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Application of cascade processes toward heterocyclic synthesis*

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Abstract: The reactions of *N*-acyliminium ions with tethered π-bonds are among the most important methods for preparing complex nitrogen-containing heterocycles. Pummerer-based cyclizations are also finding widespread application in both carbo- and heterocyclic syntheses. As part of a program concerned with new methods for alkaloid synthesis, we became interested in using a linked Pummerer/*N*-acyliminium ion cyclization sequence since we felt that this combination offers unique opportunities for the assemblage of complex target molecules. A synthetic method that combines transformations of different reaction types significantly broadens the scope of such procedures in synthetic chemistry. α-Thiocarbocations generated from the Pummerer reaction of β-phenylsulfinylmethyl-α,β-unsaturated amides can be intercepted by the adjacent amido group to produce transient amino-substituted furans, which undergo subsequent Diels–Alder cycloadditions. Using this *domino amido-Pummerer/Diels–Alder cascade*, we were able to assemble novel polycyclic systems in a single operation. 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

Sequential transformations enable the facile synthesis of complex target molecules from simple building blocks in a single preparative step [1–3]. Their value is amplified if they also create multiple stereogenic centers [4–8]. Moreover, the utilization of a domino sequence often leads to a reduction in the amount of solvent, eluent, and undesired by-products, thereby contributing to the protection of the environment. One of the earliest examples of a domino process reported in the literature involves cationic cyclization chemistry [9]. The synthetic potential of this reaction is well recognized, and this sequence has been greatly probed and extended in recent years [10]. Many different precursors have been used to initiate the cationic cascade. This cyclization sequence also plays an important role in heterocyclic natural product synthesis [11]. The reactions of *N*-acyliminium ions with tethered π-bonds are among the most important methods for preparing complex nitrogen-containing heterocycles [11–14]. Pummerer-based cyclizations are also finding widespread application in both carbo- and heterocyclic syntheses [15]. As part of a program concerned with new methods for alkaloid synthesis, we became interested in using a linked Pummerer/*N*-acyliminium ion cyclization sequence since we felt that this combination offers unique opportunities for the assemblage of complex target molecules [16].

The Pummerer reaction constitutes a versatile and effective method for the generation of thionium ions from sulfoxide precursors [15]. The initially formed cation is readily trapped by a nucleophilic

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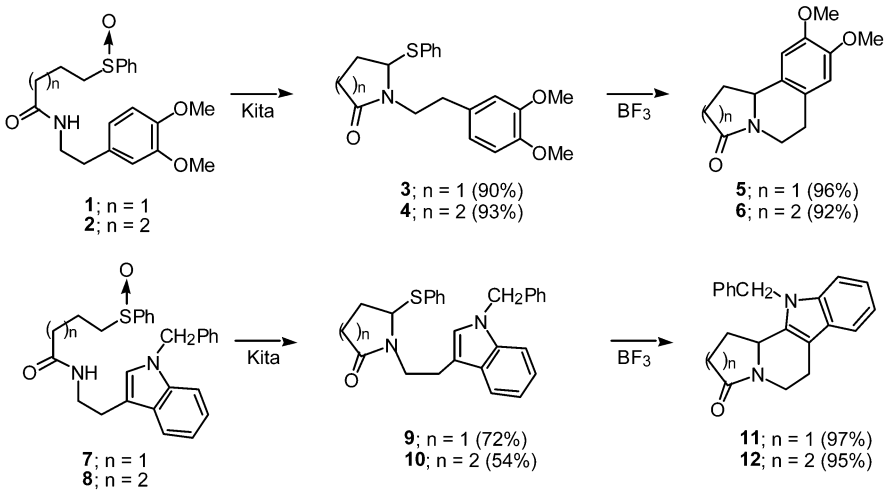
species present in the reaction medium. The interaction of thionium ions with electron-rich π-systems has proved to be extremely useful in natural product synthesis. Acid anhydrides or acids are generally employed as promoters in the majority of synthetic applications of the Pummerer reaction [17]. Thionium ions have also been generated from other sulfur-containing precursors (Scheme 1) [18]. A reaction that is often compared to the Pummerer rearrangement is the α-halogenation of sulfides [19]. In 1981, Trost and Murayama reported that dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) exhibits a remarkably high thiophilicity for cationic initiation reactions of thioketals [20]. Surprisingly, this alternative method for thionium ion generation has not been extensively exploited in synthesis, although there are a few scattered reports where this reagent has been used in complex target molecule synthesis [21]. The paucity of examples is somewhat surprising since thioketals are easily available by metalation and alkylation reactions of thioacetals [22]. Furthermore, the normally inert thioketal group can be carried through a series of transformations before it is chemoselectively unmasked to reveal the reactive thionium ion.

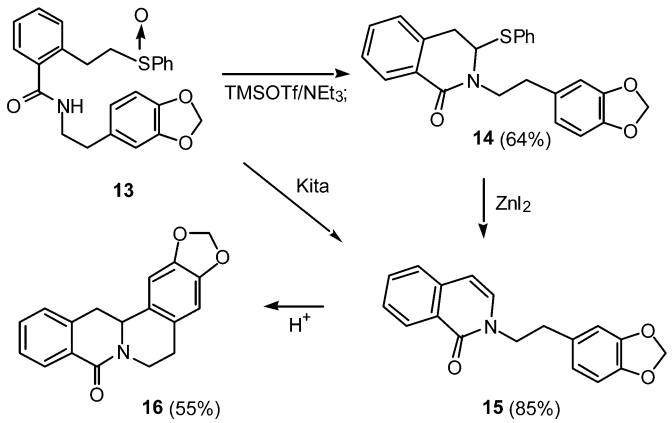
CONSECUTIVE THIONIUM/MANNICH ION CYCLIZATION SEQUENCE

