ChemComm
FEATURE ARTICLE

The domino cycloaddition/*N*-acyliminium ion cyclization cascade

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Various applications of the domino cycloaddition/ *N*-acyliminium ion cyclization cascade are reported. The key step in the process involves the generation of a reactive *N*-acyliminium ion by fragmentation of an amino substituted [4 + 2]-cycloadduct. The successful synthesis of a number of alkaloids by this sequence of reactions reveals the usefulness and importance of this unique domino cascade.

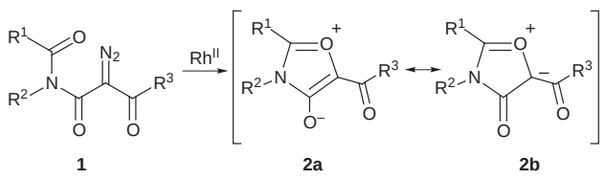
Introduction

Domino processes belong to a growing family of reactions which allow for the regio- and stereo-controlled formation of several carbon–carbon bonds and/or ring systems in a single operation.[1] Cationic reactions that proceed in a domino fashion are featured in the biosynthesis of important natural products, and synthetic applications of both biomimetic and non-biomimetic cationic cyclizations have been widely developed.[2] Important contributions to this area have also been realized utilizing a combination of anionic, radical, carbenoid and transition metal-catalyzed processes.[3] The combination of a sequence of individually powerful methods often has a value significantly greater than the sum of the individual reactions and has become of great interest to the synthetic community. Corey has termed such a sequence as a tactical combination.[4]

In recent years, consecutive pericyclic reactions involving at least one cycloaddition have also been utilized for the synthesis of complex polycyclic ring systems.[5] In the realm of synthesis, in which a premium is put on the rapid construction of polyfunctional, highly bridged carbon and heteroatom networks, the [4 + 2]-cycloaddition has emerged as one of the foremost synthetic methods.[6] Well known and extensively studied for many decades, the Diels–Alder reaction is frequently employed for the construction of six-membered ring systems. The high regio- and stereo-selectivity typically displayed by this pericyclic process and the ease of execution have contributed toward its popularity. Carbon–carbon bond-forming reactions involving *N*-acyliminium ions play an extremely important role in the synthesis of nitrogen heterocycles. Speckamp[7] and Hart,[8] in particular, were the pioneers in this area, showing that *N*-acyliminium ions are valuable intermediates in the synthesis of a broad range of alkaloids. A combination of these two powerful synthetic methods would allow for the rapid, stereocontrolled synthesis of a variety of azapolycyclic products. This feature article describes some of our recent work in this area.

Cycloaddition of 1,3-oxazolium 4-oxides

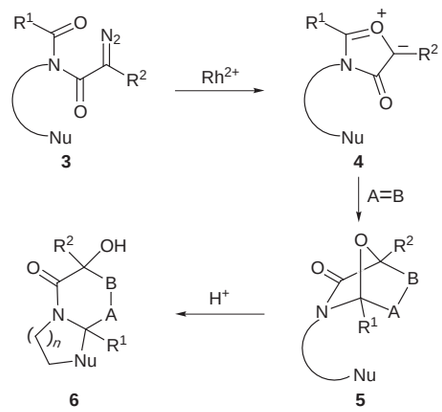
In 1994 we started work in our laboratory to synthesize ring-fused polyheterocycles based on a *sequential cycloaddition/* N-*acyliminium ion cyclization process.*[9] These two types of reaction provide an opportunity for linking two disparate ring-forming reactions in a novel sequential manner. We believed that such a 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 1).[10] This type



1 **2a** **2b**

Scheme 1

of mesoionic ylide corresponds to the cyclic equivalent of a carbonyl ylide and was found to readily undergo [4 + 2]-cycloaddition with suitable dipolarophiles.[10] 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.[11] 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**.[10] 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 its treatment with a Lewis acid.[12] 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/[4 + 2]-cycloaddition/cationic* π-cyclization protocol as a method for the construction of complex nitrogen polyheterocycles of type **6** (Scheme 2). This



