The Evolution of a Heterocyclic Chemist. From Photochemistry to Alkaloids

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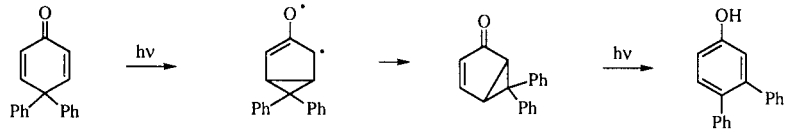
Retracing a road traveled over the past thirty-five years provides for a nostalgic journey, both in terms of the scientific challenges along the way as well as the many pleasant interactions with numerous collaborators who populated my laboratory at three different universities. This lecture constitutes a personal account of how our current projects in the area of heterocyclic synthesis developed over a period of three decades. It begins with some of the early success we achieved in the area of mechanistic organic photochemistry that eventually led us into the field of alkaloid synthesis.

The story commences in 1962 at the University of Wisconsin, where I was employed as an NSF postdoctoral research associate under the tutelage of Howard E. Zimmerman. Having been trained as a physical organic free radical chemist with Cheves Walling at Columbia University [1], I decided to broaden my horizon and work in the area of organic photochemistry studying the di-π-methane photorearrangement of cyclohexadienones (Scheme I) [2]. At that time, I was also eager to gain academic employment and find a research area of my own. In this connection, I was intrigued by the possibilities that were offered by using a "photon of light" for organic synthesis.

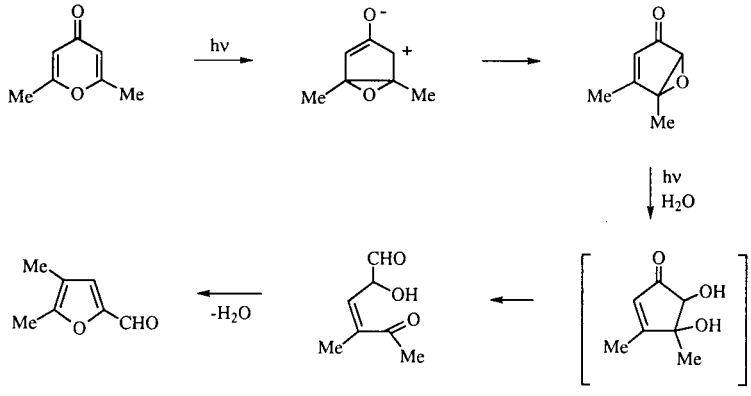
In early 1963, the late Peter Yates published a paper in the *Journal of the American Chemical Society* describing the photochemistry of several 4-pyrone derivatives [3]. Contained within the manuscript was a brief description of an unusual photorearrangement reaction whereby a dimethyl substituted 4-pyrone was transformed into an isomeric furan aldehyde on exposure to uv light. I reasoned that the transformations shown in Scheme II must have taken place. The key step seemingly involved a di-π-methane reaction of the starting 4-pyrone to produce a transient epoxy ketone as an intermediate. I found this to be a rather novel photorearrangement and made a mental note to keep track of any future developments in the area of epoxy ketone photochemistry.

Armed with an understanding of the principles of organic photochemistry and some good advice from Howie Zimmerman, I migrated east to start an Assistant Professorship at Ohio State University in Columbus, Ohio.

Scheme I

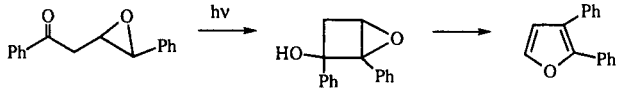


Scheme II



I was now in a position to write a modest research grant to the Petroleum Research Fund proposing a study of the excited state behavior of α,β-epoxy ketones [4]. I was encouraged by the alacrity with which my new colleagues (especially Paul Gassman and Leo Paquette) accepted the feasibility of my proposal. It was at this point that I was joined by my first graduate student, Richard Hartman, who undertook an exploration of this chemistry as part of his efforts to obtain a Ph. D. degree. During the course of his work, I thought it worthwhile to extend our investigations toward β,γ-epoxy ketones and so we discovered another interesting photorearrangement whereby the epoxy ketone shown in Scheme III was converted into 2,3-diphenylfuran [5]. With some care, it was possible to isolate a labile epoxy cyclobutanol derivative formed by γ-hydrogen abstraction followed by biradical coupling. Treatment of this tertiary alcohol with a trace of acid afforded our first legitimate heterocycle.

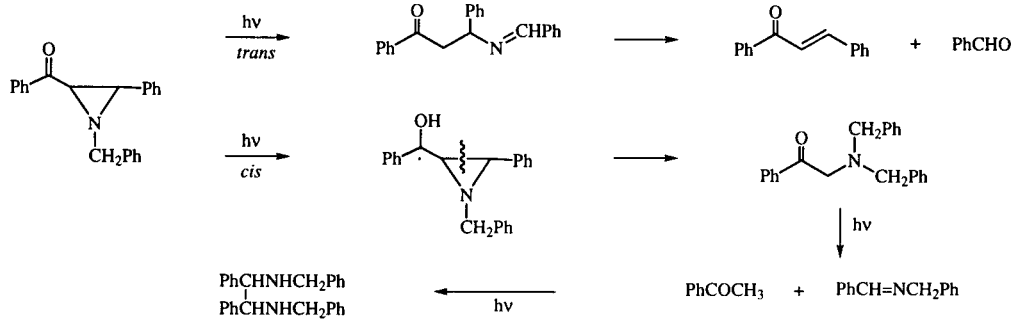
Scheme III



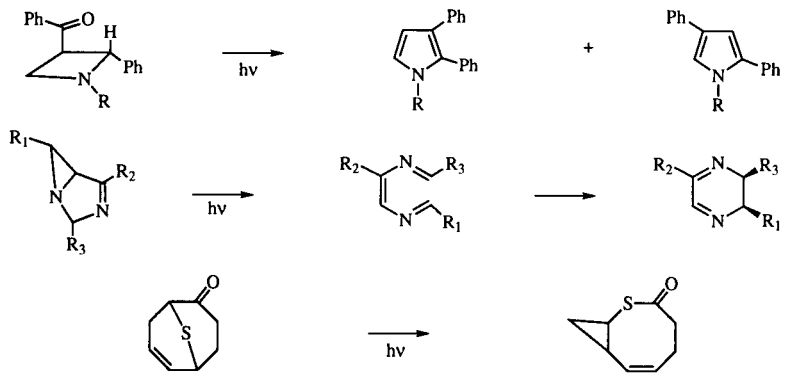
By the end of my first year at OSU, we had tested a range of epoxy ketones and started to extend our photochemical studies toward the structurally related aziridine system [6]. In early 1964 Lou Hamilton, my second Ph. D. student, set about to examine the photochemical behavior of several *cis* and *trans* benzoyl aziridines shown in Scheme IV [7]. At first, we were surprised to discover such fundamentally different photobehavior from this class of small ring heterocycles. The *trans*-isomer underwent a photoinduced Norrish type II reaction to eventually produce benzaldehyde and chalcone *via* a ring opened intermediate. Since it was not possible for the *cis*-isomer to undergo a related internal hydrogen transfer due to steric crowding, bimolecular abstraction occurred ultimately providing an amino-substituted ketone. A subsequent photoreaction *via* electron transfer [8] produced a benzaldimine derivative which was further converted into a 1,2-diamine by a novel chemical sensitization reaction [9].

In the fall of 1966 I was offered an Associate Professorship at the State University of New York at Buffalo and decided to return to my native state. At SUNY Buffalo we continued our ongoing photochemical program using a variety of heterocyclic systems and encountered some remarkably interesting photorearrangements along the way [10]. A few of the many systems that were examined are outlined in Scheme V.