While developing a Pummerer approach toward the synthesis of alkaloids [23], we uncovered a versatile amido annulation process based on a consecutive thionium/Mannich ion cyclization sequence [24]. A synthetic method that combines transformations of different reaction types significantly broadens the scope of such procedures in synthetic chemistry. One of the first systems that we examined in our laboratory involved the silicon-induced Pummerer reaction of amido sulfoxides **1** and **2** [24]. The sequential cyclization proceeded in excellent yield. These compounds were easily prepared by addition of thiophenol to the appropriate alkenoic acid π-bond, and this was followed by reaction of the in situ-generated acyl chloride with 3,4-dimethoxyphenethyl amine. The silicon-induced Pummerer reaction of these amido sulfoxides was carried out using Kita's conditions [25], which led to the very clean formation (>90 %) of 2-thio substituted lactams **3** and **4**. Iminium ion-aromatic π-cyclization was readily accomplished by treatment of **3** or **4** with 1.2 equiv of $BF_3 \cdot 2AcOH$ in CH_2Cl_2 at 25 °C to provide bicyclic lactams **5** or **6** in 96 % and 92 % yield, respectively (Scheme 1). A related set of reactions occurred using the indolyl-substituted amido sulfoxides **7** and **8**, which afforded indoles **11** and **12** in excellent yield from the initially formed Pummerer products **9** and **10**.



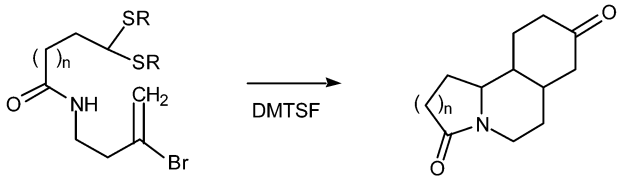
Scheme 1

Our interest in establishing amido sulfoxides as useful building blocks for heterocyclic synthesis prompted us to use the Pummerer methodology for the preparation of a member of the protoberberine alkaloid family [26]. The protoberberines are a large class of natural products typically characterized by a tetracyclic ring skeleton with an isoquinoline core [27]. Considerable efforts have been expended in the study of these molecules for both their synthetic and biological significance. These alkaloids exhibit wide-ranging and important biological activity, including antiinflammatory, antileukemic, and antitumor properties. Most of the synthetic approaches are generally plagued by the nonavailability of starting materials, multistep procedures, and moderate-to-poor yields [28]. A short synthesis of the berberine derivative **16** was carried out as depicted in Scheme 2 in order to highlight the method. This particular compound has been isolated from the Oriental shrub *Acangelissa gusanlung* and given the name gusanlung D [30]. This berberine is one of a number of alkaloids found in the plant, the stem of which has been used in Chinese folk medicine for many years. Subjection of the easily available amido sulfoxide **13** to trimethylsilyl triflate (TMSOTf)/NEt_3 as the Pummerer initiator afforded 2-thiophenyl lactam **14** in 64 % yield. Interestingly, when the Kita silicon conditions were used to trigger the Pummerer reaction [25], only enamide **15** (85 %) was obtained. The reaction of **14** with Lewis acids such as ZnI_2 resulted in the formation of enamide **15** in 93 % yield. When **15** was exposed to acidic conditions, it was transformed into the berberine derivative **16** in 55 % yield.



Scheme 2

Although the sequential process outlined above proved valuable for a number of substrates, we faced several limitations during our attempts to extend the scope of the reaction toward the synthesis of a number of other alkaloids. Thus, in many of the cases examined, it was necessary to isolate and purify the initially formed 2-phenylthiolactam intermediate before subjecting it to various electrophilic reagents so as to induce the second ring closure. In addition, formation of the *N*-acyliminium ion intermediate required the use of a strong Lewis acid and, as a result, the yield associated with the cyclization was variable. We reasoned that by replacing the sulfoxide functionality with a thioacetal group, it might be possible to bring about a "one-pot" cascade. Indeed, we have found that the desired reaction occurred in high yield when DMTSF was used as the reagent to initiate the process [31]. A typical example involved the DMTSF reaction of the bromoalkenyl-substituted amido thioacetals **17** and **18** (Scheme 3). When **17** was subjected to the DMTSF conditions followed by an aqueous workup, the initially cyclized product was hydrolyzed to ketolactam **19** in 65 % overall yield. A related set of reactions occurred with amido thioacetal **18**, ultimately producing the known octahydroquinolizin-4,8-dione **20** in 58 % yield. These two examples further demonstrate the facility with which the thionium/iminium ion cascade can occur [32].



