, 2H), 2.50-2.75 (m, 3H), 2.20-2.45 (m, 3H), 2.05-2.15 (m, 1H), 1.55-2.00 (m, 4H), 0.86 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 208.82, 169.94, 140.74, 130.80, 128.49, 125.17, 123.68, 115.56, 67.12, 59.41, 57.49, 43.81, 37.92, 31.13, 25.65, 25.33, 23.96, 18.01, -5.82, -5.88; IR (CH_2Cl_2) 2950, 1705, 1660, 1590, 1480, 1460, 1395 cm^{-1}; MS m/e calc'd for $C_{23}H_{33}NO_3Si$: 399.22297, found 399.22261; 342, 250, 240, 198, 186, 157, 127, 101, 75.

6-(Trimethylsilyloxy)-6a-(2-(*tert*-butyltrimethylsilyloxy)ethyl)-2,3,3a,4,6a,7a-hexahydropyrido[3,2,1-jk]carbazole (82): To a solution of the ketone **81** (1.05 g, 2.63 mmol) in 1,2-dichloroethane (20 ml) at 0°C were added hexamethyldisilazane (1.11 ml, 5.26 mmol) and triethylamine (0.73 ml, 5.26 mmol). This mixture was stirred 5 min and iodotrimethylsilane (0.60 ml, 4.21 mmol) was added. The resulting mixture was stirred at 0°C for 4 h and allowed to warm to room temperature overnight. The mixture was recooled to 0°C and poured into ice-cold saturated $NaHCO_3$. The layers were separated and the aqueous layer extracted with ether (2 x 20 ml). The combined organic extracts were washed once with ice-cold brine, dried, concentrated and the resulting oil purified by flash column chromatography (3:1 hexanes: ethyl acetate, 18 g of silica gel in a 30 mm column with a flow rate of 2.5 in/min) to yield 1.12 g (94%) of the desired material: R_f 0.37 (3:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=8.0 Hz, 1H), 7.51 (d, J=7.7 Hz, 1H), 7.22 (dt, J=1.2, 7.8 Hz, 1H), 7.01 (dt, J=0.6, 7.4 Hz, 1H), 4.97 (dd, J=1.6, 7.0 Hz, 1H), 4.18 (d, J=10.7 Hz, 1H), 3.52-3.65 (m, 2H), 2.42-2.70 (m, 2H), 2.14 (ddd, J=16.0, 7.0, 3.8 Hz, 1H), 1.83-2.05 (m, 4H), 1.47-1.64

(m, 2H), 0.86 (s, 9H), 0.27 (s, 9H), -0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.04, 151.21, 140.46, 134.50, 127.79, 124.82, 123.26, 115.61, 101.82, 66.82, 59.88, 50.26, 43.37, 36.03, 31.27, 26.92, 25.74, 24.40, 24.35, 17.95, 0.14, 0.06, -5.58.

1,6-Dioxo-4-(2-propenyl)-6a-(2-(*tert*-butyltrimethylsilyloxy)ethyl-2,3,3a,4,5,6,6a,7a-octahydropyrido[3,2,1-jk]carbazole (83): To a solution of the inseparable mixture of the saturated and unsaturated ketones (0.34 g) in CH_2Cl_2 (20 ml) at -78°C was added $TiCl_4$ (0.19 ml, 1.71 mmol). This mixture was stirred 5 min and allyltrimethylsilane (0.34 ml, 2.14 mmol) was added. Stirring was continued at -78°C for 2 h, The -78°C bath was replaced with a 0°C bath and stirring was continued for another 2 h. The mixture was then recooled to -78°C and the reaction was quenched by added 20 ml of water. The reaction mixture was diluted with CH_2Cl_2 and the layers separated. The organic layer was washed once with brine, dried and concentrated. Purification by flash column chromatography yielded 0.16 g of the desired material as a single diastereomer and 0.12 g of the saturated ketone: m.p. 107°C; R_f 0.36 (3:1 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J=8.0 Hz, 1H), 7.27 (dt, J=1.3, 7.8 Hz, 1H), 7.21 (dd, J=1.0, 7.4 Hz, 1H), 7.04 (dt, J=1.0, 7.4 Hz, 1H), 5.65-5.81 (m, 1H), 5.13 (d, J=9.2 Hz, 1H), 5.10 (dd, J=1.3, 15.9 Hz, 1H), 4.62 (d, J=10.6 Hz, 1H), 3.51-3.63 (m, 1H), 3.41-3.51 (m, 1H), 2.74 (dd, J=2.0, 17.4 Hz, 1H), 2.46-2.70 (m, 3H), 2.40 (ddd, J=1.4, 5.8, 17.5 Hz, 1H), 2.05-2.20 (m, 2H), 1.88-2.04 (m, 5H), 0.85 (s, 9H), -0.039 (s, 3H), -0.042 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.82, 171.37, 141.04, 135.51, 131.03, 129.09, 123.96, 117.52, 116.06, 64.82, 59.80, 58.32, 43.59, 42.66, 41.55, 34.18,