Scheme IV



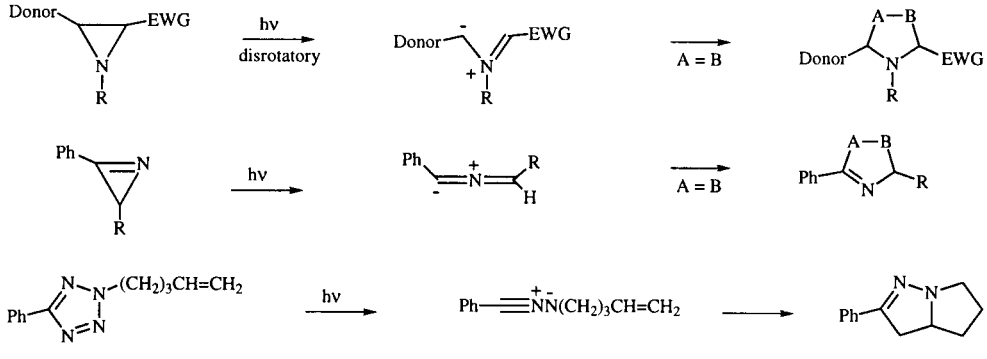
Scheme V



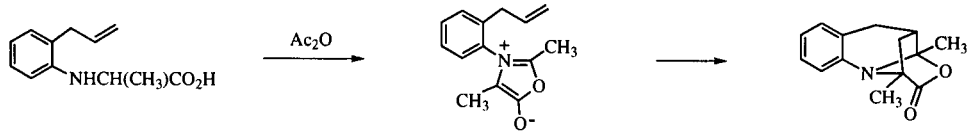
It was in the late 60's that Lou Hamilton made an experimental observation that eventually directed us toward the field of alkaloid synthesis. In connection with his photochemical studies, Lou noticed that several of the benzoyl aziridines he was working with developed a deep pink coloration on exposure to light and this pink coloration faded on standing in the dark. The colored species produced in this photoinduced reversible reaction was assigned as a 1,3-dipole (*i.e.*, azomethine ylide) [11]. In a series of investigations, we proceeded to study the photochemical cleavage reaction of aziridines and their 1,3-dipolar additions to reactive multiple π-bonds (Scheme VI) [12]. We soon discovered that irradiation of the closely related 2*H*-azirine system resulted in irreversible ring opening and formation of a nitrile ylide as a reaction intermediate [13]. This dipole was intercepted with a variety of dipolarophiles to furnish five-membered heterocycles. Over the next several years we came to recognize that the 1,3-dipolar cycloaddition reaction, popularized by Rolf Huisgen and his students [14], represents an astonishingly fruitful synthetic method for the synthesis of five-membered heterocycles. Numerous possibilities for variation are possible by simply changing the structure of both the dipolarophile and dipole. In the early 70's we made extensive use of photochemical activation as a method to generate a wide assortment of 1,3-dipoles and to study their cycloaddition chemistry [15].

By 1977 we had abandoned our photochemical program and had immersed ourselves in research which focused primarily on various aspects of dipolar cycloaddition chemistry [16]. The facility of the [3+2]-cycloaddition, the rapid accumulation of functionalities in a relatively small molecular framework, the high stereochemical control of the cycloaddition, and the good predictability of its regiochemistry were some of the factors that led us in this direction. Some of the various systems that were examined during this period of time are shown in Schemes VII and VIII. Studies were carried out using mesoionic heterocycles such as sydnones and münchnones as a method to synthesize various pyrroles and pyrrolidines [17].

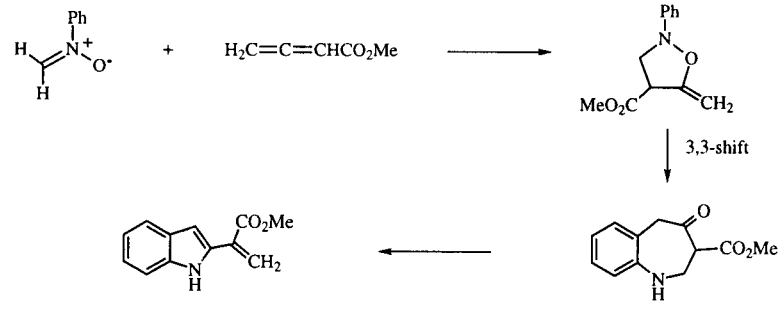
Scheme VI



Scheme VII



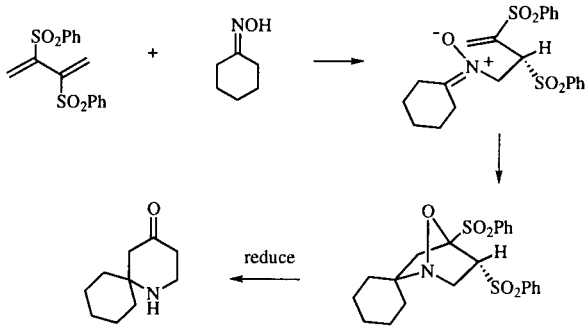
Scheme VIII



The 1,3-dipolar cycloaddition chemistry of nitrones was found to be an extremely powerful method to prepare nitrogen containing heterocycles. We used the [3+2]-cycloaddition reaction of *N*-phenyl-*C*-nitrones with activated allenes as a method to prepare vinyl substituted indole derivatives as shown in Scheme VIII [18].

Related nitrone studies were carried out using the reaction of oximes with 2,3-*bis*(phenylsulfonyl)-1,3-butadiene [19]. The reaction gave rise to a bicyclic isoxazolidine by initial conjugate addition of the oxime onto the diene. The resulting nitrone undergoes a subsequent intramolecular dipolar cycloaddition to produce the bicyclic adduct. The isoxazolidine derived from cyclohexanone oxime and *bis*(phenylsulfonyl)diene was converted to the azaspiro[5.5]undecane ring system, which is representative of the key skeleton of the perhydrohistrionicotoxin family of alkaloids (Scheme IX).

Scheme IX

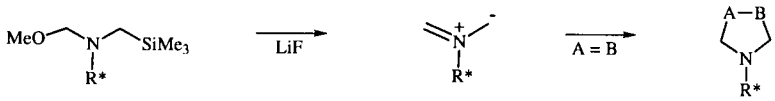


The 1,3-dipolar cycloaddition of azomethine ylides also attracted our attention as a particularly appealing method for pyrrolidine synthesis, especially since this ring system is found in many alkaloids. The desilylation reaction of *N*-(trimethylsilyl)methylamino ethers was found to be a very convenient method for azomethine ylide generation [20]. Treatment of these compounds with lithium fluoride in the presence of a reactive dipolarophile afforded dipolar cycloadducts in high yield. Our interest in the asymmetric synthesis of substituted pyrrolidine derivatives by this process led us to study the [3+2]-cycloaddition of chiral azomethine ylides. The dipole precursors were prepared from enantiomerically pure α-methylbenzylamines and the diastereoselectivity of the [3+2]-cycloaddition was studied in some detail (Scheme X) [21].

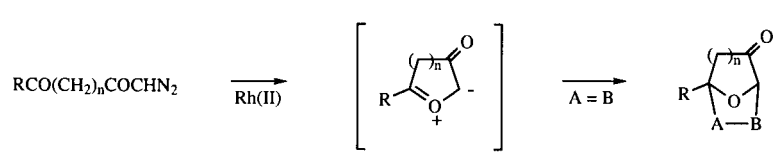
It was in late January of 1977, that a winter storm dropped more than four feet of snow in Buffalo. By the early afternoon I was stranded in my office since a state of emergency was in effect, with all non-essential vehicles barred from the streets. Because the roads were impassable, I was unable to return to my home for three days. It was during this period that I received a phone call from Leon Mandell, chairman of the chemistry department at Emory University. This initial contact eventually led to my moving to Emory University (Atlanta, Georgia) during the summer of 1979. Soon thereafter, we started a program at Emory dealing with intramolecular dipolar cycloaddition chemistry [22]. We rapidly discovered that when the reacting components are themselves cyclic or contain ring substituents, complex multicyclic arrays such as those contained in drugs and natural products could be constructed in a single step.