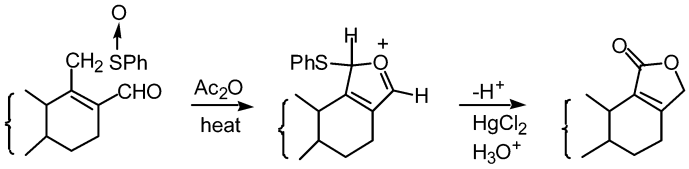
17; n = 1; R = Et
18; n = 2; R = Me

19; n = 1
20; n = 2

Scheme 3

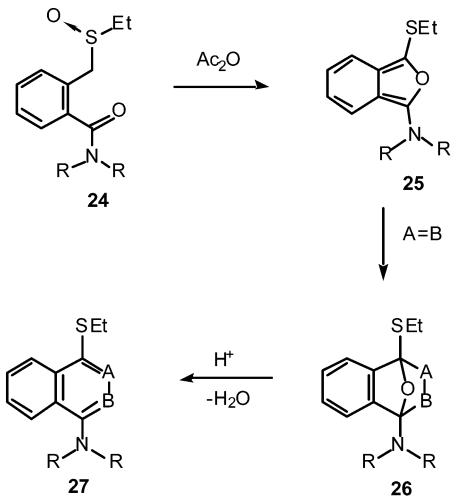
DOMINO PUMMERER/CYCLOADDITION/*N*-ACYLIMINIUM ION CYCLIZATION CASCADE

As part of our work in this area, we have also been interested in another type of Pummerer cascade, which we refer to as the *domino Pummerer/cycloaddition/*N-*acyliminium ion cyclization cascade*. Many structurally diverse heterocyclic compounds can be easily accessed via this method. Several years ago, De Groot and coworkers [33] developed a procedure for butenolide formation in which the key step involves a Pummerer-induced cyclization of aldehydic sulfoxides of type **21** into butenolides **23** (Scheme 4). It was assumed that the neighboring carbonyl group attacks the initially formed thionium ion to give an oxy-stabilized cation **22**, which loses a proton to generate a 2-thio-substituted furan, 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 an adjacent amido carbonyl group as a method to prepare a variety of novel heterocycles. The strategy was first tested on amido sulfoxide **24** (Scheme 5). The α-thiocarbocation derived from the Pummerer reaction of **24** was readily intercepted by the adjacent amido group to produce isobenzofuran **25** as a transient intermediate, which



21 **22** **23**

Scheme 4

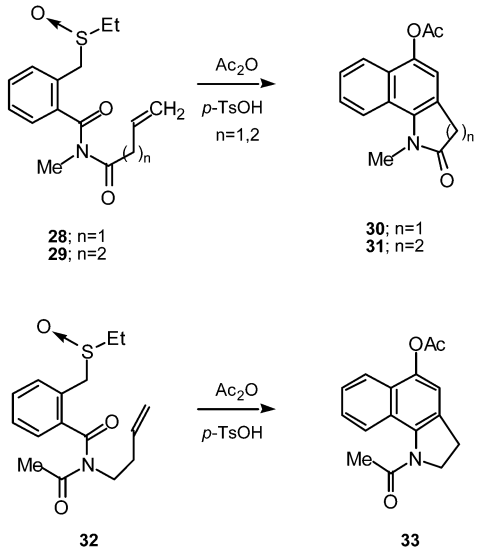


24 **25** **26** **27**

Scheme 5

underwent a subsequent Diels–Alder cycloaddition with an added dienophile. The resulting cycloadduct **26** was readily converted to representatives of several types of amino-substituted naphthalene lignans **27** [34].

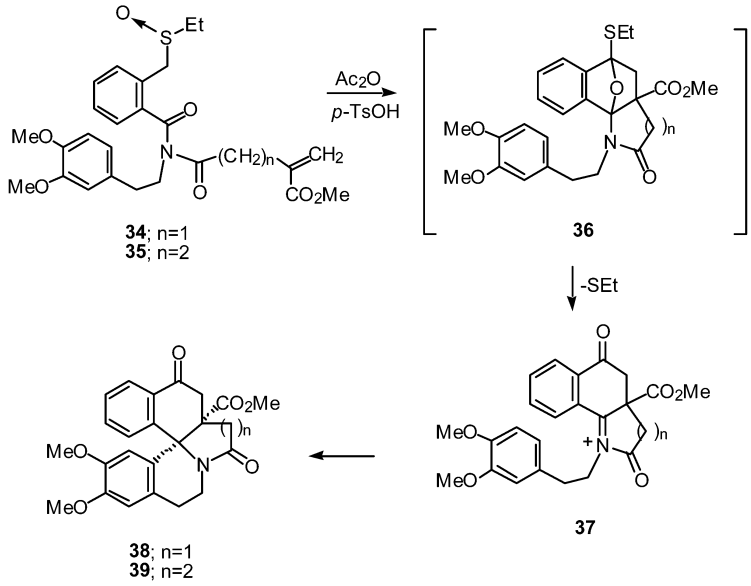
In order to access synthetically more valuable targets, we focused our attention on an intramolecular variation of the *domino amido-Pummerer/Diels–Alder reaction sequence.* The one-pot intramolecular cascade process occurred smoothly when a carbonyl group was located adjacent to the nitrogen atom of the 2-amino-substituted isobenzofuran (Scheme 6) [35]. 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 **28** and **29** delivered cyclized products bearing a carbonyl within the newly formed rings in good-to-excellent yields. Externalization of the C=O as in **32** 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 reactivity discrepancy can be rationalized in terms of 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- and transition-state energies either separately or simultaneously.