32.82, 31.70, 25.81, 21.91, 18.03, -5.58, -5.67; IR ($CDCl_3$) 2950, 2925, 1700, 1665, 1590, 1475, 1460, 1390, 1305, 1190, 835 cm^{-1}; MS m/e calc'd for $C_{26}H_{37}NO_3Si$: 439.25427, found 439.25419; 382, 352, 290, 262, 222, 197, 168, 131, 101, 75.

1,6-Dioxo-4-(2-propenyl)-6a-(2-iodoethyl)-2,3,3a,4,5,6,6a,7a-octahydropyrido[3,2,1-jk]carbazole (88): To a solution of the silyl ether **83** (0.35 g, 0.80 mmol) in CH_2Cl_2 (10 ml) at room temperature was added iodotrimethylsilane (0.12 ml, 0.84 mmol) with stirring. This mixture was allowed to stir for 1 h and poured into 10% $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with ether (2 x 10 ml). The combined organic extracts were then washed with brine, dried and concentrated. The resulting oil was purified to yield 0.34 g (96%) of the desired material: m.p. 201°C; R_f 0.34 (7:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J=7.9 Hz, 1H), 7.31 (dt, J=1.2, 7.7 Hz, 1H), 7.22 (dd, J=1.0, 7.7 Hz, 1H), 7.08 (dt, J=1.0, 7.4 Hz, 1H), 5.79-5.64 (m, 1H), 5.15 (d, J=9.9 Hz, 1H), 5.11 (dd, J=1.1, 17.5 Hz, 1H), 4.00 (d, J=10.4 Hz, 1H), 2.96 (ddd, J=4.2, 8.8, 13.5 Hz, 1H), 2.48-2.82 (m, 6H), 2.40 (ddd, J=1.4, 5.4, 17.1 Hz, 1H), 2.32 (dt, J=4.6, 13.2 Hz, 1H), 2.05-2.15 (m, 1H), 1.91-2.05 (m, 3H), 1.67-1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.31, 171.50, 141.06, 134.87, 129.74, 128.61, 124.32, 123.94, 118.00, 116.26, 65.56, 60.20, 45.18, 43.89, 41.56, 34.22, 32.97, 31.66, 21.60, -2.15; IR ($CDCl_3$) 2920, 1700, 1670, 1592, 1475, 1410, 1390, 1280, 1175 cm^{-1}; MS m/e calc'd for $C_{20}H_{22}NO_2I$: 435.06953, found 435.06977; 435, 280, 266, 236, 222, 184.

12-(2-Propenyl)-9-oxo-2,3,10,11,11a,11b,12,13-octahydro-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (89): Ammonia was bubbled through a

