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Tandem methodology for heterocyclic synthesis*

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Abstract: Tandem methodology for heterocyclic synthesis represents a powerful approach for the rapid buildup of molecular complexity from potentially simple starting materials. Work from our laboratory has shown that the rhodium(II)-catalyzed cyclization cascade of α-diazo imides represents an effective method for the synthesis of a variety of heterocyclic systems. As an extension of these studies, 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. Application of the process for the preparation of the stenoma alkaloid stenine was recently carried out in our laboratory.

INTRODUCTION

Nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties [1,2]. Accordingly, novel strategies for the stereoselective synthesis of azapolycyclic ring systems continue to receive considerable attention in the field of synthetic organic chemistry [3–9]. Tandem methodology for heterocyclic synthesis represents a powerful approach for the rapid buildup of molecular complexity from potentially simple starting materials [10–12]. In the ongoing search for new domino processes in our laboratory, emphasis has been laid on sequential reactions which proceed cleanly and without forming by-products [13–21]. As a prerequisite for an ideally proceeding one-pot sequential transformation, the reactivity pattern of all participating components has to be such, that each building block gets involved in a reaction only when it is supposed to do so. The development of sequences that combine transformations of differing fundamental mechanism broadens the scope of such procedures in synthetic chemistry [22–34].

In 1986, we started work in our laboratory to synthesize bridged hetero-substituted bicycloalkanes from the rhodium(II)-catalyzed cyclization-cascade of 1-diazoalkanediones [35]. The domino reaction was shown to proceed by the formation of a rhodium carbenoid intermediate and subsequent

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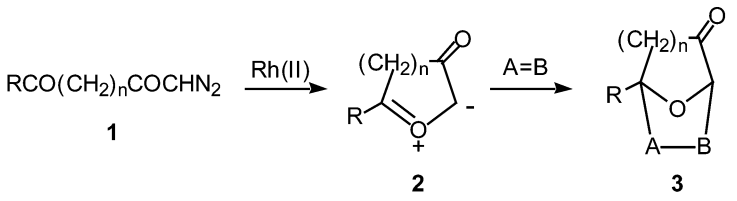
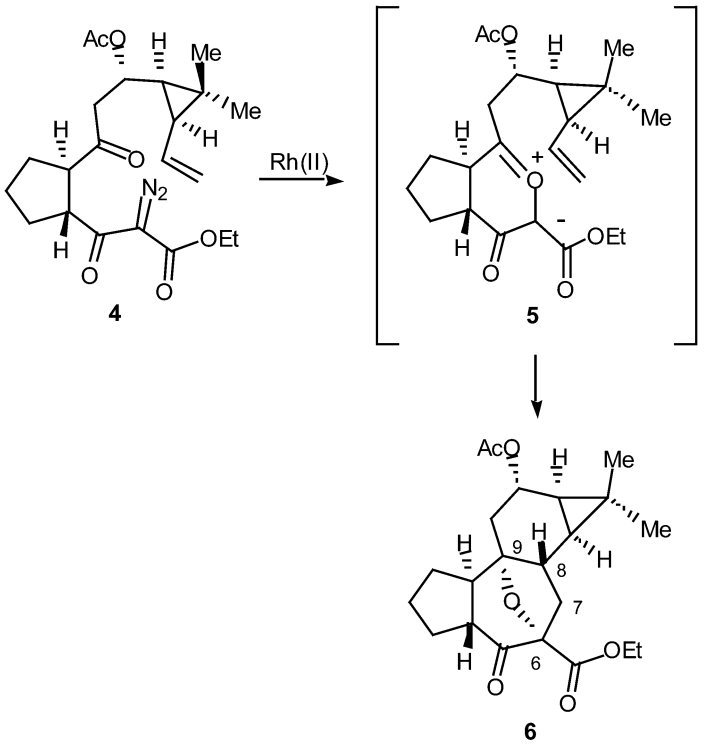
transannular cyclization of the electrophilic carbon onto the adjacent keto group to generate a cyclic carbonyl ylide, followed by 1,3-dipolar cycloaddition (Scheme 1) [36]. The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting centers be sufficiently close so that effective overlap of the lone pair of electrons of the carbonyl group with the metallocarbenoid can occur [37]. Most of our studies were carried out with five- and six-membered ring systems [35]. The resulting cyclic dipole (i.e., **2**) always contained a carbonyl group within the ring. We [38] and others [39] have found that the intramolecular trapping of carbonyl ylide dipoles with tethered alkenes represents an effective method for the synthesis of a variety of natural products. An interesting application of this method is found as the central step of Dauben's synthesis of the tigliane ring system [40].