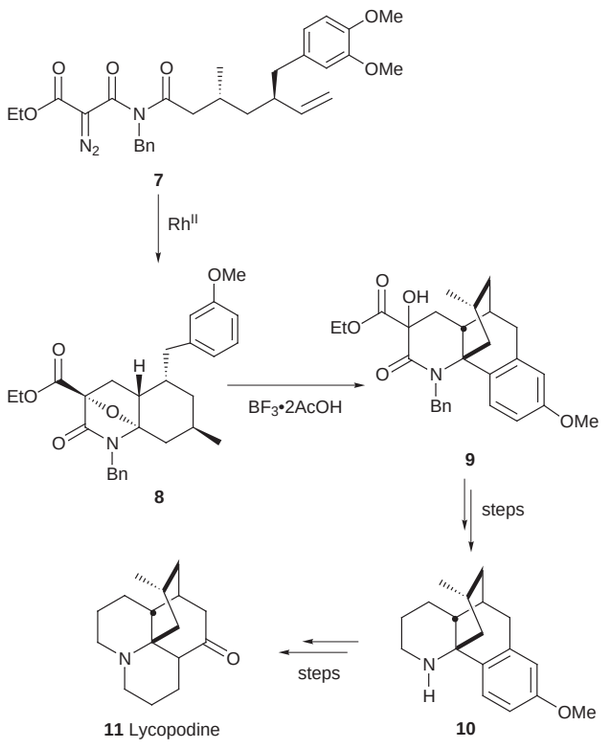
3 **4** **6** **5**

Scheme 2

sequence represents the first example where a [4 + 2]-cycloaddition and *N*-acyliminium ion cyclization are coupled in a one-pot sequence. The novelty of the process lies in the method of *N*-acyliminium ion generation, which to the best of our knowledge is unprecedented. *N*-Acyliminium ions are traditionally generated from the *N*-acylation of imines,[13]

N-protonation[14] and oxidation of amides,[15] electrophilic additions to enamides,[16] and the heterolysis of amides bearing a leaving group adjacent to nitrogen.[7] 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 3).[17] The isomünchnone cycloadduct **8** was



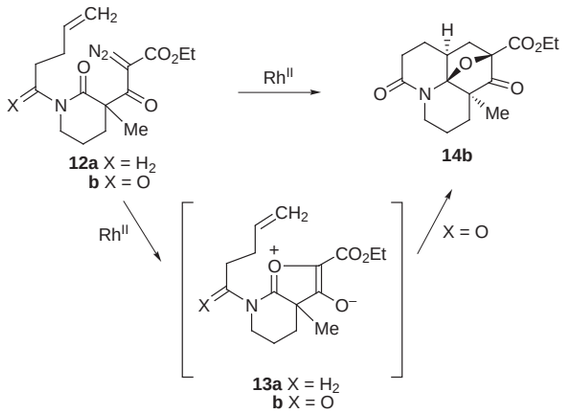
Scheme 3

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).[18] 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 chair-like conformation.[18,19] Indeed, cyclization of the aromatic ring onto the *N*-acyliminium ion center readily occurred from the axial position.[20] The rearranged product **9** was then converted into the key intermediate previously used by Stork for the synthesis of (±)-lycopodine **11**.[18]

Application of the domino cyclization/cycloaddition sequence to the pentacyclic skeleton of the aspidosperma ring system

Prompted by our work dealing with the internal [4 + 2]-cycloaddition reaction of mesoionic oxazolium ylides,[10] we became interested in the rhodium(II)-catalyzed reactions of diazo ketoamides such as **12**. Attack of the amido oxygen at 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 4).[21]

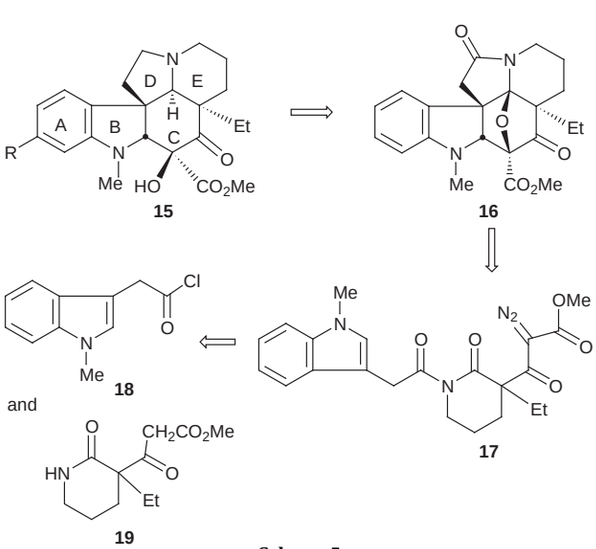
Without the C=O functionality (*i.e.* **12a**, X = H), only decomposition products were observed. By performing *ab initio* transition state geometry optimizations, we learned that a severe



Scheme 4

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.[21] 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.[21]