A major challenge in organic synthesis is to devise reactions that can form several carbon-carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control. In a series of papers published in the late 80's, we described the formation of bridged oxabicyclo[3.2.1]heptanes from the rhodium(II)-catalyzed reaction of 1-diazopentanediones (Scheme XI) [23]. The reaction involves the formation of a rhodium carbenoid and subsequent transannular cyclization of the electrophilic carbon onto the adjacent keto group to generate a cyclic carbonyl

Scheme X



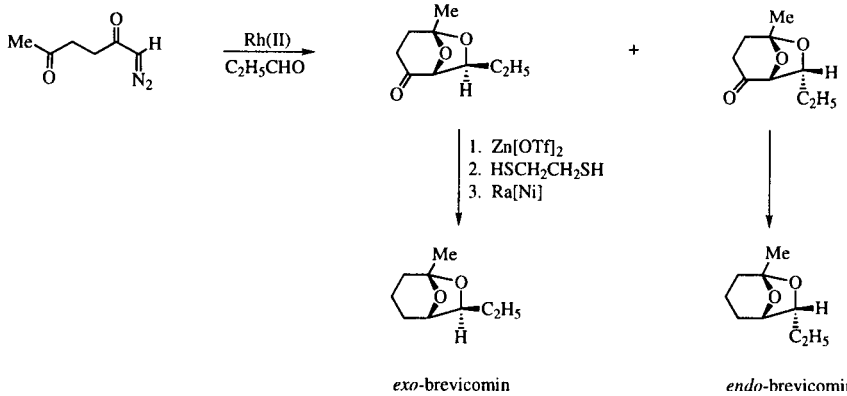
Scheme XI



ylide, followed by 1,3-dipolar cycloaddition. Application of this methodology toward the synthesis of both *exo*- and *endo*-brevicomin was carried out [24]. The *exo* and *endo* isomers of brevicomin are exuded by the female Western Pine Beetle and the *exo* isomer is known to be a key component of the aggregation pheromone of this destructive pest. Cycloaddition of 1-diazo-2,5-hexanedione with rhodium(II) acetate using propionaldehyde as the dipolarophile afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in high yield as a 2:1-mixture of *exo* and *endo* isomers. Separation of the diastereomers followed by reduction of the carbonyl group afforded *exo* and *endo*-brevicomin in good yield (Scheme XII).

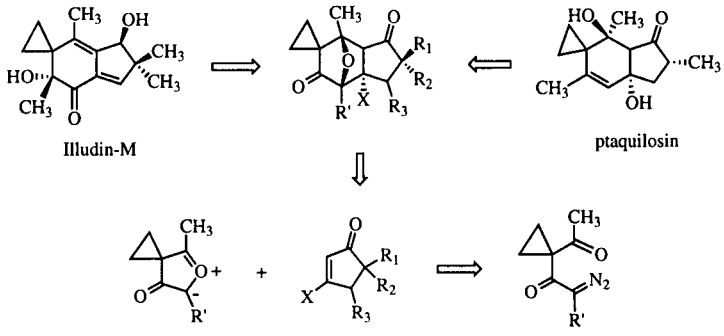
We soon discovered that products of five-membered carbonyl ylide cycloadditions derived from the cyclopropyl diazoketone shown in Scheme XIII could be

Scheme XII



exo-brevicomin *endo*-brevicomin

Scheme XIII

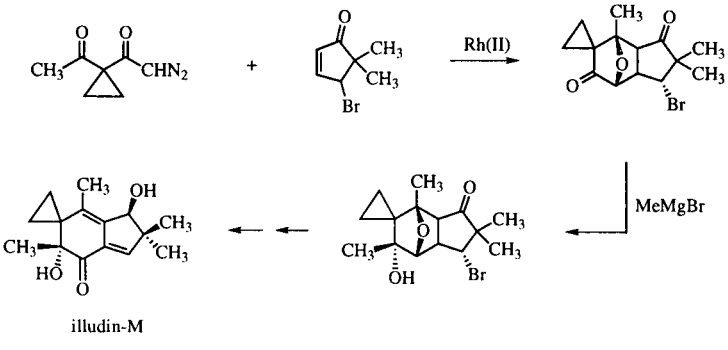


induced to undergo cleavage of the oxabicyclic ring system to produce the core structure of the illudin and ptaquilosin family of sesquiterpenes. This strategy provided for a rapid assembly of the basic core unit of these novel target molecules with most of the requisite functionality already in place [25].

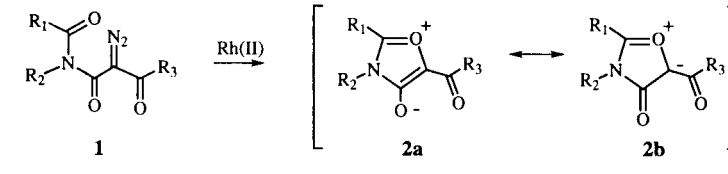
(±)-Illudin-M, a toxic sesquiterpene isolated from the Jack-o-lantern mushroom, has been synthesized *via* this strategy [26]. The key step of the synthesis consisted of a carbonyl ylide 1,3-dipolar cycloaddition reaction with a substituted cyclopentenone to form a dipolar cycloadduct which underwent cycloaddition with high diastereoselectivity. Several functional group manipulations were carried out to eventually give illudin M (Scheme XIV).

By the 90's we started work in our laboratory to synthesize ring-fused polyheterocycles based on a *sequential cycloaddition-N-acyliminium ion cyclization* process [27]. These two types of reactions provided an opportunity for linking two disparate ring forming reactions in a novel sequential manner. The combination of a sequence of individually powerful methods often has a value significantly greater than the sum of individual reactions and has become of great interest to the synthetic community. We believed that this protocol would provide one-pot access to target molecules possessing a high degree of complexity which would otherwise require technically demanding multi-step syntheses. Our early studies showed that 1,3-oxazolium-4-oxides (isomünchnones) **2** can be generated by the rhodium(II)-catalyzed cyclization of a suitable diazo imide **1** (Scheme XV) [28]. This type of mesoionic ylide corresponds to the cyclic equivalent of a carbonyl ylide and was found to readily undergo [3+2]-cycloaddition

Scheme XIV

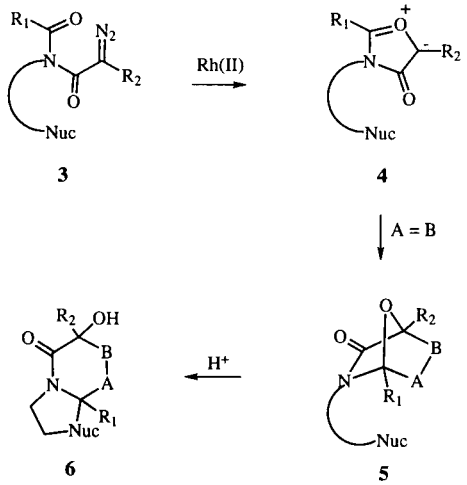


Scheme XV



with suitable dipolarophiles. Construction of the prerequisite diazo imides necessary for betaine generation was accomplished by the transformation of the corresponding carboxylic acids to their respective amides. Conversion to the diazo imides was straightforward using established malonylacylation and diazotization procedures [29]. Formation of the isomünchnone ring proceeds by initial generation of a rhodium carbenoid species, followed by an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic ylide **2**. The resultant isomünchnone may be trapped with electron rich or electron deficient dipolarophiles to give the cycloadducts in high yield. These uniquely functionalized cycloadducts (*i.e.*, **5**) contain a "masked" *N*-acyliminium ion which is generated by treatment with a Lewis acid [30]. By incorporating an internal nucleophile on the tether, annulation of the original cycloadduct **5** allows for the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologues of the erythrinane family of alkaloids. Starting from simple acyclic diazo imides **3**, we established a *domino carbenoid cyclization-[3+2]-cycloaddition-cationic π-cyclization protocol* as a method for the construction of complex nitrogen polyheterocycles of type **6** (Scheme XVI). This sequence represented the

Scheme XVI



3 4 5 6

first example where a [3+2]-cycloaddition and *N*-acyliminium ion cyclization were coupled in a one-pot sequence. The novelty of the process lies in the method of *N*-acyliminium ion generation, which to our knowledge, was unprecedented. *N*-Acyliminium ions are traditionally generated from the *N*-acylation of imines, *N*-protonation and oxidation of amides, electrophilic additions to enamides, and the heterolysis of amides bearing a leaving group adjacent to nitrogen [31]. These reactive intermediates readily react with a wide assortment of nucleophiles to effect an overall α-amido alkylation.