1 **2** **3**

Scheme 1

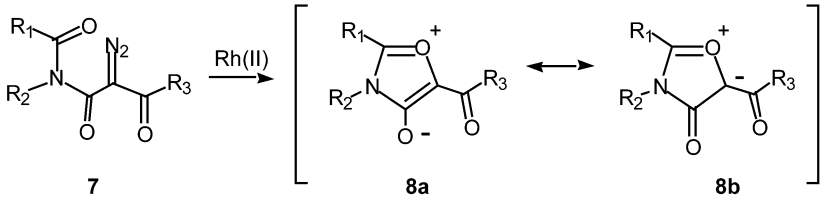
Carbonyl ylide **5**, generated from the diazo carbonyl **4** in the presence of a catalytic amount of rhodium(II) acetate, underwent intramolecular addition with the olefin to form the C6, C9-oxido bridge tigliane ring system **6** (Scheme 2). The two new stereocenters at C8 and C9 were formed with the correct configurations relative to C14 and C15 presented by the natural tigliane compounds.



4 **5** **6**

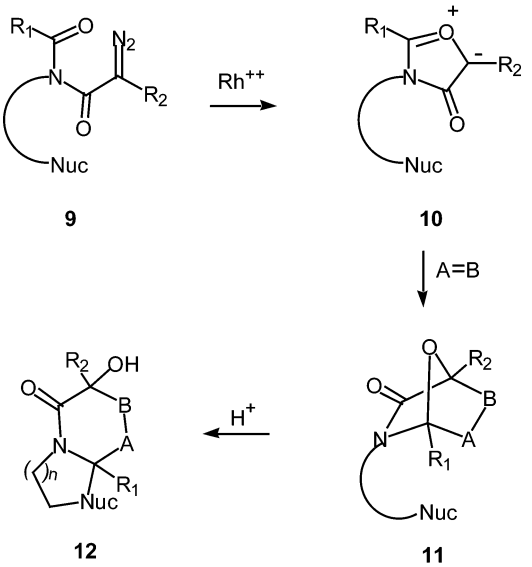
Scheme 2

More recent work from our laboratory has shown that the rhodium(II)-catalyzed cyclization/cycloaddition cascade of α-diazo imides **7** represents a general strategy for the synthesis of ring-fused polyheterocycles [41]. 1,3-Oxazolium 4-oxides (isomünchnones) are easily generated in this manner. This mesoionic ylide corresponds to the cyclic equivalent of a carbonyl ylide and was found to readily undergo [4+2]-cycloaddition with suitable dipolarophiles. Formation of the isomünchnone dipole proceeds by initial generation of a rhodium carbenoid species, followed by an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic ylide **8** [42]. The resultant isomünchnone may be trapped with electron-rich or -deficient dipolarophiles to give the cycloadducts in high yield. These uniquely functionalized cycloadducts (i.e., **11**) contain a "masked" *N*-acyliminium ion which is generated by its treatment with a Lewis acid [43]. By incorporating an internal nucleophile on the tether, annulation of the original cycloadduct **11** allows for the construction of a more complex nitrogen heterocyclic system, particularly B-ring homologues of the erythrinane family of alkaloids [44].



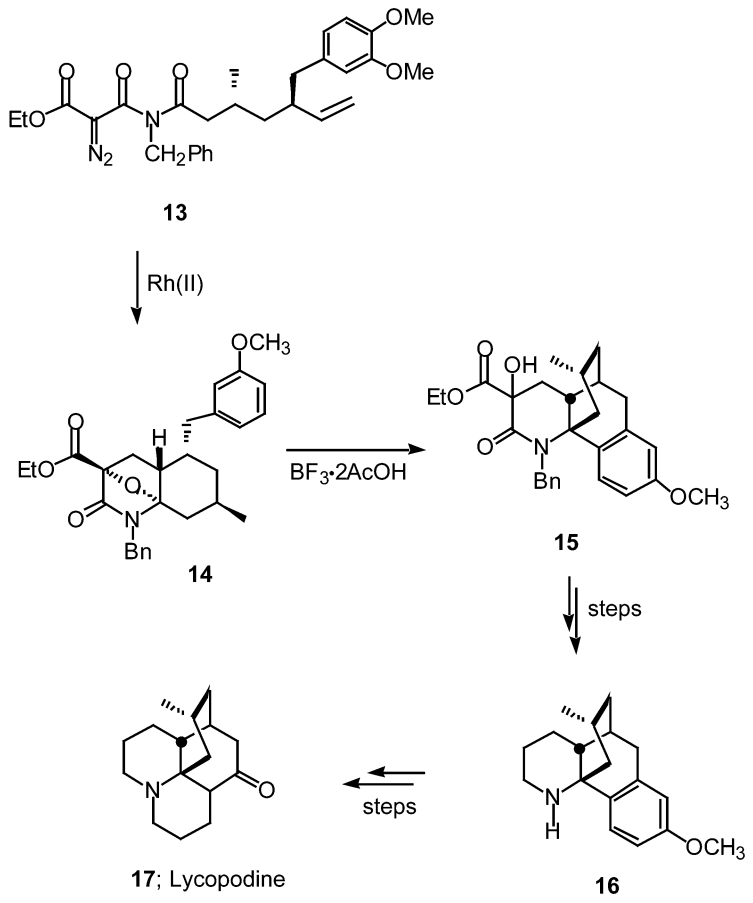
Scheme 3

Starting from simple acyclic diazo imides **9**, 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 **12** (Scheme 4) [42]. This sequence represents the first example where a [3+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. An early application of the domino cascade process toward the construction of