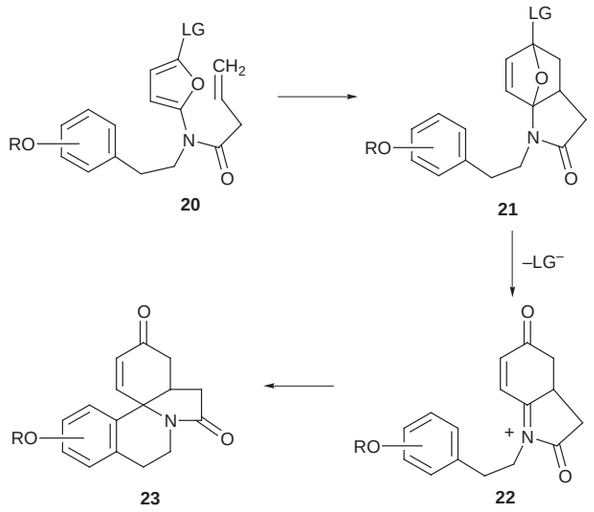
As an extension of these studies, we have developed a fundamentally new approach to the construction of the pentacyclic skeleton of the aspidosperma ring system which involves a related domino cascade sequence.[22] This strategy was successfully applied to the synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine **15**. The approach used is outlined in Scheme 5 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 the *tandem rhodium*(II)-*catalyzed cyclization/cycloaddition* of α-diazoimide **17**. Cycloaddition of the initially formed dipole across the pendant indole π-system[23] would be expected to result in the simultaneous generation of the CD-rings of the aspidosperma skeleton.[24] The stereospecific nature of the internal cycloaddition reaction should also lead to the correct relative stereochemistry of the four chiral centers about the C-ring. In a recent publication, we described our results which verified the underlying viability of this approach to the aspidosperma skeleton (Scheme 5).[22]



Scheme 5

The 2-aminofuran Diels–Alder strategy

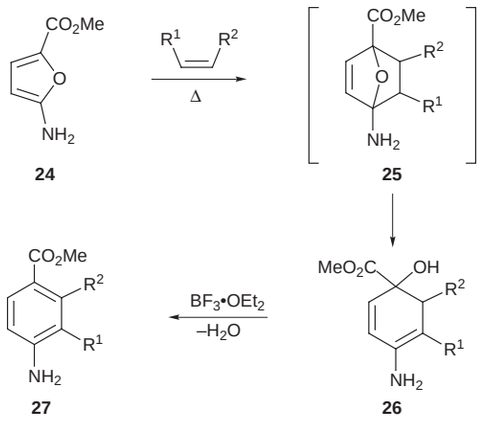
In the next phase of our work, we decided to reconsider some aspects of our domino cascade strategy. It occurred to us that we could also utilize a series of 2-amino-substituted furans for the critical [4 + 2]-cycloaddition step rather than the highly reactive 1,3-dipole, which on occasion was prone to undergo hydrolytic decomposition.[10] 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 6). The resultant cycloadduct



Scheme 6

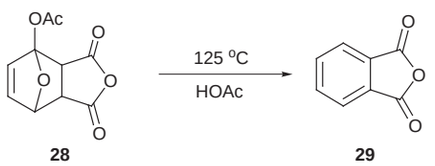
was expected to undergo ring opening to generate a vinylogous *C*-acyliminium ion of type **22**. Our intention was to use this sequence of reactions for a rapid entry into the erythrinane family of alkaloids. With this goal in mind, some model studies were undertaken to determine the facility with which 2-amino-furans would undergo Diels–Alder cycloadditions.[25]

Heterocycles such as furan, thiophene and pyrrole undergo Diels–Alder reactions despite their stabilized 6π-aromatic electronic configuration.[26] By far the most extensively studied heteroaromatic system for Diels–Alder cycloaddition is furan and its substituted derivatives.[26] The resultant 7-oxabicyclo[2.2.1]heptanes are valuable synthetic intermediates that have been further elaborated to substituted arenes, carbohydrate derivatives and various natural products.[26] A crucial synthetic transformation employing these intermediates involves the cleavage of the oxygen bridge to produce functionalized cyclohexene derivatives.[27] In many cases, however, this strategy is not feasible because of the low reactivity of furan toward monoactivated dienophiles. Lewis acid catalysis, interaction with metals, or use of high pressure helps to overcome the sluggishness of furan toward Diels–Alder cycloaddition.[26] MO 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 HOMO energy relative to that of furan.[28] A significant increase in the HOMO 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.[28] 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 7). 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