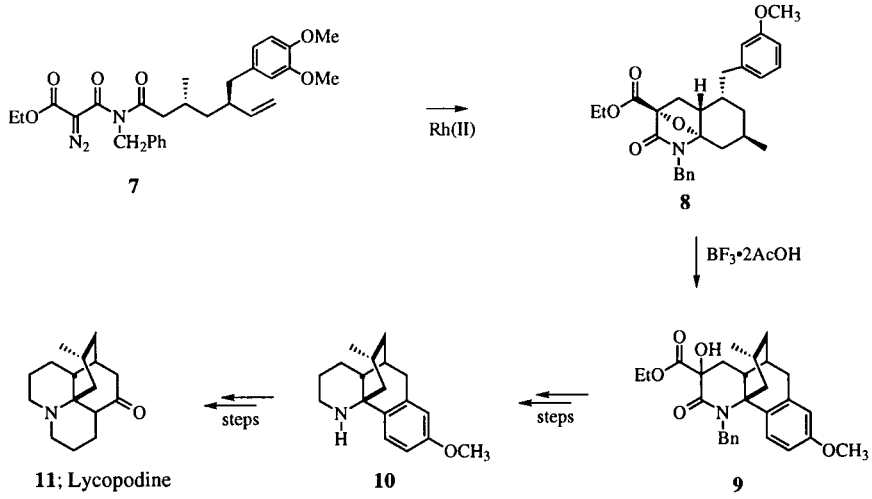
An early application of the domino cascade process toward the construction of alkaloids involved the synthesis of (±)-lycopodine (**11**) (Scheme XVII) [32]. The isomünchnone cycloadduct **8** was formed from the Rh(II)-catalyzed reaction of diazo imide **7** and was found to be the precursor of the key Stork intermediate **10** (*via* **9**). Our plan involved formation of **9** by a Pictet-Spengler cyclization of the *N*-acyliminium ion derived from **8**. Central to this strategy was the expectation that the bicyclic iminium ion originating from **8** would exist in a chairlike conformation [33,34]. Indeed, cyclization of the aromatic ring onto the *N*-acyliminium ion center readily occurred from the axial position [35]. The rearranged product **9** was then converted into the key intermediate previously used by Stork for the synthesis of (±)-lycopodine **11**.

Prompted by our work dealing with the internal [3+2]-cycloaddition reaction of mesoionic oxazolium ylides, we became interested in the rhodium(II)-catalyzed reactions of diazo ketoamides such as **12**. Attack of the amido oxygen on to the rhodium carbenoid produced a carbonyl ylide dipole (*i.e.*, **13**) that is isomeric with the isomünchnone class of mesoionic betaines (**4**). We found that the rhodium(II)-catalyzed formation of carbonyl ylide intermediates derived from cyclic diazo amides furnished tetracycles such as **14b** in good yield, provided that the tether engaged in ring formation carried a carbonyl group (*i.e.*, **12b**, X = O) (Scheme XVIII) [36].

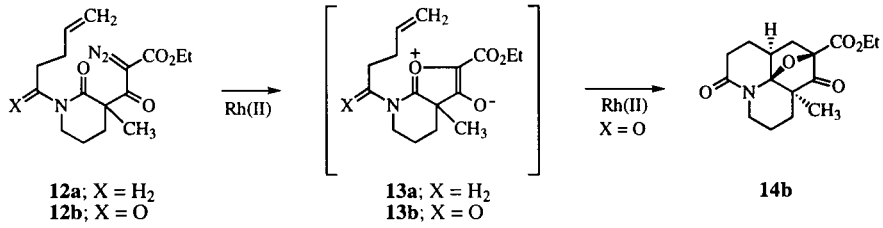
Without the C=O functionality (*i.e.*, **12a**, X = H_2), only decomposition products were observed. By performing *ab initio* transition state geometry optimizations, we learned that a severe cross-ring 1,3-diaxial interaction caused by the bridgehead methyl group promoted a boat or twist-boat conformation in the piperidine ring fused to the newly forming one. The presence of a carbonyl group on the tether apparently helps to relieve the steric congestion by favoring a second boat conformation in the latter ring. When the side chain is devoid of a carbonyl group, the calculated reaction barrier is much larger, thereby permitting competing processes to intervene. Thus, the reactivity discrepancy between diazo amido esters **12a** and **12b** can be attributed to steric effects in the transition states.

As an extension of these studies, we developed a fundamentally new approach to the construction of the pentacyclic skeleton of the aspidosperma ring system which involved a related domino cascade sequence [37]. This strategy was successfully applied to the synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine (**15**). The approach used is outlined in Scheme XIX and is centered on the construction of the key oxabicyclic intermediate **16**. We reasoned that **15** should be accessible by reduction of the *N*-acyliminium ion derived from **16**, which, by analogy with our previous work, should be available by

Scheme XVII



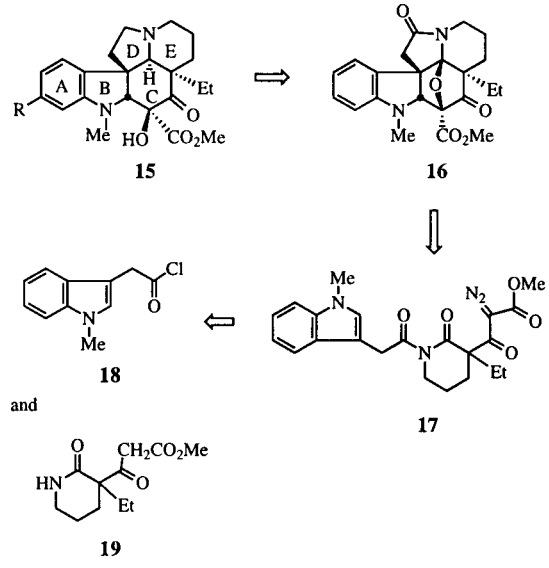
Scheme XVIII



the *tandem rhodium(II)-catalyzed cyclization cycloaddition* of α-diazoimide **17**. Cycloaddition of the initially formed dipole across the pendant indole π-system [38] would be expected to result in the simultaneous generation of the CD-rings of the aspidosperma skeleton [39]. The stereospecific nature of the internal cycloaddition reaction should also lead to the correct relative stereochemistry of the 4 chiral centers about the C-ring. Recent work in our laboratory has verified the underlying viability of this approach for the synthesis of the aspidosperma skeleton (Scheme XIX).