Scheme 4

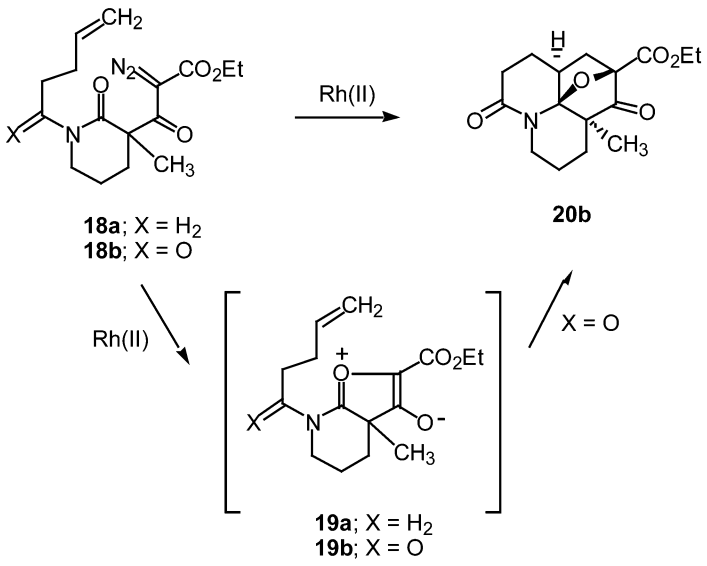
alkaloids involved the synthesis of (±)-lycopodine **17** (Scheme 5) [45]. The isomünchnone cycloadduct **14** was formed from the Rh(II)-catalyzed reaction of diazo imide **13** and was found to be the precursor of the key Stork intermediate **16** (via **14**) [46].



Scheme 5

APPLICATION OF THE DOMINO CYCLIZATION–CYCLOADDITION SEQUENCE TO THE PENTACYCLIC SKELETON OF THE ASPIDOSPERMA RING SYSTEM

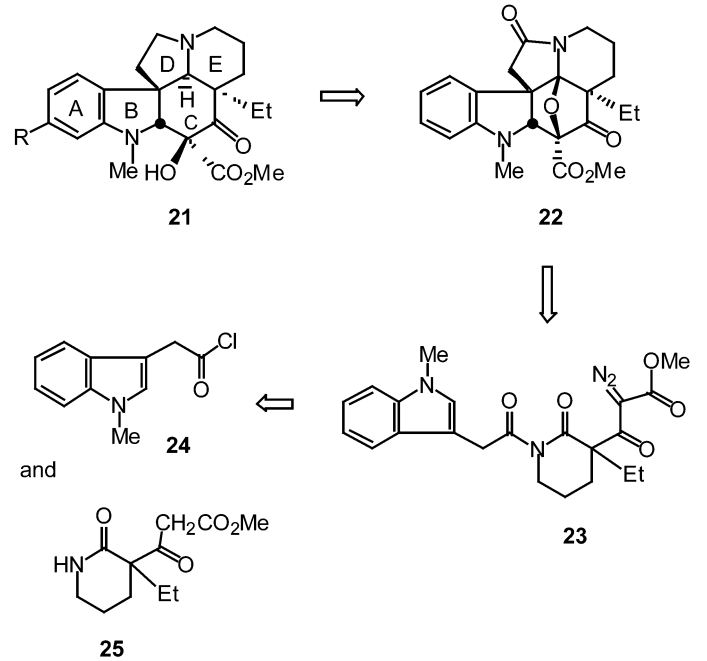
As part of our studies in this general area, we also became interested in the rhodium(II)-catalyzed reactions of diazo ketoamides such as **18**. Attack of the amido oxygen at the rhodium carbenoid produced a carbonyl ylide dipole (i.e., **19**) that is isomeric with the isomünchnone class of mesoionic betaines (**8**). We found that the rhodium(II)-catalyzed formation of carbonyl ylide intermediates derived from cyclic diazo amides furnished tetracycles such as **20b** in good yield, provided that the tether engaged in ring formation carried a carbonyl group (i.e., **18b**, X=O) (Scheme 6) [47]. Without the C=O functionality (i.e., **18a**, X=H), 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 [47]. 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



Scheme 6

processes to intervene. Thus, the reactivity discrepancy between diazo amido esters **18a** and **18b** can be attributed to steric effects in the transition states [21].

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 involves a related domino cascade sequence [48]. This strategy was successfully applied to the synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine (**21**). The approach used is outlined in Scheme 7 and is centered on the construction of the key oxabicyclic intermediate **22**. We reasoned that **21** should be accessible by reduction of the *N*-acyliminium ion derived from **22**, which should be available by a *tandem rhodium(II)-catalyzed cyclization*