Scheme 7

cleavage only when treated with acetic acid at elevated temperatures (125 °C) (Scheme 8).[29]

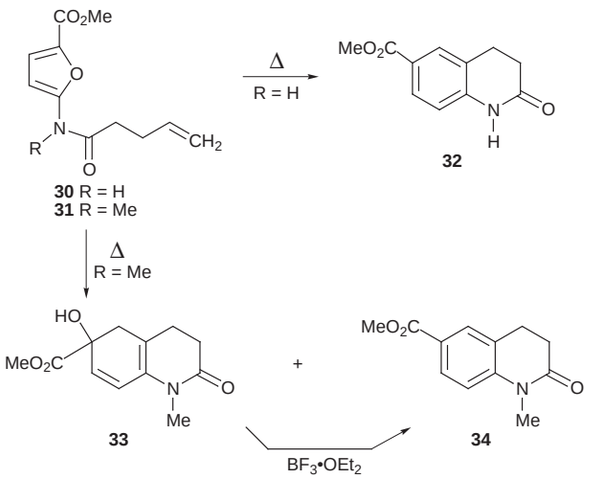


Scheme 8

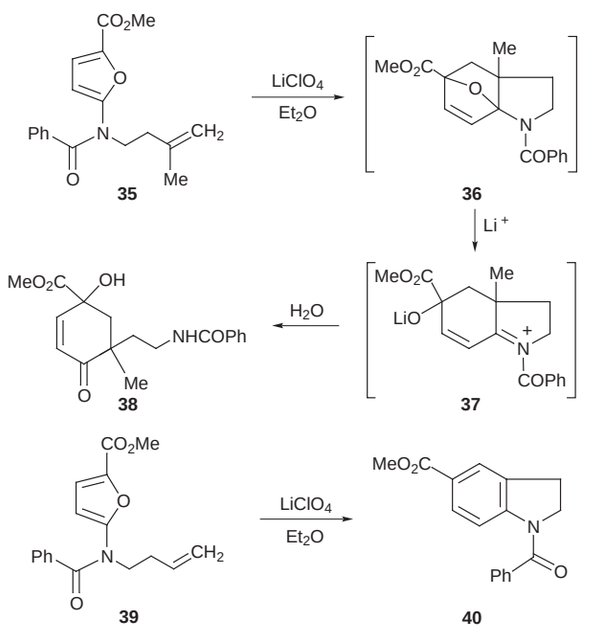
IMDAF Cycloaddition as a method for the preparation of pyrrolophenanthridine alkaloids

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.[26] Not only do IMDAF reactions allow for the preparation of complex oxygenated polycyclic compounds, they often proceed at lower temperatures than their intermolecular counterparts.[30] 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 more rare are examples in which the heteroatom is directly attached to the furan ring.[25] 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/cyclization* cascade. Tethered amidofurans **30** and **31** were easily synthesized starting from aminofuran **24** and pent-4-enoyl chloride. The thermal reaction of **30** at 200 °C for 24 h afforded tetrahydroquinolinone **32** in 66% yield. Likewise, heating a sample of the *N*-methylated analog **31** at 160 °C furnished a 6 : 1-mixture of cyclohexadienol **33** (77%) and tetrahydroquinoline **34** (13%), the former being easily converted to **34** by treatment with $BF_3 \cdot OEt_2$. 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 9).

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 $LiClO_4$ as solvent.[31] Under these conditions, furanamide **35** underwent cycloaddition at a much lower temperature and in higher yield than under strictly thermal conditions. The 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 10). The Grieco conditions[31] were also successfully employed using the unactivated four-carbon tethered furanamide **39** which gave dihydroindole **40** in 73% isolated yield.