Scheme 6

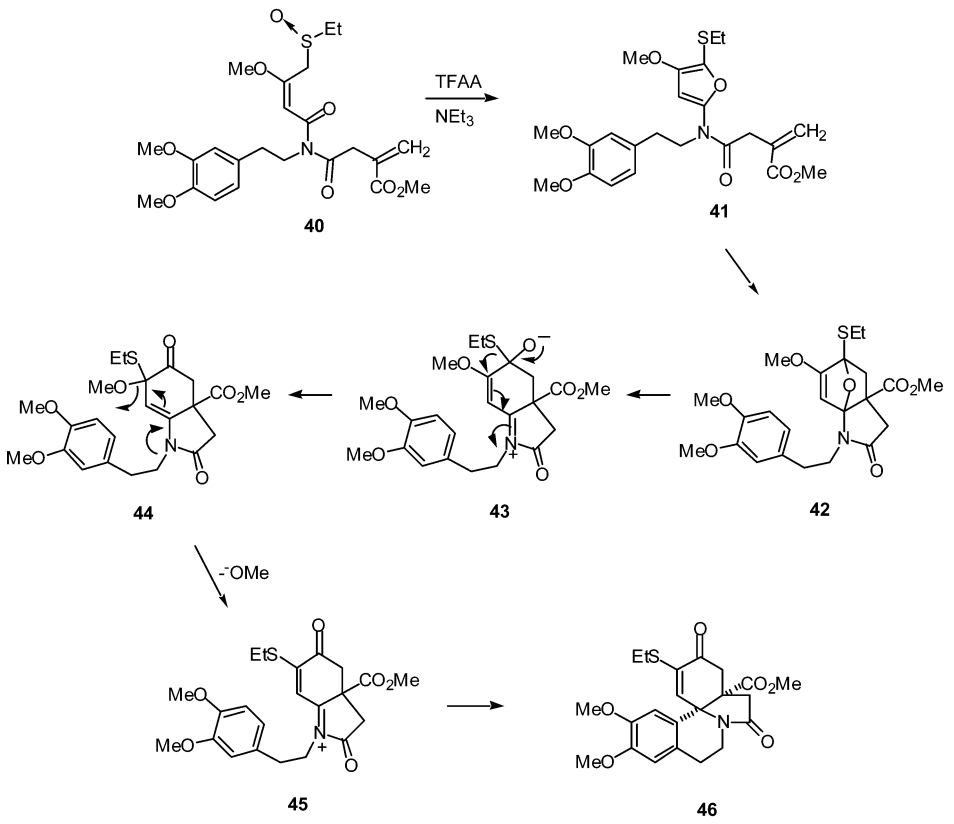
EFFICIENT ONE-POT APPROACH TOWARD THE ERYTHRINANE ALKALOID SKELETON

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 [36]. In order to avoid the deprotonation (aromatization) step, we prepared sulfoxides **34** and **35**, each possessing a carbomethoxy 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 frontier molecular orbital (FMO) considerations. *N*-Acyliminium ion **37** derived from the internal cycloadduct **36** underwent stereoselective spirocyclization to furnish the *cis*-3,4-benzoerythrinane **38** or homoerythrinane derivative **39** in good yield (Scheme 7). The overall triple cascade sequence represents an efficient one-pot approach toward the erythrinane alkaloid skeleton [37] in which the spirocyclic ABC skeleton is assembled in a single operation.

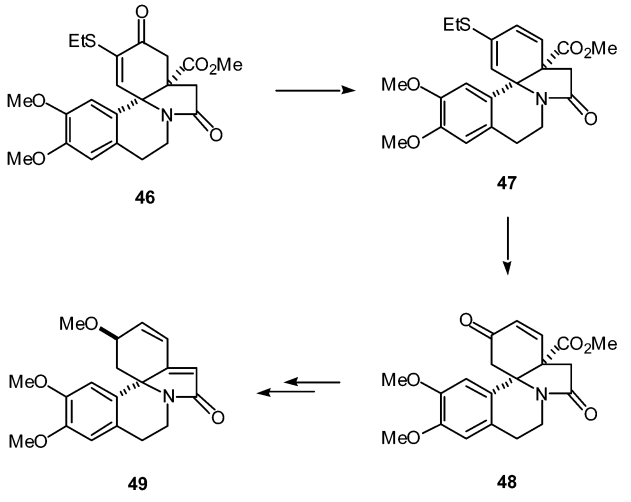


Scheme 7

A synthesis of (±)-erysotramidine (**49**) was undertaken in order to further test the viability of the triple cascade process as an entry into the erythrinane skeleton. The requisite starting imido sulfoxide **40**, possessing both a dienophilic and diactivated aromatic π-tether, was efficiently synthesized from known starting materials. Subjection of **40** to the Pummerer conditions gave compound **46** as a single diastereomer in 83 % yield. The *cis* A/B ring fusion present in **46** was unequivocally established by X-ray crystallographic analysis and is identical to the stereochemical relationship found in the naturally occurring erythrina alkaloids. The conversion of **40** into **46** is believed to follow the pathway outlined in Scheme 8. The initially formed α-thiocarbocation intermediate generated from the Pummerer reaction of **40** is intercepted by the adjacent imido carbonyl to produce the α-amido substituted furan **41**. This transient intermediate undergoes a subsequent intramolecular Diels–Alder cycloaddition across the tethered π-bond to furnish cycloadduct **42**. Nitrogen-assisted ring opening of the oxabicyclic bridge results in the formation of zwitterionic intermediate **43**, which undergoes a 1,2-thioethyl shift followed by methoxide ion ejection. Cyclization of the diactivated-aromatic tether onto *N*-acyliminium ion **45** ultimately provides the tetracyclic amide **46**. With a supply of **46** in hand, this enone was converted into the corresponding vinyl triflate, which, in turn, was subjected to a palladium-catalyzed formate reduction to give **47**. The resulting thio-substituted diene was subsequently transformed into ketone **48** via a titanium-mediated hydrolysis (Scheme 9). The present sequence constitutes a formal synthesis of (±)-erysotramidine (**49**) based on the successful conversion of **48** into **49** by Tsuda and coworkers [38].