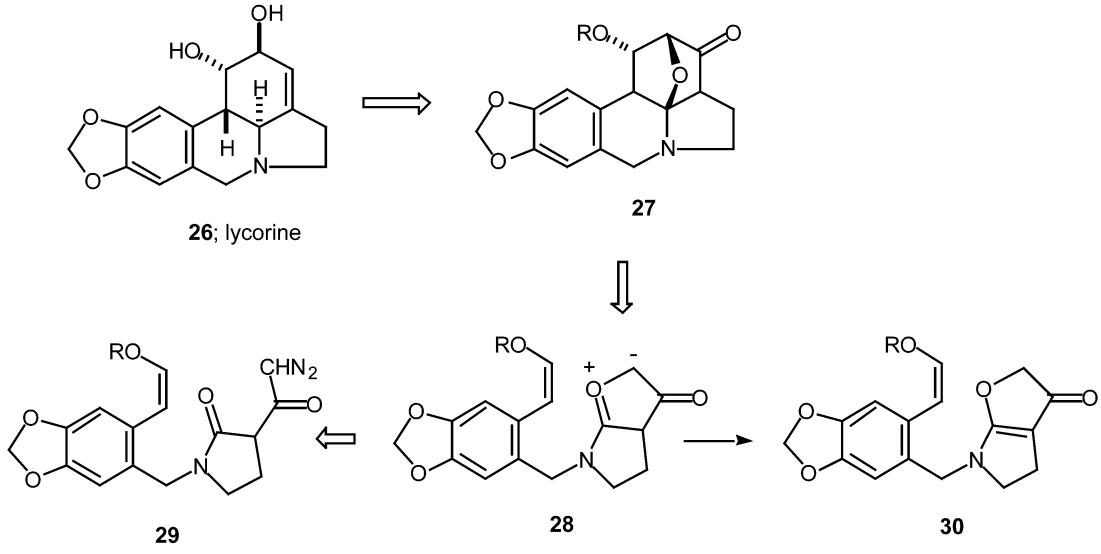


Scheme 7

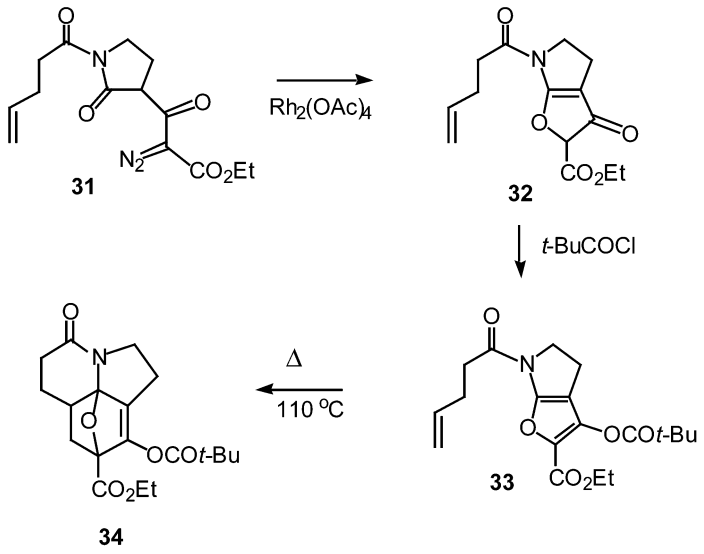
cycloaddition of α-diazoimide **23**. Cycloaddition of the initially formed dipole across the pendant indole π-system [49] would be expected to result in the simultaneous generation of the CD-rings of the aspidosperma skeleton [50]. The stereospecific nature of the internal cycloaddition reaction should also lead to the correct relative stereochemistry of the four chiral centers about the C-ring. In an earlier publication, we described our results which verified the underlying viability of this approach to the aspidosperma skeleton (Scheme 7) [48].

Prompted by our studies dealing with the internal dipolar-cycloaddition reaction of push–pull carbonyl ylides for the synthesis of the aspidosperma skeleton, we became interested in determining whether a related process could be used to assemble the carbon framework of lycorine (**26**).

We envisioned diazoamide **29** functioning as a possible precursor for the generation of dipole **28**. Intramolecular cycloaddition across the neighboring enol ether π-bond followed by reductive ring opening of the transient azabicyclic adduct **27** would provide the lycorine skeleton with the correct relative stereochemistry (Scheme 8). We found however, that a rapid [1,4]-hydrogen shift to furanone **30** occurred before intramolecular cycloaddition [52]. Although the formation of **30** from **28** was somewhat disappointing, it came as no real surprise since one of the characteristic reactions of carbonyl ylides derived from the reaction of α-diazoalkanes with ketones consists of an intramolecular proton transfer [53]. At this point in time, we decided to use the furanone ring to our advantage for an anticipated Diels–Alder cycloaddition. It was envisioned that acylation of the furanone would provide a fused amidofuran that could be subsequently utilized in an intramolecular Diels–Alder reaction. As was encountered with related systems, the decomposition of diazoimide **31** using $Rh_2(OAc)_4$ provided the intermediate furanone **32** which was reacted with pivalyl chloride to furnish amidofuran **33** (Scheme 9). Heating a toluene solution of **33** at reflux provided cycloadduct **34** as the only detectable product in high overall yield for the three-step process (70 %) [54].