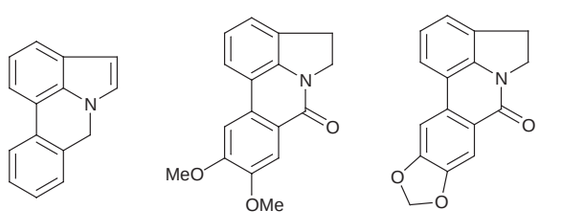


Scheme 9

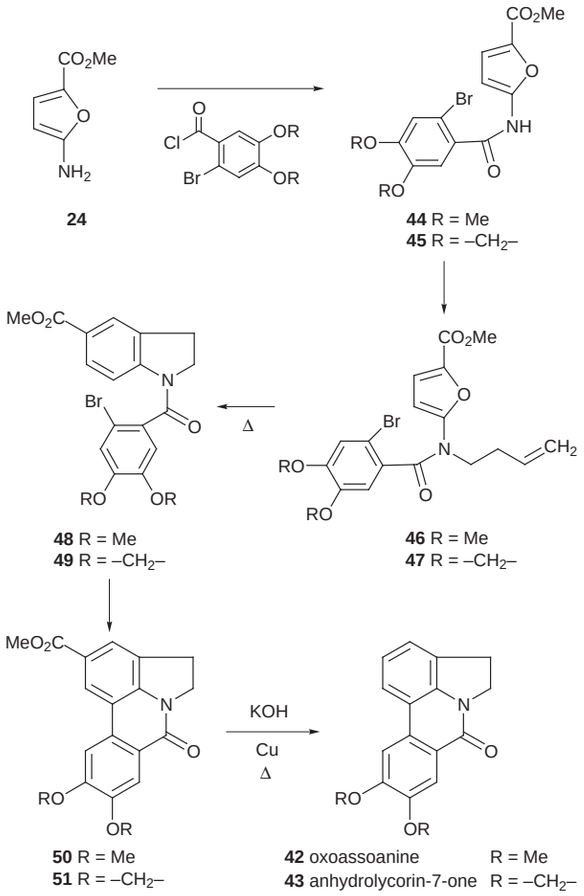


Scheme 10

Having established the suitability of 2-amidofurans to generate dihydroindoles, we turned our attention to the application of the method toward the synthesis of oxoassoanine[32] **42** and anhydrolycorin-7-one **43**.[33] These compounds are



members of the pyrrolophenanthridine class of alkaloids which have been isolated from various species of amaryllidaceae.[34] 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 lack generality.[35] A short synthesis of **42** and **43** was carried out as depicted in Scheme 11. This approach is centered

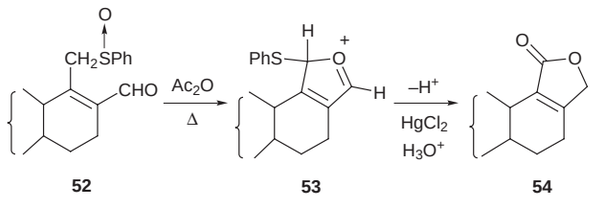


Scheme 11

on the construction of the key dihydroindoles **48** and **49** which are formed by a 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.

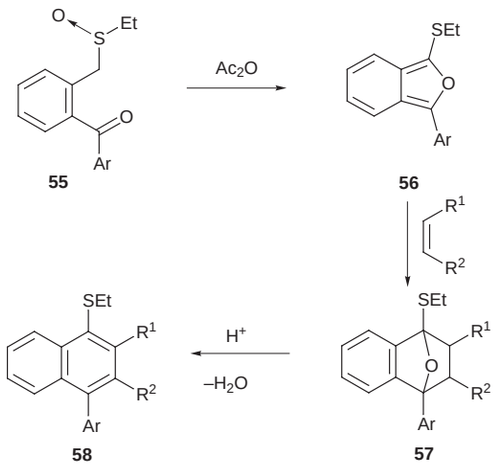
The domino Pummerer Diels–Alder sequence

Much of the chemistry utilized in the two preceding sections relied on our ability to synthesize the requisite 2-aminofurans. One limitation of the method is that sometimes the 2-aminofuran system is not 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.[36] α-Acyl thionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently with nucleophilic carbon species.[37] Bimolecular addition of the cation to various carbon–carbon double bonds is well known.[38] In the realm of natural product synthesis, most success has been achieved using intramolecular Friedel–Crafts cyclization of the Pummerer thionium ion intermediate.[39] Far fewer examples exist for heteroatom interception of the Pummerer intermediate.[40] De Groot and co-workers recently developed an efficient procedure for butenolide formation in which the key step involves a Pummerer induced cyclization of aldehydic sulfoxides of type **52** into butenolides **54** (Scheme 12).[41] It was assumed that the neighboring carbonyl group attacks the initially formed thionium ion to give an oxy-stabilized cation **53** which loses a proton to generate a 2-thio-substituted furan



Scheme 12

which is subsequently converted to the butenolide upon hydrolysis. On the basis of this transformation we decided 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 keto sulfoxide **55** (Scheme 13). The α-thiocarbocation derived from