Scheme 8

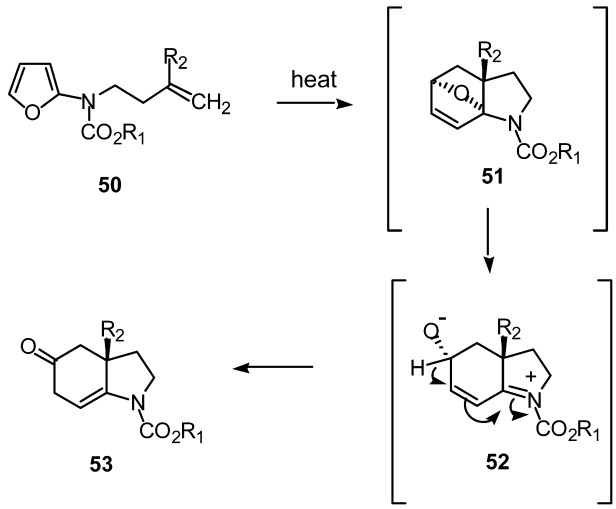


Scheme 9

[4+2]-CYCLOADDITION CHEMISTRY OF FURANYL CARBAMATES

As an outgrowth of the above approach toward the erythrinane family, we undertook a subsequent study directed toward the synthesis of the lycorine type of alkaloids by utilizing the [4+2]-cycloaddition chemistry of furanyl carbamates [39]. Our synthetic strategy was to take advantage of an intramolecu-

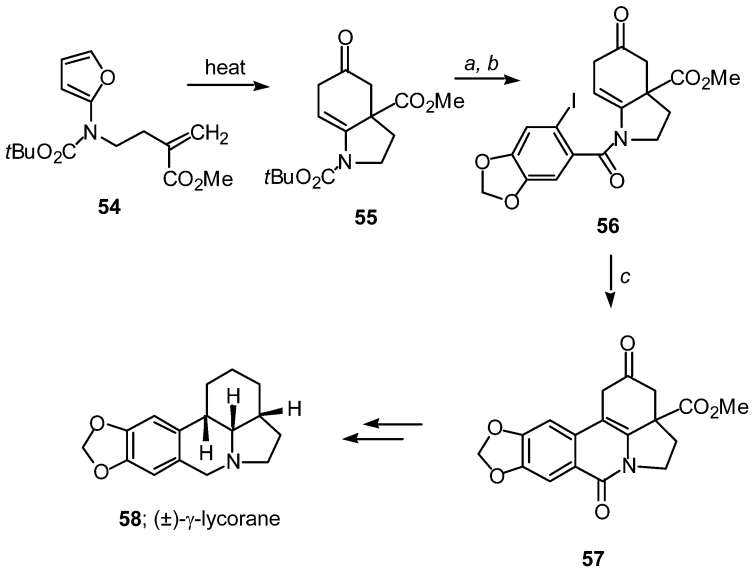
lar Diels–Alder of an alkenyl-substituted furanyl carbamate derivative (IMDAF) [40,41]. In our approach to the core hexahydroindoline skeleton of this family of natural products, we examined the ring-opening reaction of an aza-substituted oxabicyclo[2.2.1]heptene derivative. Oxabicyclic compounds are known to be valuable intermediates for the synthesis of a variety of molecules of biological interest [42]. We found that the [4+2]-oxabicyclic adduct **51**, initially formed from the intramolecular Diels–Alder cycloaddition of a suitably substituted furanyl carbamate such as **50**, underwent a nitrogen-assisted ring opening. A subsequent hydrogen shift of the resulting zwitterion **52** gave the hexahydroindolinone ring system **53** (Scheme 10).



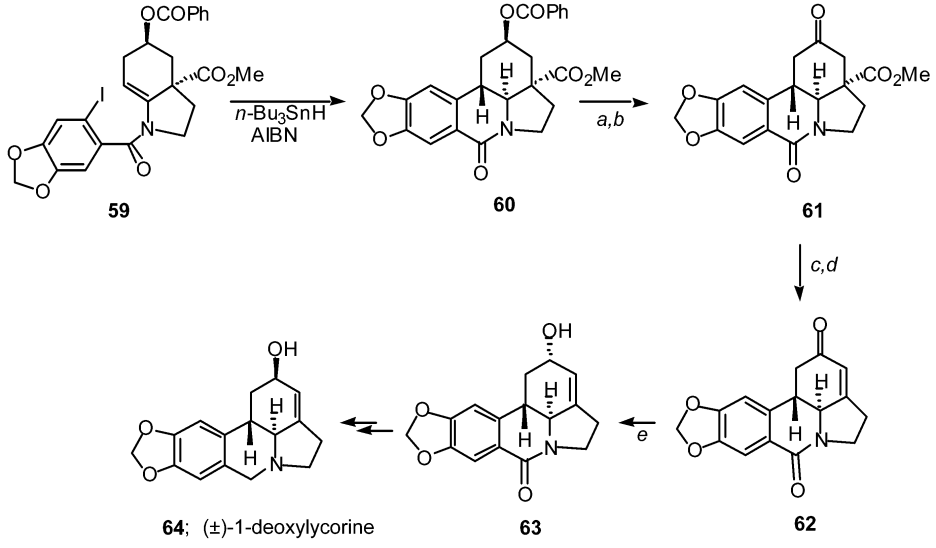
Scheme 10

To highlight the method, we applied the synthetic strategy to the synthesis of (±)-γ-lycorane (**58**) (Scheme 11) [43]. The initially formed [4+2]-cycloadduct **55** derived from furanyl carbamate **54** undergoes nitrogen-assisted ring opening followed by deprotonation/reprotonation of the resulting zwitterion to give a rearranged hexahydroindolinone **56**. The stereochemical outcome of the IMDAF cycloaddition has the side-arm of the tethered alkenyl group oriented *syn* with respect to the oxygen bridge. Removal of the *t*Boc group in **55** followed by reaction with 6-iodobenzo[1,3]-dioxole-5-carbonyl chloride afforded enamide **56**. Treatment of this compound with $Pd(OAc)_2$ provided the galanthan tetracycle **57** in good yield. Compound **57** was subsequently converted into (±)-γ-lycorane **58** using a 4-step procedure to establish the *cis*-B,C ring junction.