solution of the iodide **88** (0.0634 g, 0.146 mmol) in CH_2Cl_2 (10 ml) at -78°C in a sealable tube for 5 min. The tube was sealed and allowed to stand at room temperature overnight. The tube was then cooled to -78°C and the tube opened. After the tube had warmed to ambient temperature for 1 h, nitrogen was bubbled through the solution for 5 min. The solution was diluted with methylene chloride and brine. The layers were separated and the aqueous layer was extracted with methylene chloride. The organic extracts were combined, dried and concentrated. The product was purified by flash column chromatography to give 0.036 g (81% yield) of the desired material: R_f 0.09 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J=7.9 Hz, 1H), 7.27 (dt, J=1.3, 7.8 Hz, 1H), 7.01 (dt, J=0.8, 7.5 Hz, 1H), 6.90 (dd, J=1.1, 7.0 Hz, 1H), 5.66-5.82 (m, 1H), 5.08 (d, J=10.5 Hz, 1H), 5.07 (dd, J=1.3, 17.2 Hz, 1H), 4.00 (dd, J=7.2, 15.5 Hz, 1H), 3.74-3.88 (m, 1H), 3.70 (d, J=10.8 Hz, 1H), 2.88 (dd, J=2.7, 14.2 Hz, 1H), 2.46-2.71 (m, 2H), 2.20-2.35 (m, 2H), 1.60-2.15 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.41, 173.24, 140.23, 135.37, 131.92, 129.14, 124.06, 122.19, 117.40, 116.64, 68.84, 60.07, 57.01, 43.31, 42.71, 35.67, 34.02, 31.69, 30.82, 21.52; IR (CH_2Cl_2) 1670, 1590, 1470, 1455, 1380 cm^{-1}.

9-Oxo-12-(2-propenyl)-1,2,3,10,11,11a,12,13,13a-decahydro-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (90): To a solution of the imine **89** (0.0356 g, 0.116 mmol) in methanol (5 ml) with a trace of bromocresol green was added 2M HCl until the solution turned yellow. Sodium cyanoborohydride (5.1 mg, 0.081 mmol) was added as a solid and 2M HCl was added to just keep the solution yellow. This was stirred for 4 h. The solvent was removed and the residue taken up in 2M NaOH (15 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The organic extracts were dried, concentrated

and purified by flash column chromatography to give 0.032 g of the desired material (90% yield): m.p. 123°C; R_f 0.096 (EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, J=1.4, 8.1 Hz, 1H), 7.27-7.19 (m, 2H), 7.06 (dt, J=1.1, 7.4 Hz, 1H), 5.91-5.76 (m, 1H), 5.11 (dt, J=1.0, 17.0 Hz, 1H), 5.10 (d, J=9.9 Hz, 1H), 3.71 (d, J=11.6 Hz, 1H), 3.63 (t, J=5.2 Hz, 1H), 3.22-3.02 (m, 2H), 2.70-2.44 (m, 2H), 2.44-2.32 (m, 1H), 2.31-2.17 (m, 1H), 2.13-1.57 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.89, 140.43, 137.50, 137.31, 127.92, 123.84, 122.24, 116.35, 115.66, 66.52, 59.66, 52.12, 45.14, 44.25, 39.72, 33.24, 33.00, 31.70, 21.45, 21.36; IR ($CDCl_3$) 2930, 1660, 1592, 1476, 1456, 1395 cm^{-1}; MS m/e calc'd for $C_{20}H_{24}N_2O$: 308.18886, found 308.18890; 265, 251, 236, 223, 198, 168, 144, 130, 56.

9-Oxo-2,3,10,11,11a,11b,13,13a-octahydro-12*H*-1,12-ethano-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (91): To a solution of the amine **90** (0.028 g, 0.092 mmol) in a mixture of CH_2Cl_2 and CH_3OH (5:1, 4.5 ml) was added trifluoroacetic acid (0.014 ml, 0.184 mmol). The resulting mixture was cooled to -78°C. Ozone was bubbled through the solution until the solution turned light blue. The ozone stream was replaced with a stream of nitrogen and nitrogen was bubbled through the solution for 5 min. Dimethylsulfide (3 drops), anhydrous Na_2CO_3 and 2M NaOH (2 drops) were added with stirring and the cold bath was removed. This mixture was allowed to warm to ambient temperature, filtered and concentrated. The crude material was purified by flash column chromatography using one inch of silica gel in a pasture pipet to give the desired material (0.020g, 75% yield): R_f 0.44 (slow decomposition on silica gel) (1:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J=8.1 Hz, 1H), 7.25 (dt, J=1.5, 7.6