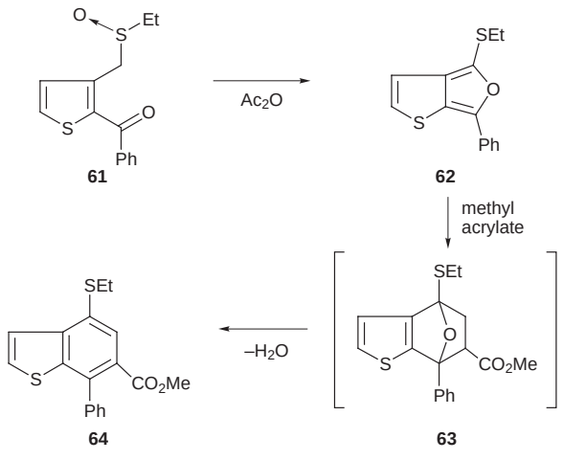


Scheme 13

the Pummerer reaction of **55** was readily intercepted by the adjacent keto group to produce isobenzofuran **56** as a transient intermediate which underwent a subsequent Diels–Alder cycloaddition with an added dienophile. The resulting cycloadduct **57** was readily converted to representatives of several types of arylnaphthalene lignans.[42]

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 **60** 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.[43] These 10π-systems are isoelectronic with the pentalene dianion and have been of some theoretical interest.[43] MO calculations on these heteroisobenzofurans indicate that they possess little or no aromatic character, and this is reflected in their high chemical reactivity.[43] Using the *domino Pummerer/Diels–Alder sequence* we were able to synthesize several thieno[2,3-*c*]furans and furo[3,4-*b*]indoles.[44] 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 14). The *domino Pummerer cyclization/cycloaddition sequence* also occurred intramolecularly using unactivated alkenyl tethers of variable length. The results clearly indicate that the domino cascade process is a powerful method for the construction of complex heteroaromatic *o*-quinodimethanes.

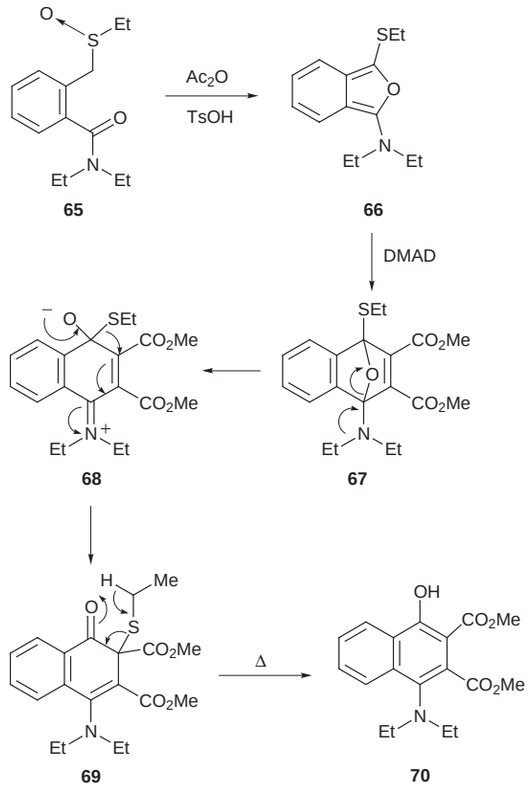


Scheme 14

Cycloaddition/ring opening/elimination sequence of 2-amino substituted isobenzofurans

Prompted by the above results, we became interested in extending the Pummerer-promoted cyclization reaction to *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.[45] When dimethyl acetylenedicarboxylate (DMAD) was used as the trapping agent, the initially formed iminium ion **68** could not undergo proton loss (Scheme 15). Instead, **68** rearranged by means of a 1,2-ethylthio shift to afford the tetralone derivative **69**. Compound **69** was converted to naphthol **70** 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.[46]

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 16).[45] The intramolecular cycloaddition behavior of the incipient isobenzofurans in response to the presence of a C=O group is striking. Five- and six-membered ring precursors **71a** and **71b** delivered cyclized products bearing a carbonyl within the newly formed rings in good to excellent yields. Externalization of the C=O as in **73** 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 observed (*i.e.* **12** → **14**).[21] 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



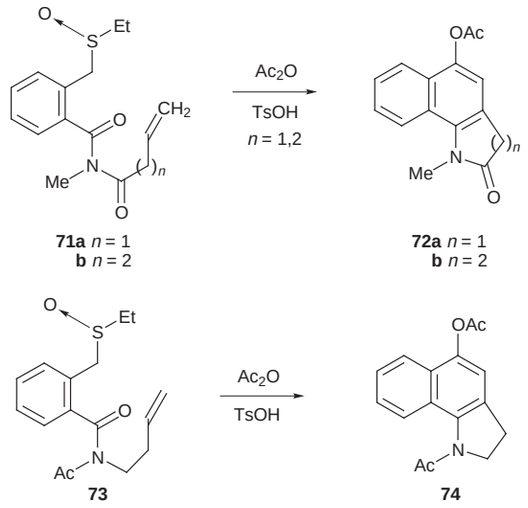
65 **66** **67** **68** **69** **70**

Scheme 15

emerged as remote-site promoters of intramolecular cycloaddition for tandem processes yielding products containing multiple fused rings.