A radical-based cyclization of the related enamide **59** was used for the synthesis of 1-deoxylycorine (**64**) (Scheme 12). Heating a benzene solution of **59** with 2,2′-azo-bis-isobutyrylnitrile (AIBN) and *n*-Bu_3SnH at reflux gave the tetracyclic compound **60** possessing the requisite *trans* fusion between rings B and C in good yield. After hydrolysis and oxidation of **60** to **61**, an oxidative decarboxylation reaction was used to provide the C_2–C_3–C_{12} allylic alcohol unit characteristic of the lycorine alkaloids. The resulting enone was eventually transformed into (±)-1-deoxylycorine (**64**) via known synthetic intermediates [44].



Scheme 11 Reagents: (a) HCl, CH_2Cl_2; (b) pyridine, 6-iodobenzo[1,3]dioxole-5-carbonyl; (c) $Pd(OAc)_2$, $[(Bu)_4N]^+Cl^-$, KOAc, DMF.

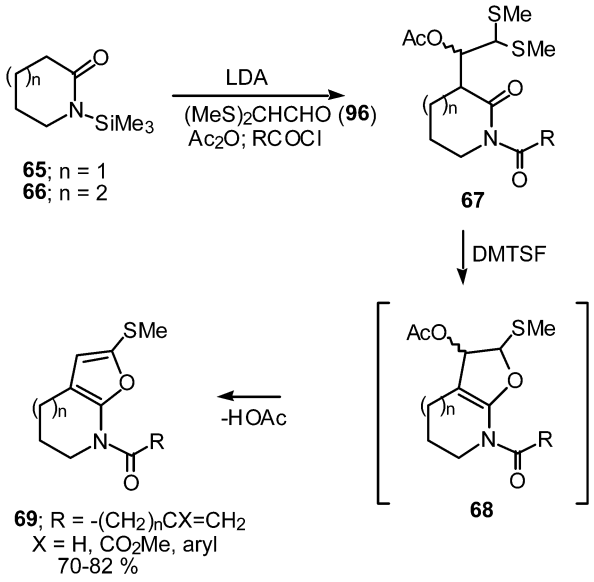


Scheme 12 Reagents: (a) $NaOCH_3$, CH_3OH; (b) Dess–Martin oxidation; (c) NaOH, MeOH, H_2O; (d) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine; (e) $NaBH_4$, MeOH.

INTRAMOLECULAR DIELS–ALDER REACTION OF CYCLIC 5-THIO-2-AMIDO-FURANS

More recently, we developed a method for preparing cyclic 5-thio-2-amido-furans since functionalized furans of this sort allows for the ready access of a variety of novel azapolycyclic ring systems [45]. The method consisted of a Pummerer-induced cyclization of imido dithioacetals of type **67** (Scheme 13). The starting substrates were prepared by the mixed aldol reaction of the *N*-trimethylsilyl-protected

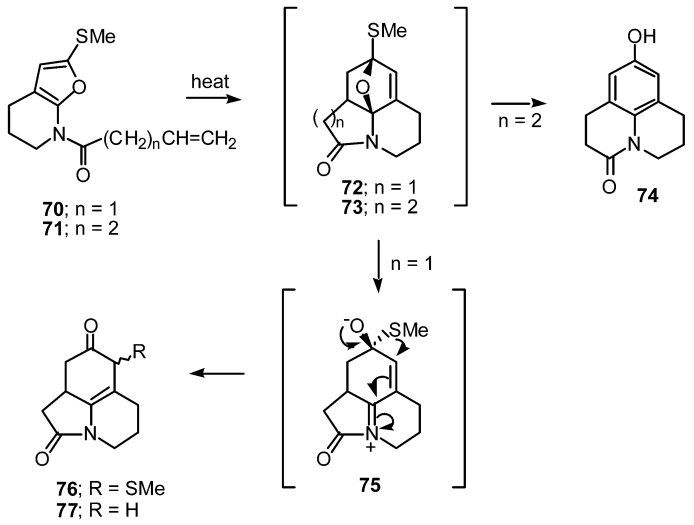
δ-valerolactam **65** (or ε-caprolactam **66**) with bis(methylsulfanyl)acetaldehyde. Quenching the reaction with acetic anhydride followed by aqueous workup provided the expected aldol product in high yield as a 4:1-mixture of diastereomers. The cyclic lactams were acylated with various acid chlorides using powdered 4Å molecular sieves as a neutral acid scavenger to provide the corresponding imides **67** in 60–98 % yield. It was known from earlier work in the literature that treatment of thioketals with DMTSF causes the carbon–sulfur bond to become labile upon methylthiolation [46]. The initially formed alkylthiosulfonium ion easily dissociates to produce a thionium ion and methyl sulfide [47]. Cyclization of the Pummerer intermediate onto the amide carbonyl group first affords dihydrofuran **68**, which undergoes a subsequent elimination of acetic acid to give the cyclic 2-thio-amido-furan system **69** in high overall yield.



Scheme 13

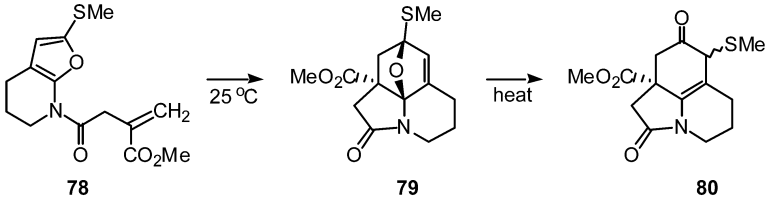
With a satisfactory method for the synthesis of the cycloaddition precursors in place, we examined the Diels–Alder reaction of the *N*-yl-but-3-en-1-one substituted amido furan **70** (*n* = 1). Thermolysis of **70** at 110 °C furnished the rearranged hexahydro-pyrroloquinolin-2-one **76** as the only isolable product in 92 % yield as a 3:2 mixture of diastereomers after silica gel chromatography (Scheme 14) [48]. Dethiomethylation occurred smoothly when a sample of **76** was subjected to Raney Ni reduction in 95 % ethanol producing **77** in 85 % yield. In contrast to the above result, thermolysis of the homologous *N*-yl-pent-4-en-1-one amido furan **71** gave phenol **74** in 82 % yield. In both cases, the initially formed oxo-bridged cycloadducts (i.e., **72** or **73**) could not be isolated, as they readily underwent ring opening to produce the observed products. Furan **71**, with the longer five-carbon tether, required more forcing conditions (200 °C) for the Diels–Alder cycloaddition, and this resulted in the formation of phenol **74**. Presumably, the initially formed cycloadduct **73** underwent ring opening/thiomethyl migration, but this was followed by elimination of methanethiol at the higher temperatures employed.