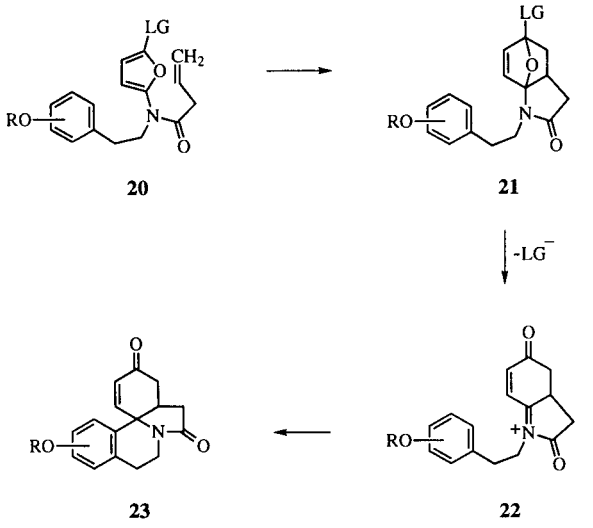
In a more recent phase of our research, we decided to reconsider some aspects of our domino cascade strategy. It occurred to us that we could also utilize a series of 2-amino substituted furans for the critical [4+2]-cycloaddition step rather than the highly reactive 1,3-dipole, which on occasion, was prone to undergo hydrolytic decomposition. Our long-range goal involved using 2-amino-substituted furans such as **20** that contain both a suitable leaving group (LG) and an olefinic tether to allow for an intramolecular Diels-Alder reaction (Scheme XX). The resultant cycloadduct was expected to undergo ring

Scheme XIX

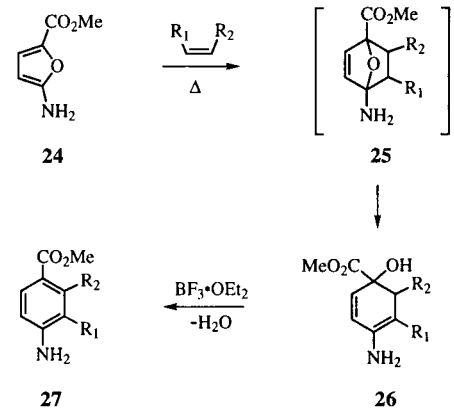


opening to generate a vinylogous C-acyliminium ion of type **22**. Our intention was to use this sequence of reactions for a rapid entry into the erythrinane family of alka-

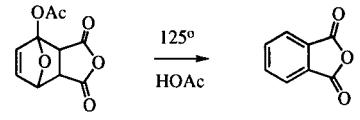
Scheme XX



Scheme XXI



Scheme XXII



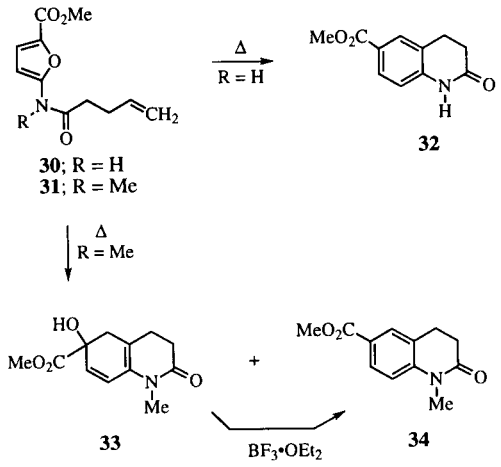
loids. With this goal in mind, some model studies were undertaken to determine the facility with which 2-aminofurans would undergo Diels-Alder cycloadditions [40].

Heterocycles such as furan, thiophene and pyrrole undergo Diels-Alder reactions despite their stabilized 6π-aromatic electronic configuration [41]. Molecular orbital calculations show that the presence of an electron donating substituent such as an amino group in the 2-position of the furan nucleus increases its highest order molecular orbital energy relative to that of furan [42]. A significant increase in the highest order molecular order coefficient at the C-5 position compared to that at the C-2 position also occurs, consistent with an increase in electron density at that position due to resonance interaction with the amino substituent. In this regard, we have recently demonstrated that simple 2-aminofurans such as **24** react with various dienophiles in an intermolecular fashion with high regioselectivity. The initial cycloadducts were not isolated, as they readily undergo ring opening to cyclohexadienols **26**, assisted by the lone pair of electrons on the adjacent nitrogen atom (Scheme XXI). The influence of the amino group is evident by the extremely facile cleavage of the oxybridge intermediates under the thermal conditions used in the reaction. This behavior stands in contrast to the related oxabicyclic system **28**, which was reported to undergo ring cleavage only when treated with acetic acid at elevated temperatures (125°) (Scheme XXII) [43].

The intramolecular Diels-Alder reaction of furans, often designated as *IMDAF*, helps to overcome the sluggishness of this heteroaromatic ring system toward [4+2]-cycloaddition. Not only do *IMDAF* reactions allow for the preparation of complex oxygenated polycyclic compounds, they often proceed at lower temperatures than their intermolecular counterparts [44]. Even more significantly, unactivated π-bonds are often suitable dienophiles for the internal cycloaddition. While the carbocyclic *IMDAF* reaction has been the subject of many reports in the literature, much less is known regarding the cycloaddition behavior of furan Diels-Alder systems that contain heteroatoms. Even rarer are examples in which the heteroatom is directly attached to the furan ring. In an effort to investigate the scope of these reactions, a number of new furan substrates were prepared in our laboratory and tested for the cycloaddition cascade. Tethered amidofurans **30** and **31** were easily synthesized starting from aminofuran **24** and 4-pentenoyl chloride. The thermal reaction of **30** at 200° for 24 hours afforded tetrahydroquinolinone **32** in 66% yield. Likewise, heating a sample of the *N*-methylated analog **31** at 160° furnished a 6:1-mixture of cyclohexadienol **33** (77%) and tetrahydroquinoline **34** (13%), the former being easily converted to **34** by treatment with borontrifluoride etherate. In both cases, the initial cycloadducts were not isolated, as they readily underwent ring opening, assisted by the lone pair of electrons on the adjacent nitrogen (Scheme XXIII).

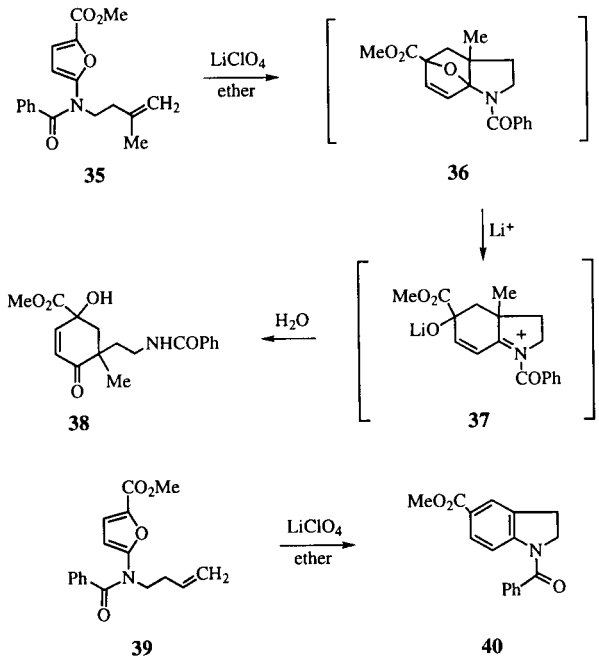
During the course of our studies we have found that the *IMDAF* cycloadditions of furanamides such as **35** can also be performed by using 4*M* ethereal lithium perchlorate as solvent [45]. Under these conditions, furanamide **35** underwent cycloaddition at a much lower temperature and in higher yield than under strictly thermal conditions. The

Scheme XXIII



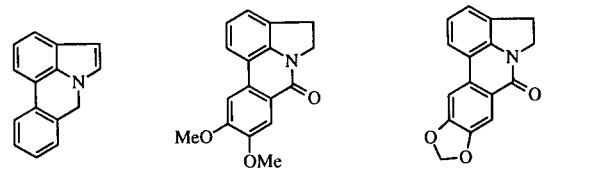
major product formed corresponded to cyclohexenone **38**. This reaction presumably involves an initial [4+2]-cycloaddition to give **36** followed by a rapid ring opening to afford iminium ion **37** which is subsequently converted to **38** upon reaction with water (Scheme XXIV). The Grieco conditions [46] were also successfully employed using the unactivated 4-carbon tethered furanamide **39** which gave dihydroindole **40** in 73% isolated yield.

Scheme XXIV



Having established the suitability of 2-amido furans to generate dihydroindoles, we turned our attention to the application of the methodolgy toward the synthesis of oxoassoanine (**42**) [47] and anhydrolycorin-7-one (**43**) [48].