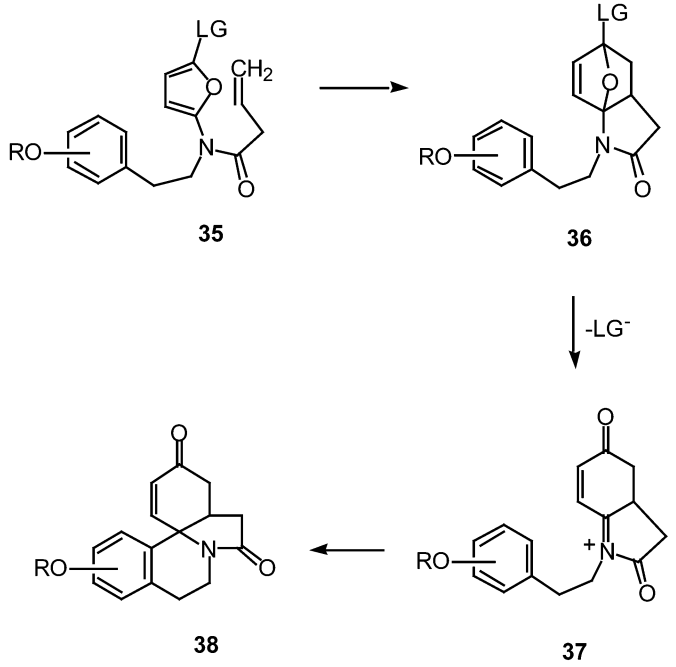


Scheme 8



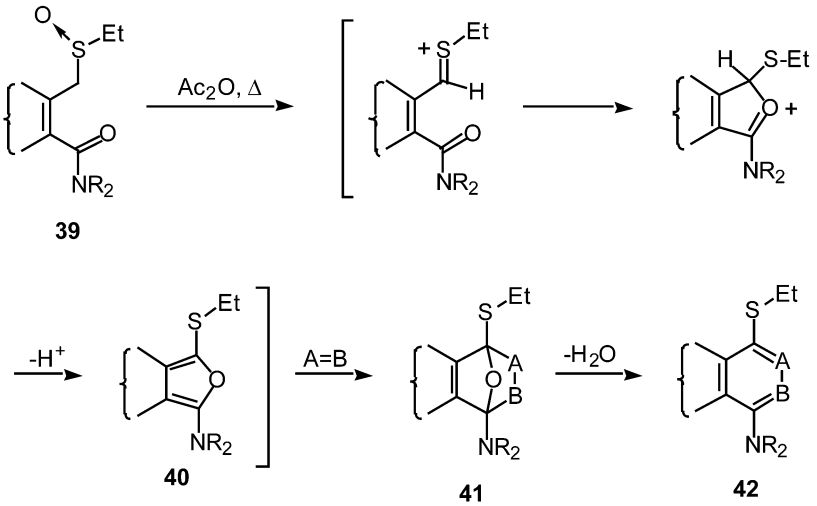
Scheme 9

In the next phase of our work, 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 and apply the methodology toward several alkaloids. Our long-range goal involved using 2-amino-substituted furans such as **35** that contain both a suitable leaving group (LG) and an olefinic tether to allow for an intramolecular Diels–Alder reaction (Scheme 10) [55]. The resultant cycloadduct was expected to undergo ring opening to generate a vinylogous *C*-acyliminium ion of type **36**. Our intention was to use this sequence of reactions for a rapid entry into the erythrinane family of alkaloids [44]. The cascade process of interest involves the combination of a Pummerer, Diels–Alder, and Mannich reaction.