Because electron-withdrawing substituents on the π-bond exhibit a powerful influence on the rate of HOMO-dienyl [4+2]-cycloadditions, a study of the thermal behavior of the 2-carbomethoxy-substituted alkenyl amido furan **78** appeared to us to be a worthwhile goal. Indeed, incorporation of this activating substituent on the alkenyl π-bond greatly facilitated the cycloaddition, and it was possible to isolate the Diels–Alder adduct **79** as a single diastereomer in 45 % yield simply by stirring a sample of **78**



Scheme 14

in benzene at 25 °C (Scheme 15). The structure of **79** was firmly established by X-ray crystallography, which revealed an *anti*-stereochemical relationship between the carbomethoxy group and oxygen bridge. The formation of this *endo*-cycloadduct is in full accord with molecular mechanics calculations, which show a large ground-state energy difference between the two diastereomers [49]. Heating a sample of **79** at 90 °C gave the rearranged hexahydropyrrolo-quinolinone **80** in 78 % yield as a 1:1 mixture of diastereomers.

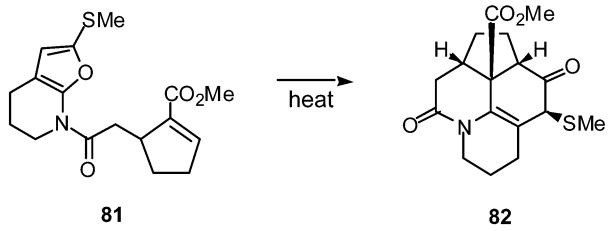


Scheme 15

SYNTHESIS OF COMPLEX POLYAZACYCLIC SYSTEMS BY THE IMDAF REACTION

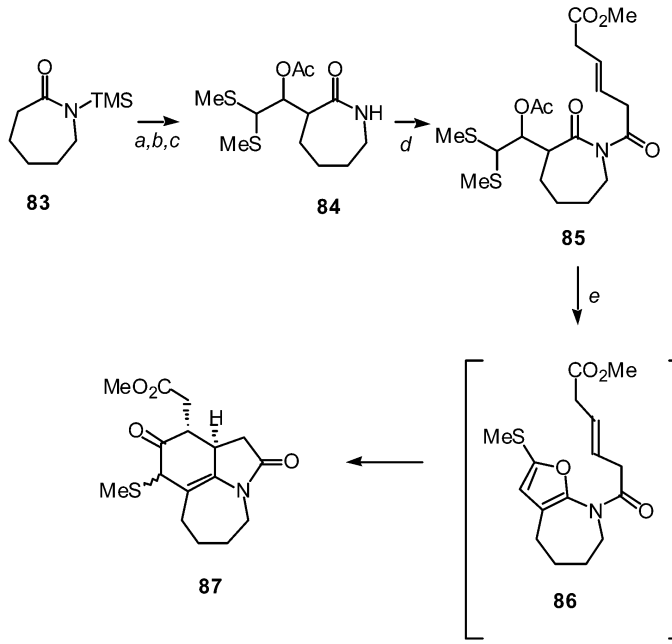
To further illustrate the viability of this sequence as a practical strategy for the synthesis of complex polyazacyclic systems, we studied the cycloaddition behavior of the related amido furan **81**. We were gratified to find that heating **81** at 110 °C for 2 h gave the rearranged amide **82** as a single diastereomer in 80 % yield (Scheme 16). The 1,2-thiomethyl shift that occurs from the transient Diels–Alder cycloadduct probably proceeds via an episulfonium ion, and consequently only one diastereomer would be expected [50]. Further transformations of **80** and **82** using the existing functional groups to establish additional stereogenic centers are currently underway.

We have also used the intramolecular Diels–Alder reaction of an IMDAF to create the azepinoindole skeleton present in the alkaloid stenine [51]. The required 2-methylthio-5-amido-furan (**86**) necessary for the intramolecular [4+2]-cycloaddition reaction was prepared by a DMTSF-induced cyclization of imido dithioacetal **85** (Scheme 17). The synthesis of **85** involved a mixed aldol reaction of *N*-trimethylsilyl ε-caprolactam (**83**) with bis(methylsulfanyl)acetaldehyde followed by quenching with acetic anhydride to give amide **84** in 80 % yield [51]. The resulting lactam was acylated with



81 82

Scheme 16



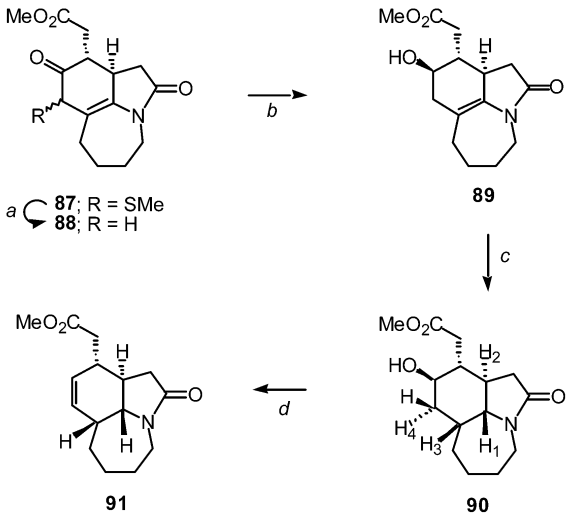
83 84 85 86 87

Scheme 17 Reagents: (a) LDA; (b) $(MeS)_2CHCHO$; (c) Ac_2O; (d) $MeO_2CCH_2CH{=}CHCH_2COCl$; (e) DMTSF, NEt_3.