These compounds are members of the pyrrolophenanthridine class of alkaloids which have been isolated from various species of amaryllidaceae [49]. The 1*H*-pyrrolo[3,2,1-*de*]phenanthridine ring system (**41**) constitutes the core structural framework of the pyrrolophenanthridine alkaloids. Although a number of synthetic routes are available for this ring system, many of these suffer from low yields and a lack of generality [50]. A short synthesis



41 **42**; oxoassoanine **43**; anhydrolycorin-7-one

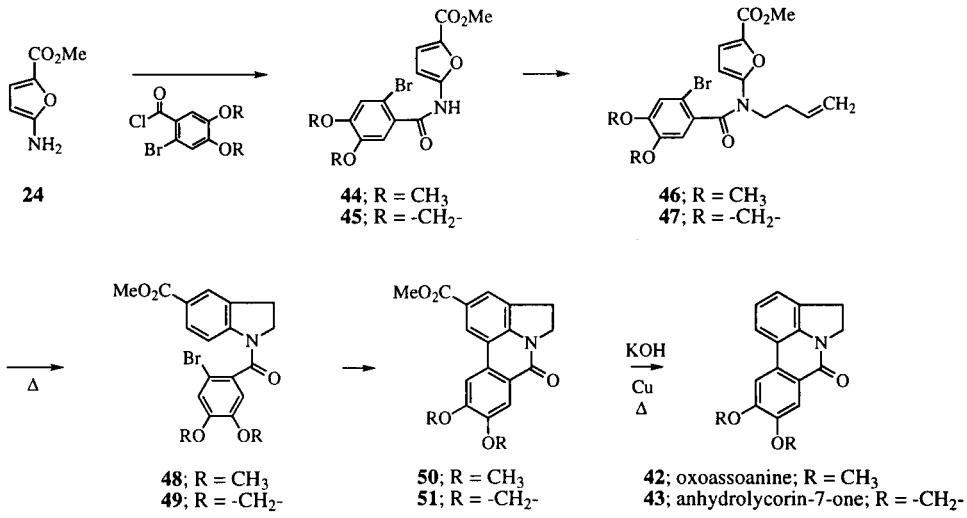
of **42** and **43** was carried out as depicted in Scheme XXV. This approach is centered on the construction of the key dihydroindoles **48** and **49** which are formed by an *IMDAF* cycloaddition followed by subsequent nitrogen atom lone pair assisted ring opening of the initially formed oxa-bridged cycloadducts. After some experimentation, it was found that using *bis*(tributyltin) under photochemical conditions afforded the aryl-coupled products **50** and **51** in high yield from the corresponding dihydroindoles **48** and **49**. Both compounds were converted to the natural products by a saponification-decarboxylation protocol.

The intramolecular [4+2]-cycloaddition of 2-amidofurans is currently being employed in our group as a new and general method for synthesizing various hexahydroindolinones [51]. Subjection of olefinic amidofurans such as **52** to thermolysis afforded the rearranged ketone **55**. The initially formed [4+2]-cycloadduct **53** is believed to undergo a nitrogen-assisted ring opening followed by deprotonation of the resulting zwitterion **54** to furnish the rearranged ketone (Scheme XXVI).

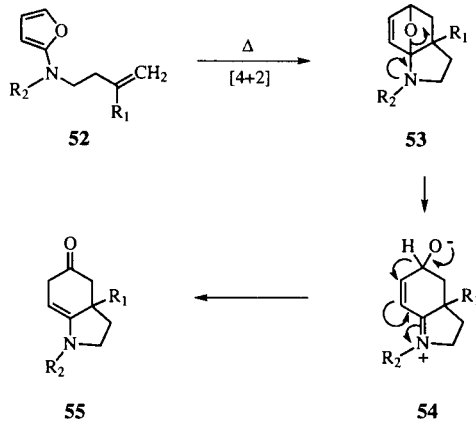
A related process is also being used to synthesize the strychnos alkaloid skeleton. Thus, thermolysis of the indolyl substituted *N*-ethylcarbamate **56** resulted in the formation of **57** by Diels-Alder cycloaddition of the furan across the indole π-bond followed by a subsequent rearrangement (Scheme XXVII).

One limitation of the above *IMDAF* method is that the 2-amidofuran system is not always easily accessible. In the context of our studies dealing with *domino cycloaddition-Mannich cyclizations*, we discovered that the Pummerer reaction can be effectively utilized to prepare the required furans [52]. α-Acyl thionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently with nucle-

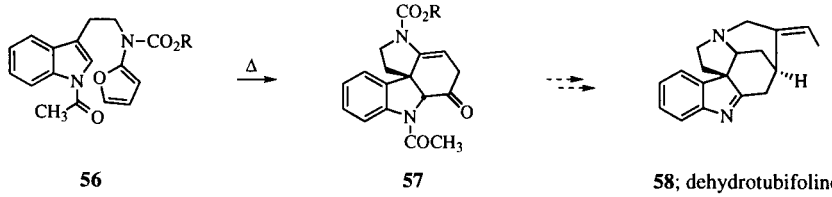
Scheme XXV



Scheme XXVI



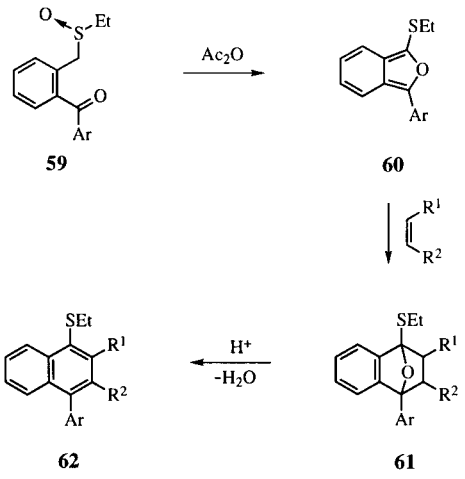
Scheme XXVII



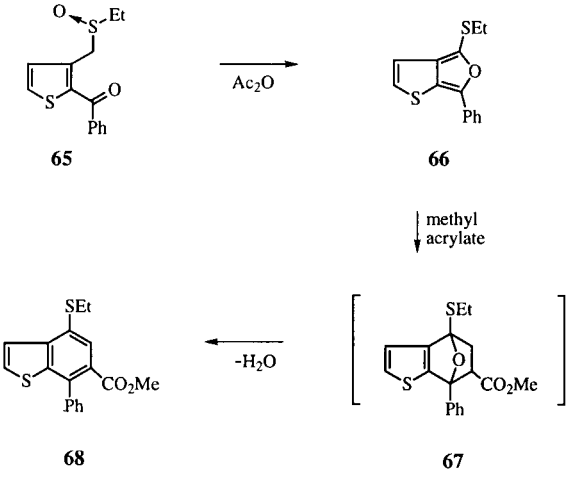
ophilic carbon species [53]. Bimolecular addition of the cation to various carbon-carbon double bonds is well known [54]. In the realm of natural product synthesis, most success has been achieved using intramolecular Friedel-Crafts cyclization of the Pummerer thionium ion intermediate [55]. Far fewer examples exist for heteroatom interception of the Pummerer intermediate [56]. The scarcity of examples prompted us to explore the internal trapping of the Pummerer cation with adjacent carbonyl groups as a method to prepare a variety of substituted furans. The strategy was first tested on ketosulfoxide **59** (Scheme XXVIII). The α-thiocarbocation derived from the Pummerer reaction of **59** was readily intercepted by the adjacent keto group to produce isobenzofuran **60** as a transient intermediate which underwent a subsequent Diels-Alder cycloaddition with an added dien-

ophile. The resulting cycloadduct **61** was readily converted to representatives of several types of arylnaphthalene lignans [57].

Scheme XXVIII

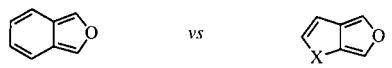


Scheme XXIX



clearly indicate that the domino cascade process is a powerful method for the construction of complex heteroaromatic *o*-quinodimethanes.