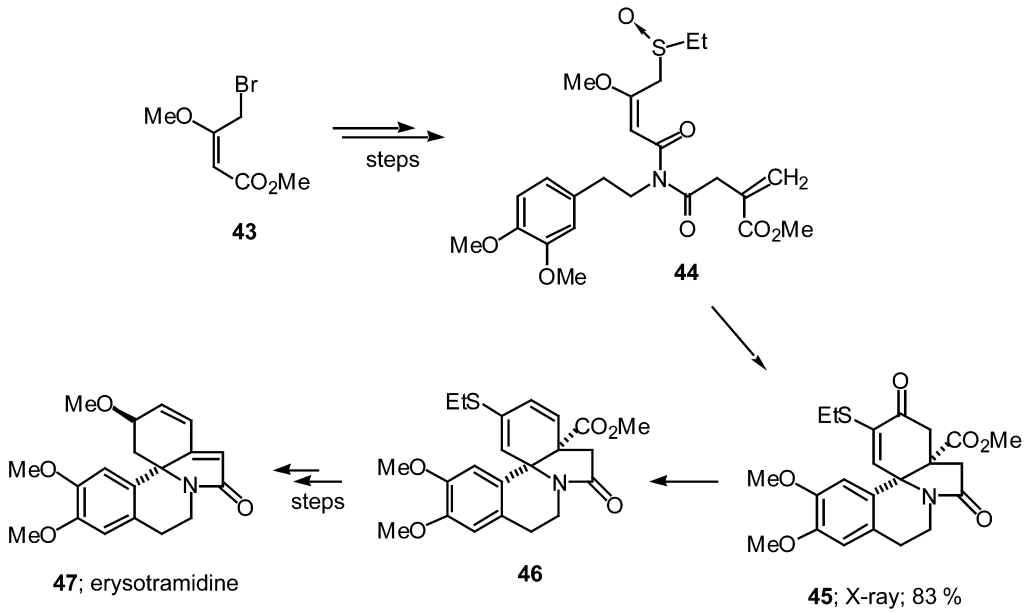
Scheme 10

We found that the required 2-amido-substituted furan (**40**) could be generated using Pummerer ion chemistry as outlined in Scheme 11. Thus, treatment of γ-sulfinyl unsaturated amide **39** with acetic anhydride resulted in cyclization to the desired furanyl system **40** which underwent a smooth Diels–Alder cycloaddition. The resulting cycloadduct **41** underwent loss of water and eventually gave the 4-thioethyl-substituted aniline derivative **42** [56].



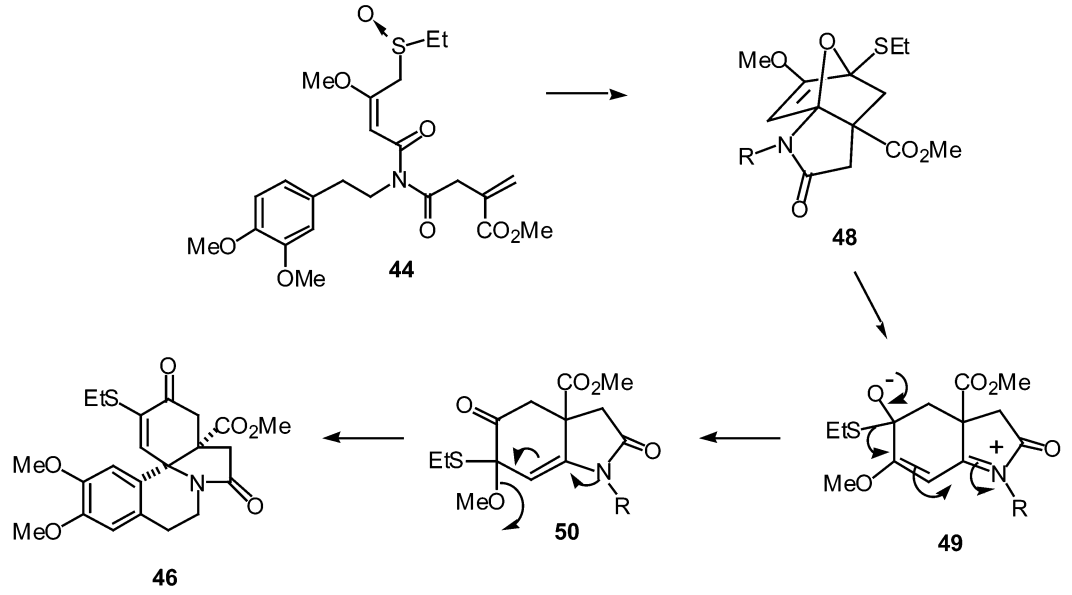
Scheme 11

A synthesis of (±)-erysotramidine (**47**) 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 **44**, possessing both a dienophilic and diactivated aromatic π-tether, was efficiently synthesized from known starting materials. Subjection of **44** to the Pummerer conditions gave compound **45** as a single diastereomer in 83 % yield (Scheme 12) [57]. The *cis* A/B ring fusion present in **45** was unequivocally



Scheme 12

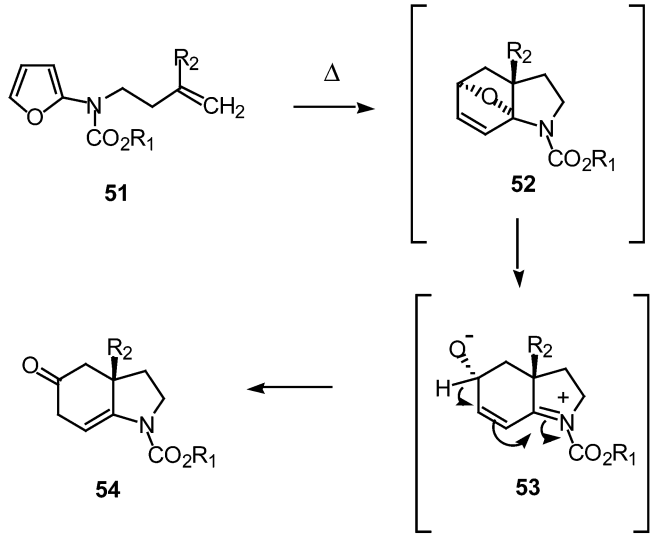
established by an X-ray crystallographic analysis and is identical to the stereochemical relationship found in the naturally occurring Erythrina alkaloids. The conversion of **44** into **45** is believed to follow the pathway outlined in Scheme 13. The initially formed α-thiocarbocation intermediate generated from the Pummerer reaction of **44** is intercepted by the adjacent imido carbonyl to produce a 2-amido-substituted furan. This transient intermediate undergoes a subsequent intramolecular Diels–Alder cycloaddition across the tethered π-bond to furnish cycloadduct **48**. 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 **49** derived from **50** 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. The resulting thio-substituted diene was subsequently transformed into (±)-erysotramidine (**47**) [58].