Triple cascade sequence for construction of the erythrinane alkaloid skeleton

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 6).[47] In order to avoid the deprotonation (aromatization) step, we prepared sulfoxides **75** and **76**, each possessing a



71a *n* = 1
b *n* = 2

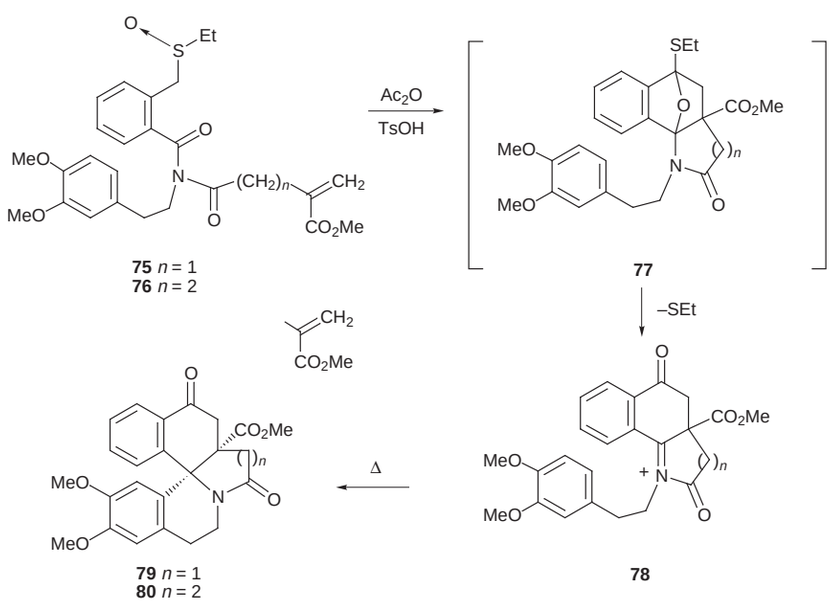
72a *n* = 1
b *n* = 2

73 **74**

Scheme 16

methoxycarbonyl group attached to the olefin tether. This substituent was selected not only to prevent deprotonation, but also because the presence of an electron-withdrawing group on the double bond enhances [4 + 2]-cycloaddition based on FMO considerations. *N*-Acyliminium ion **78** derived from the internal cycloadduct **77** underwent stereoselective spirocyclization to furnish the *cis*-3,4-benzoerythrinane **79** or homoerythrinane derivative **80** in good yield (Scheme 17). The overall triple cascade sequence represents an efficient one-pot approach towards the erythrinane alkaloid skeleton[34] in which the spirocyclic ABC skeleton is assembled in a single operation.

At this point, we decided to undertake a synthesis of (±)-erysotramidine **90** in order to further test the viability of the triple cascade process as an entry into the erythrinane skeleton.[34] The requisite starting imido sulfoxide **81**, possessing both a dienophilic and diactivated aromatic π-tether, was efficiently synthesized from known starting materials. Subjection of **81** to the Pummerer conditions gave compound **87** as a single diastereomer in 83% yield. 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 **81** into **87** is believed to follow the pathway