As heteroaromatic isobenzofuran analogs have not been extensively studied in the literature, we focused our attention on the Pummerer reaction of several *o*-heteroaroyl substituted sulfoxides as a method to generate reactive heteroaromatic *o*-xylylenes. Most notable among the heteroaromatic isobenzofurans (**64**) reported in recent years are the furo[3,4-*b*]furans, thieno[2,3-*c*]furans, furo[3,4-*d*]-isoxazoles, and furo[3,4-*b*]indoles [58]. These 10π-systems are isoelectronic with the pentalene dianion and have been of some theoretical interest. Molecular orbital calculations on these heteroisobenzofurans indicate that they



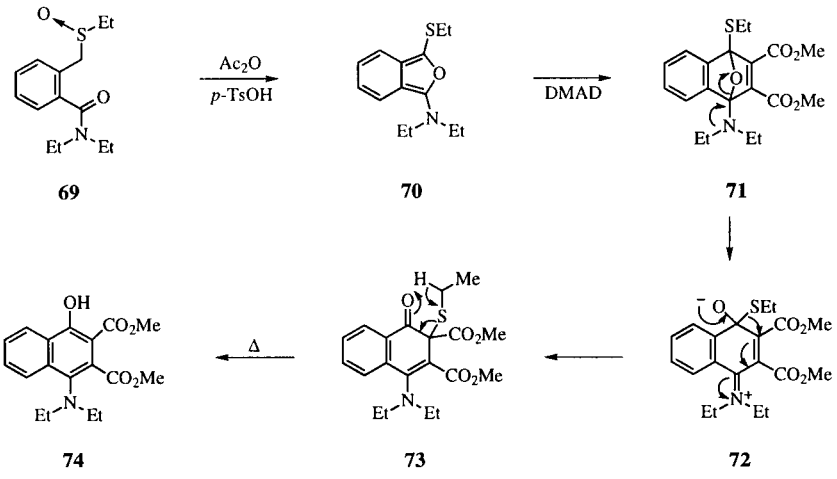
63 **64**; X = O, S, N

possess little or no aromatic character, and this is reflected in their high chemical reactivity. Using the *domino Pummerer Diels-Alder sequence* we were able to synthesize several thieno[2,3-*c*]furans and furo[3,4-*b*]indoles [59]. In the presence of a suitable dienophile, the reactive *o*-xylylene underwent [4+2]-cycloaddition followed by an acid-catalyzed ring-opening and aromatization to give heteroaromatic naphthalene derivatives (Scheme XXIX). The *domino Pummerer cyclization-cycloaddition sequence* also occurred intramolecularly using unactivated alkenyl tethers of variable length. The results

Prompted by the above results, we became interested in extending the Pummerer promoted cyclization reaction of *o*-amido substituted sulfoxides since this would allow for the rapid stereocontrolled synthesis of a variety of azapolycyclic products. Indeed, the *domino Pummerer/Diels-Alder sequence* readily afforded 2-amino substituted isobenzofurans as transient species which were too labile to isolate but underwent rapid [4+2]-cycloaddition with added dienophiles [60]. When dimethyl acetylenedicarboxylate (DMAD) was used as the trapping agent, the initially formed iminium ion **72** could not undergo proton loss (Scheme XXX). Instead, **72** rearranged by means of a 1,2-ethylthio shift to afford the tetralone derivative **73**. Compound **73** was converted to naphthol **74** in high yield upon further heating. This process presumably proceeds by elimination of thioacetaldehyde in a hetero-retro-ene fashion, for which there is ample precedence in the literature [61].

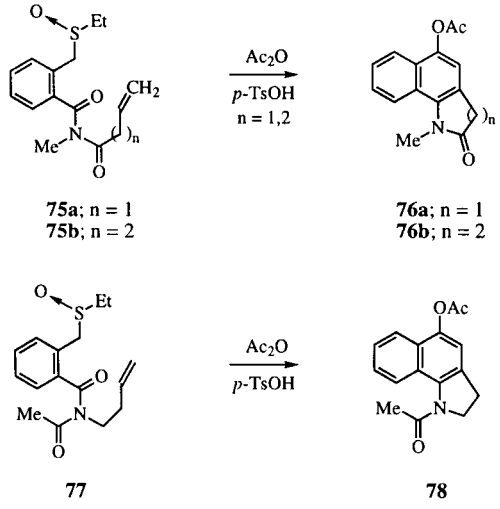
In order to access synthetically more valuable targets, we focused our attention on an intramolecular variation of the *domino amido-Pummerer-Diels-Alder reaction sequence*. The one-pot intramolecular cascade process occurred smoothly when the olefin tether was activated by an ester or when a carbonyl group was located adjacent to the nitrogen atom of the 2-amino substituted isobenzofuran (Scheme XXXI) [60]. The intramolecular cycloaddition behavior of the incipient isobenzofurans in response to the presence of a C=O group is striking. Five and six ring-membered precursors **75a** and **75b** delivered cyclized products bearing a carbonyl within the newly formed

Scheme XXX



rings in good to excellent yields. Externalization of the C=O as in **77** likewise led to a facile internal cyclization. Removal of the C=O functionality, however, suppressed intramolecular cycloaddition in favor of the traditional Pummerer reaction. The amine-amide effect is not limited to isobenzofurans. In our previous study of the intramolecular cycloaddition of carbonyl ylide dipoles and tethered alkenyl π-bonds, a similar phenomenon was

Scheme XXXI

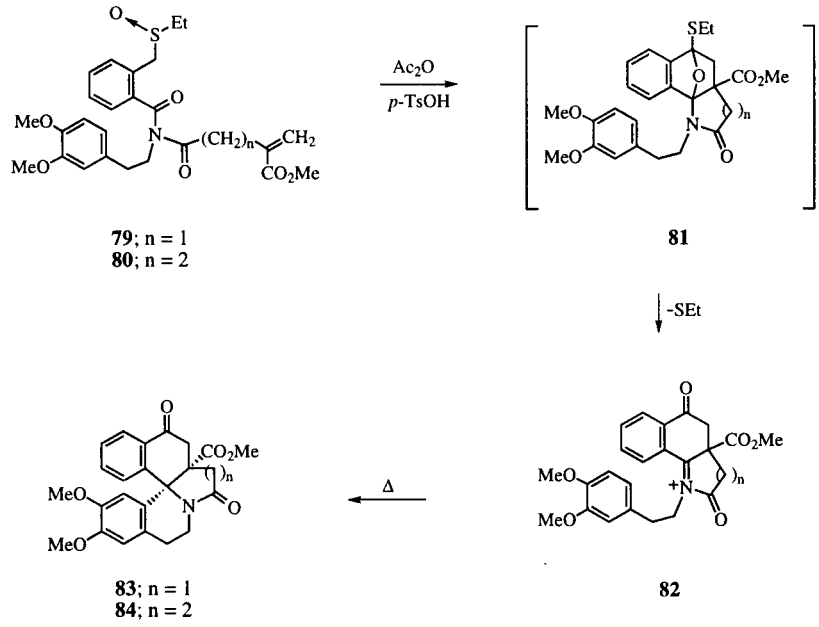


observed. Intermediates with carbonyl groups in the tether provided cycloaddition products; those lacking the C=O group failed to cyclize. The reactivity discrepancy in both cases can be traced to steric effects in the transition states. The incorporation of an amido group is clearly of synthetic advantage as it offers the opportunity to accelerate intramolecular cycloaddition by steric adjustment of ground-state and transition state energies either separately or simultaneously. Both examples underscore the unexpected complexity of intramolecular cycloaddition processes that create several fused rings in a domino cascade and simultaneously induce steric effects remote from the reacting centers. Amide tethers have emerged as remote-site promoters of intramolecular cycloaddition for tandem processes yielding products containing multiple fused rings.