Scheme 13

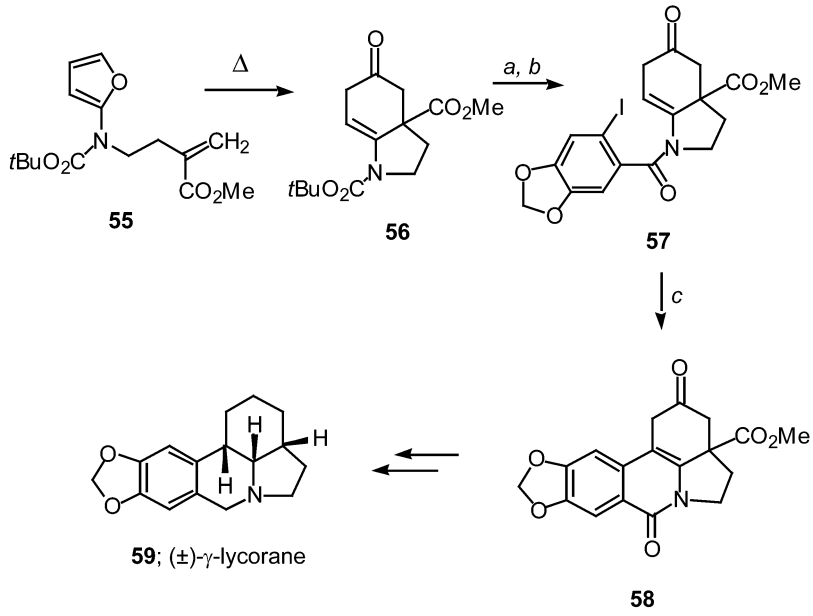
[4+2]-CYCLOADDITION CHEMISTRY OF FURANYL CARBAMATES

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 [59]. Our synthetic strategy was to take advantage of an intramolecular Diels–Alder of an alkenyl-substituted furanyl carbamate derivative (IMDAF) [60,61]. 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 [62]. We found that the [4+2]-oxabicyclic adduct **52**, initially formed from the intramolecular Diels–Alder cycloaddition of a suitably substituted furanyl carbamate such as **51**, underwent a nitrogen-assisted ring opening. A subsequent hydrogen shift of the resulting zwitterion **53** gave the hexahydroindolinone ring system **54** (Scheme 14).



Scheme 14

To highlight the method, we applied the synthetic strategy to the synthesis of (±)-γ-lycorane (**59**) [63]. The initially formed [4+2]-cycloadduct **56** derived from furanyl carbamate **55** undergoes nitrogen-assisted ring opening followed by deprotonation/reprotonation of the resulting zwitterion to give a rearranged hexahydroindolinone **57** (Scheme 15). The stereochemical outcome of the IMDAF cycloaddition has the sidearm of the tethered alkenyl group oriented *syn* with respect to the oxygen bridge. Removal of the *t*Boc group in **56** followed by reaction with 6-iodobenzo[1,3]-dioxole-5-carbonyl chlo-

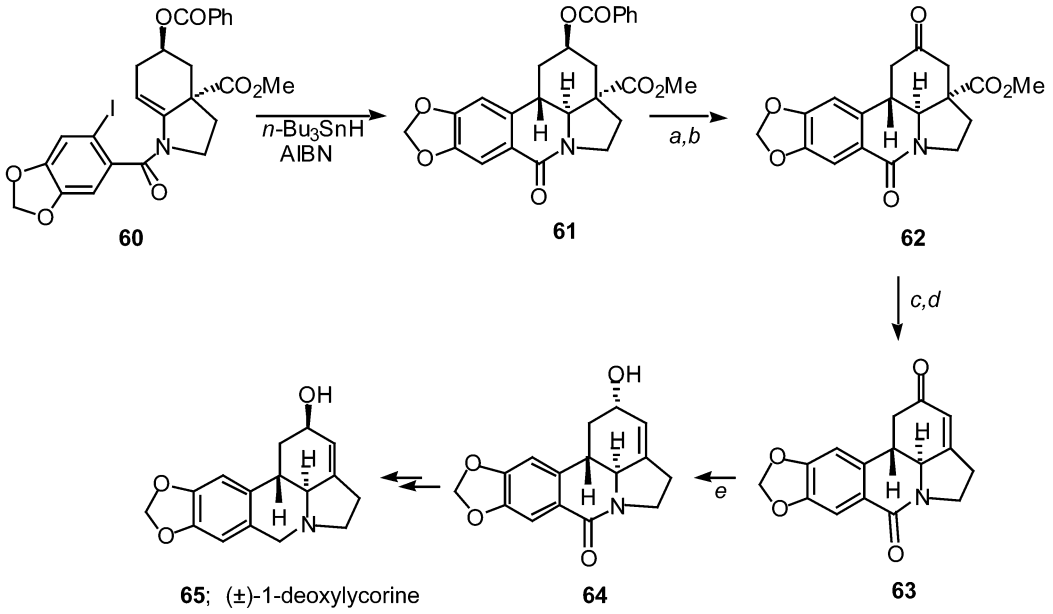


[a]Reagents: (a) HCl, CH_2Cl_2; (b) pyridine, 6-iodobenzo[1,3]dioxole-5-carbonyl chloride; (c) $Pd(OAc)_2$, $[(Bu)_4N]^+Cl^-$, KOAc, DMF.