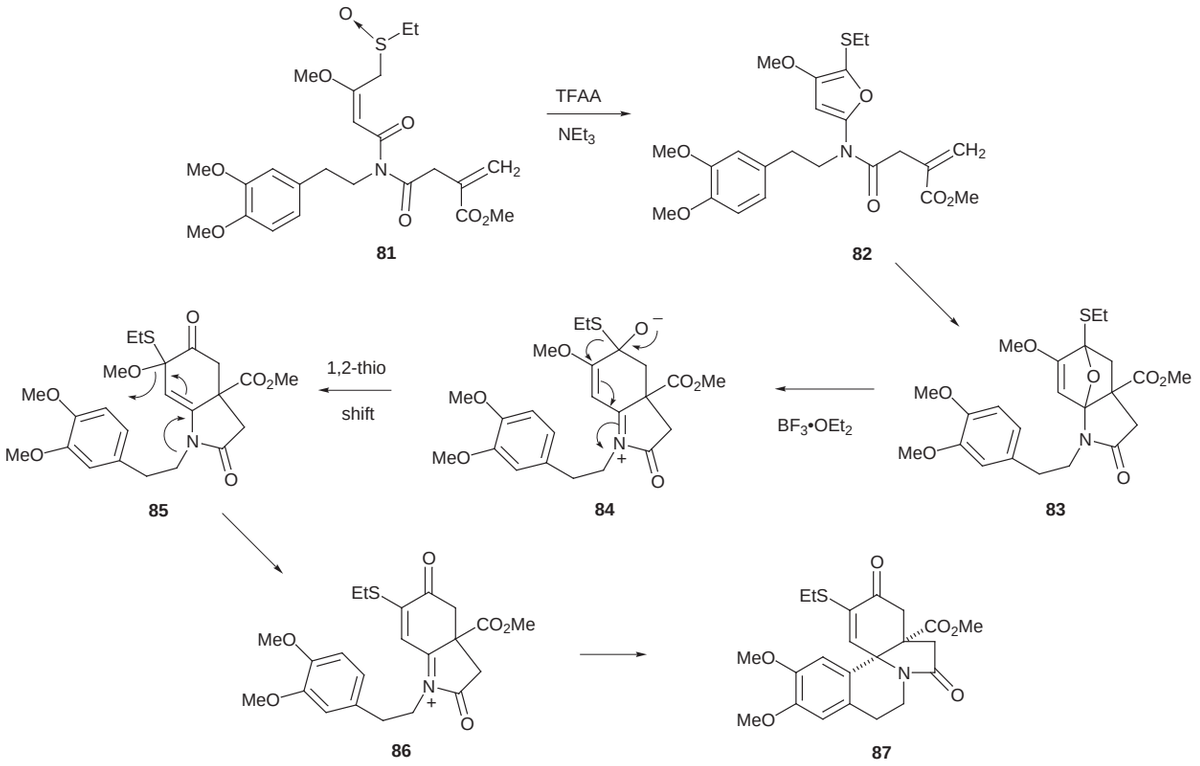
75 *n* = 1
76 *n* = 2

77

78

79 *n* = 1
80 *n* = 2

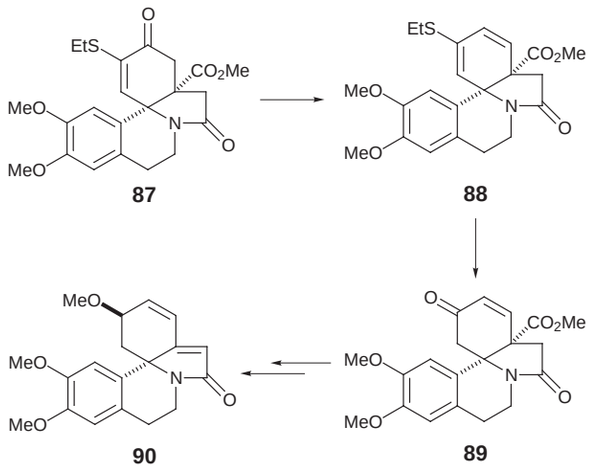
Scheme 17



Scheme 18

outlined below (Scheme 18). The initially formed α-thiocarbocation intermediate generated from the Pummerer reaction of **81** is intercepted by the adjacent imido carbonyl to produce the α-amido substituted furan **82**. This transient intermediate undergoes a subsequent intramolecular Diels–Alder cycloaddition across the tethered π-bond to furnish cycloadduct **83**. Nitrogen-assisted ring opening of the oxabicyclic bridge results in the formation of zwitterionic intermediate **84** which undergoes a 1,2-thioethyl shift followed by methoxide ion ejection. Cyclization of the diactivated aromatic tether onto *N*-acyliminium ion **86** 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 **88**. The resulting thio-substituted diene was subsequently transformed into ketone **89** *via* a titanium mediated hydrolysis.[48] The present sequence constitutes a formal synthesis of (±)-erysotramidine **90** based on the successful conversion of **89** into **90** by Tsuda.[49]



Scheme 19

Concluding remarks

Over the past four years we have shown that many structurally diverse heterocyclic compounds can be readily accessed *via* the *domino cycloaddition*/N-*acyliminium ion 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. It is a reasonable expectation that future years will see a continued evolution of this unique domino cascade toward other synthetic targets.

Acknowledgments

I thank my enthusiastic and gifted co-workers, whose names appear in the appropriate references, and the National Institute of Health for financial support.

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