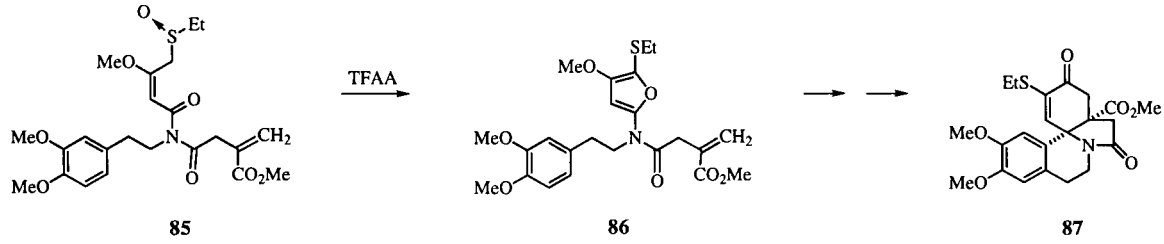
Having established the facility with which *N*-acyliminium ions can be formed from the Pummerer reaction of *o*-amido substituted sulfoxides, we next focused our attention on the final cyclization step of the proposed cascade process (*i.e.*, **22→23** in Scheme XX) [62]. In order to avoid the deprotonation (aromatization) step, we prepared sulfoxides **79** and **80**, each possessing a carbomethoxy group attached to the olefin tether. This substituent was selected not only to prevent deprotonation, but also to enhance the [4+2]-cycloaddition based on FMO considerations. *N*-Acyliminium ion **82** derived from the internal cycloadduct **81** underwent stereoselective spiro-cyclization to furnish the *cis*-3,4-benzoerythrinane **83** or homoerythrinane derivative **84** in good yield (Scheme XXXII). The overall triple cascade sequence represents an efficient one-pot approach toward the erythrinane alkaloid skeleton in which the spirocyclic ABC skeleton is assembled in a single operation.

At this point, we decided to undertake a synthesis of (±)-erysotramidine (**94**) in order to further test the viability of the triple cascade process as an entry into the erythrinane skeleton [49]. The requisite starting imidosulfoxide **85**, possessing both a dienophilic and diactivated aromatic π-tether, was efficiently synthesized from known starting materials. Subjection of **85** to the Pummerer conditions gave compound **87** as a single diastereomer in 83% yield (Scheme XXXIII). The *cis* A/B ring fusion present in **87** was unequivocally established by an X-ray crystallographic analysis and is identical to the stereochemical relationship found in the naturally occurring Erythrina alkaloids. The conversion of **85** into **87** is believed to fol-

Scheme XXXII



Scheme XXXIII



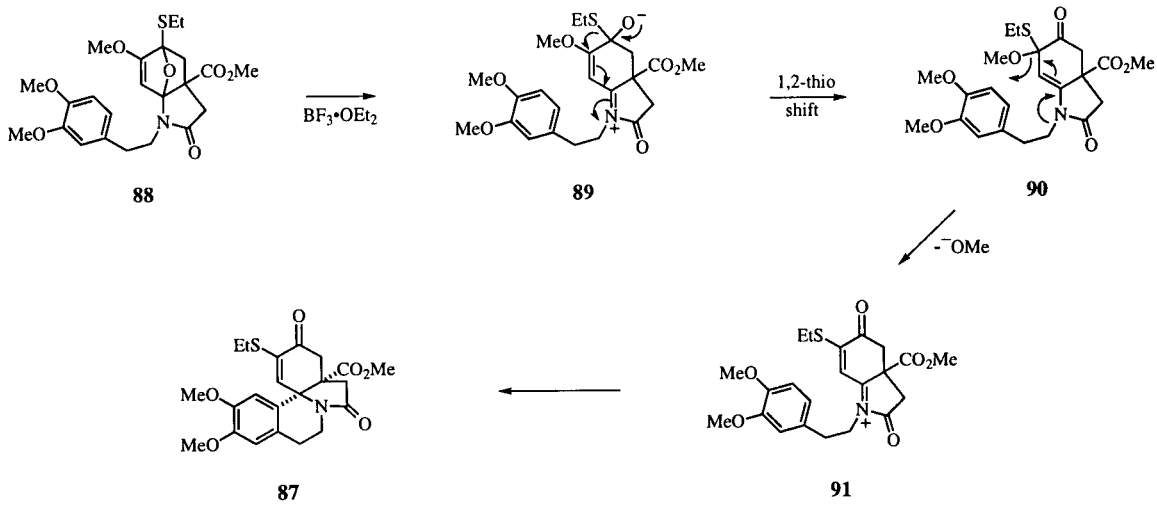
low the pathway outlined below (Scheme XXXIV). The initially formed α-thiocarbocation intermediate generated from the Pummerer reaction of **85** is intercepted by the adjacent imido carbonyl to produce the α-amido substituted furan **86**. This transient intermediate undergoes a subsequent intramolecular Diels-Alder cycloaddition across the tethered π-bond to furnish cycloadduct **88**. Nitrogen-assisted ring opening of the oxabicyclic bridge results in the formation of zwitterionic intermediate **89** which undergoes a 1,2-thioethyl shift followed by methoxide ion ejection to give **90**. Cyclization of the diactivated aromatic tether onto the resulting *N*-acyliminium ion **91** ultimately provides the tetracyclic amide **87**.

With a supply of **87** in hand, this enone was converted into the corresponding vinyl triflate which, in turn, was subjected to a palladium catalyzed formate reduction to give **92**. The resulting thio-substituted diene was subsequently transformed into ketone **93** *via* a titanium mediated hydrolysis (Scheme XXXV). The present sequence constitutes a formal synthesis of (±)-erysotramidine (**94**) based on the successful conversion of **93** into **94** by Tsuda and coworkers [63].

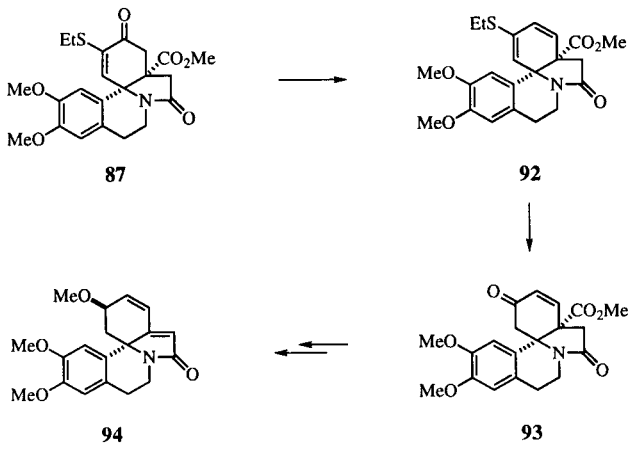
Over the past decade we have shown that many structurally diverse heterocyclic compounds can be readily accessed *via* the *domino cycloaddition/cyclization cascade*. The key step in this process involves the generation of a reactive *N*-acyliminium ion by fragmentation of an amino substituted [4+2]-cycloadduct. This triple cascade is applicable toward the preparation of a broad range of alkaloids and we are further utilizing this unique domino sequence toward other synthetic targets.

In conclusion, I would like to express my heartfelt gratitude to my many talented students and collaborators whose names appear in the appropriate references cited herein. The major funding of our heterocyclic program has come from the NSF and NIH for which I am eternally

Scheme XXXIV



Scheme XXXV



grateful. The support and encouragement of various colleagues throughout my career is most appreciated. In particular, I cherish the good fellowship and chemical advice from the late Paul Gassman as well as Leo Paquette at Ohio State University, Joseph Tufariello at SUNY Buffalo, Leon Mandell (now at the University of South Florida), Lanny Liebeskind at Emory University and Jeff Seeman (Philip Morris). I owe special thanks to Rolf Huisgen (University of Munich) for both his kindness and helpfulness over the years, to Al Meyers (Colorado State University) who has always been there for me, and to my good buddy, Will Pearson (University of Michigan), who has been willing to join me in an array of heterocyclic projects. Finally, I wish to express my thanks to the ISHC for bestowing upon me this year's award in heterocyclic chemistry.

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