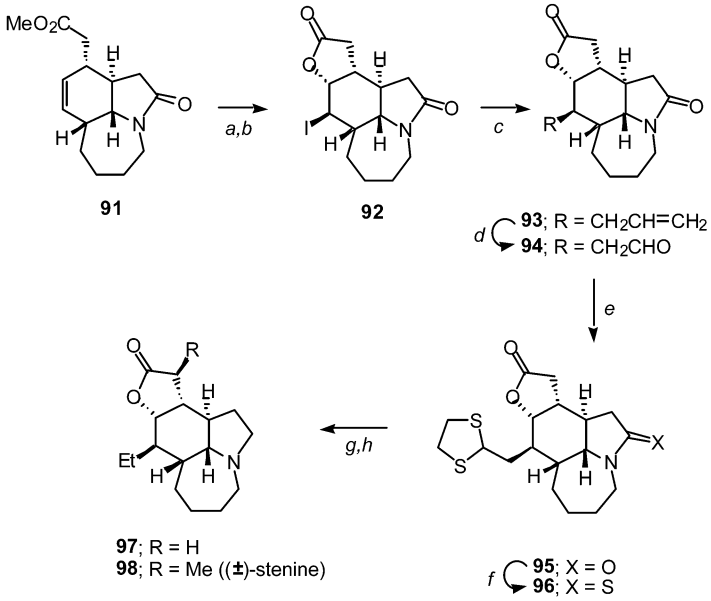
trans-5-chlorocarbonyl-pent-3-enoic acid methyl ester in the presence of 4Å powdered molecular sieves as a neutral scavenger to furnish imide **85** in 85 % yield as a 4:1 mixture of diastereomers. Methylsulfenylation of one of the methylthio groups of **85** with DMTSF induces a thionium-promoted cyclization, and the resulting dihydrofuran readily loses acetic acid to furnish the desired furan. Interestingly, amido furan **86** could not be isolated under the conditions of its formation, as it rapidly rearranged at room temperature to afford azepinoindole **87** in 80 % yield as a 1:1 mixture of diastereomers. Conformational effects imposed by the placement of a carbonyl group within the tether, combined with a rotational bias about the C(2)–N bond apparently enhances the rate of the IMDAF reaction of **86** so that it occurs readily at 25 °C [49].

Removal of the methylthio group was easily accomplished by treating **87** with Raney Ni in ethanol, which afforded azepinoindole **88** as a single diastereomer in 92 % isolated yield. Subsequent reduction of the keto group provided alcohol **89** in 77 % isolated yield as a single diastereomer (Scheme 18). The next step involved a controlled hydrogenation of the enamide π-bond. Excellent stereochemical control could be obtained by hydrogenation of **89** with the Crabtree catalyst [52]. The addition of hydrogen is directed by the presence of the C_{10} hydroxyl group delivering the desired *syn/anti* stereochemistry at the ring fusion sites. Confirmation of the stereochemistry comes from a single-crystal X-ray analysis of

90. Regiocontrolled dehydration of alcohol **90** to alkene **91** sets the stage for the formation of the butyrolactone ring. Alcohol **10** was converted to the corresponding mesylate, and this was followed by treatment with DBU in refluxing toluene to effect elimination providing **91** in 64 % yield. The conversion of **91** to stenine (**98**) was accomplished using the sequence of reactions outlined in Scheme 19. Thus, hydrolysis of the methyl ester with LiOH followed by treatment with iodine gave iodolactone **92** in 60 % yield. Subsequent Keck allylation with allyltributyl-stannane [53] using the Hart–Wipf protocol [54] furnished **93** in 62 % yield and with excellent diastereoselectivity. Johnson–Lemieux oxidation of the allyl group afforded the expected aldehyde **94**, which was treated with 1,2-ethanedithiol and



Scheme 18 Reagents: (a) Raney–Ni, EtOH; (b) $NaBH_4$, $CeCl_3$, MeOH; (c) Crabtree's catalyst, H_2, CH_2Cl_2; (d) MsCl, NEt_3, DBU.



Scheme 19 Reagents: (a) LiOH, H_2O; (b) I_2, MeCn; (c) $CH_2{=}CHCH_2SnBu_3$, AIBN, (d) OsO_4, $NalO_4$; (e) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$; (f) Lawesson's reagent; (g) Raney Ni; (h) LDA, HMPA, MeI.

$BF_3 \cdot Et_2O$ to give **95** in 48 % yield for both steps. Conversion of the amide to the corresponding thioamide with Lawesson's reagent provided **96** in 73 % yield. Desulfurization with Raney Ni furnished **97** in 93 % yield. Methylation of the lactone enolate derived by treating **97** with LDA followed by reaction with methyl iodide afforded racemic stenine (**98**) [51].

In conclusion, our investigations have shown that many structurally diverse heterocyclic compounds can be easily accessed via the domino Pummerer/cycloaddition/*N*-acyliminium ion cyclization cascade. The key step in this process involves the generation of an amino-substituted furan by a Pummerer-induced cyclization reaction. After the Diels–Alder reaction occurs, the [4+2]-cycloadduct undergoes a subsequent fragmentation to generate a reactive *N*-acyliminium ion. 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.

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