Hz, 1H), 7.21 (dd, J=1.2, 7.0 Hz, 1H), 7.10 (dt, J=1.0, 7.4 Hz, 1H), 5.98 (d, J=7.7 Hz, 1H), 4.84 (dt, J=1.2, 6.8 Hz, 1H), 3.72 (br s, 1H), 3.45 (d, J=10.3 Hz, 1H), 3.36 (ddd, J=7.4, 10.0, 12.0 Hz, 1H), 3.16 (ddd, J=4.0, 8.9, 12.4 Hz, 1H), 2.66 (ddd, J=7.8, 11.1, 16.1 Hz, 1H), 2.49 (ddd, J=2.7, 8.2, 16.1 Hz, 1H), 2.32-2.22 (m, 2H), 2.17-2.10 (m, 1H), 1.91-1.70 (m, 4H), 1.49-1.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.20, 141.49, 139.91, 134.15, 128.28, 124.16, 121.86, 116.06, 102.19, 69.37, 59.32, 53.45, 51.53, 47.37, 46.36, 31.72, 28.37, 27.39, 22.54.

N-Formyl-9-oxo-12-(2-propenyl)-1,2,3,10,11,11a,11b,12,13,13a-decahydro-9H-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (93): To a solution of the amine (0.0143 g, 0.0464 mmol) in THF (2 ml) at 0°C were added triethylamine (32.3 μl, 0.232 mmol) and acetic formic anhydride[39] (0.0082 g, 00.0929 mmol). This was allowed to stir overnight, warming to room temperature. The mixture was then diluted with CH_2Cl_2 (10 ml) and washed with brine (2 X 10 ml). The organic layer was dried, concentrated and purified by thin layer chromatography to give 0.0156 g (quantitative yield) of the desired material: R_f 0.17 (1:3 H:EA); ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (s, 0.6H), 8.34 (s, 0.4H), 8.16 (d, J=8.1 Hz, 0.6H), 8.14 (d, J=8.1 Hz, 0.4H), 7.25-7.35 (m, 1H), 6.98-7.17 (m, 2H), 5.64-5.85 (m, 1H), 5.00-5.18 (m, 1H), 4.45 (t, J=6.3 Hz, 0.4H), 4.08-4.18 (m, 1.6H), 3.75-3.92 (m, 2H), 3.61-3.73 (m, 1H), 3.48-3.61 (m, 1H), 2.50-2.68 (m, 2H), 2.34-2.48 (m, 1H), 1.55-2.30 (m, 7H).

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OVERALL CONCLUSION

The intramolecular Diels-Alder reaction has been known for many decades. We have studied this reaction with regard to the indole nucleus and have applied our new found knowledge in an approach toward the synthesis of strychnine.

Our initial efforts indicate that the indole nucleus can participate in an intramolecular Diels-Alder reaction as either the 2π or the 4π component. In these efforts it was determined that an amide or an urea moiety could be utilized as part of the tether joining the diene and the dienophile. However, no success was found in using a carbamate as part of the tether.

Our later efforts have concentrated on extending this intramolecular Diels-Alder reaction to the synthesis of strychnine. Although we have not completed this goal, we have synthesized several advanced intermediates. Both the enamine **91** and the formamide **93** were synthesized in 12 steps from readily available materials.

Many obstacles have been overcome, including selective functional group manipulations and the addition of an allyl group with remarkable stereo-control. There does, however, remain one obstacle that our initial efforts did not surpass. That is the conversion of an amide into an α,β-unsaturated amide. Efforts in this area will continue.

ACKNOWLEDGEMENTS

As I think about what to write on this page, I realize that there are many people who have had a hand in this work. I would like to thank Dr. George A. Kraus for his guidance and friendship throughout my graduate career. His continued enthusiasm has made my work here very enjoyable.

I would also like to take this opportunity to thank Dr. David Klopotek for his guidance and friendship throughout my undergraduate and graduate education. He is one of the people who opened the doors of organic chemistry for me.

I also must express my gratitude to members of the Kraus group, both present and past, especially P. J. Thomas, Jeff Raggon, Steve Laramay, Mark Schwinden and Jackie Applegate.

All of these aforementioned people have molded me into the chemist I am today and have laid the foundation for the chemist I will become.

I would also like to thank my wife, Julie, for her continued understanding. Only she can comprehend the frustration and joy of graduate work and offer the support needed to overcome the tough times. I would like to thank my parents, Cliff and Shirley, who have made me the person I am today. Their support encouraged me to continue my education and to appreciate the important things in life.

Finally, I would like to thank John Sowa and Mike Schmitz for their friendship and for helping to complete a foursome.