Scheme 15

ride afforded enamide **57**. Treatment of this compound with $Pd(OAc)_2$ provided the galanthan tetracycle **58** in good yield. Compound **58** was subsequently converted into (±)-γ-lycorane **59** using a four-step procedure to establish the *cis*-B,C ring junction.

A radical-based cyclization of the related enamide **60** was used for the synthesis of 1-deoxylycorine (**65**). Heating a benzene solution of **60** with 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 (Scheme 16). After hydrolysis and oxidation of **61** to **62**, 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 (**65**) via known synthetic intermediates [64].

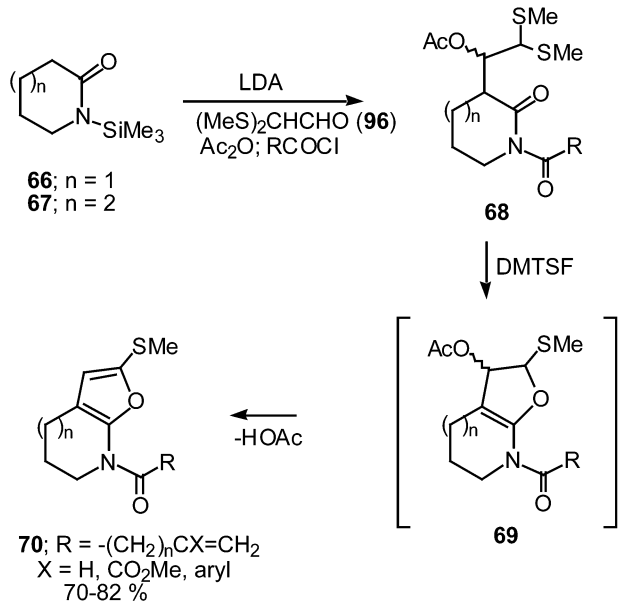


[a]Reagents: (a) $NaOCH_3$, CH_3OH; (b) Dess-Martin oxidation; (c) NaOH, MeOH, H_2O; (d) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine; (e) $NaBH_4$, MeOH.

Scheme 16

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

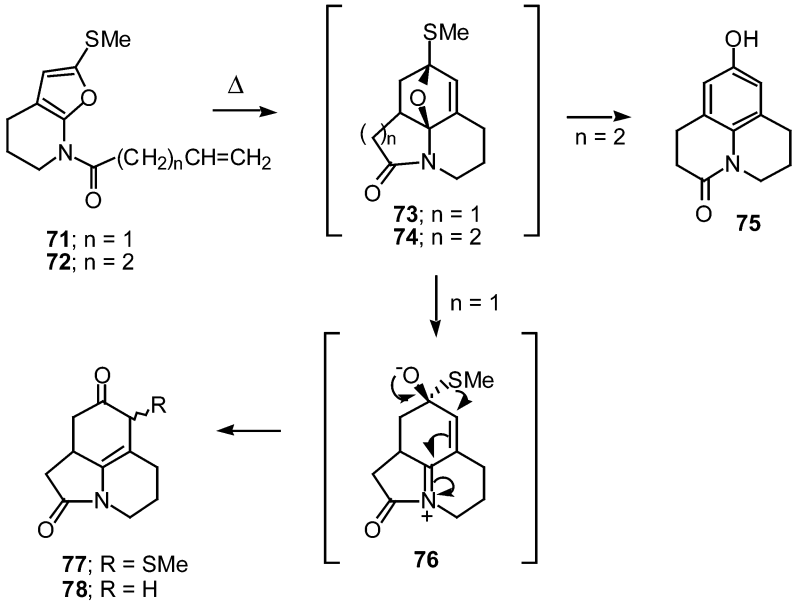
More recently, we developed a method for preparing cyclic 5-thio-2-amido-furans since functionalized furans of this sort allows for the ready access of a variety of novel azapolycyclic ring systems [65]. The method consisted of a Pummerer-induced cyclization of imido dithioacetals of type **68** (Scheme 17). The starting substrates were prepared by the mixed aldol reaction of the *N*-trimethylsilyl protected δ-valerolactam **66** (or ε-caprolactam **67**) 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 4 Å molecular sieves as a neutral acid scavenger to provide the corresponding imides **68** in 60–98 % yield. It was known from earlier work in the literature that treatment of thioketals with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) causes the carbon–sulfur bond to become labile upon methylthiolation [66]. The initially formed alkylthiosulfonium ion easily dissociates to produce a thionium ion and methyl sulfide [67]. Cyclization of the Pummerer intermediate onto the amide



Scheme 17

carbonyl group first affords dihydrofuran **69** which undergoes a subsequent elimination of acetic acid to give the cyclic 2-thio-amidofuran system **70** in high overall yield.

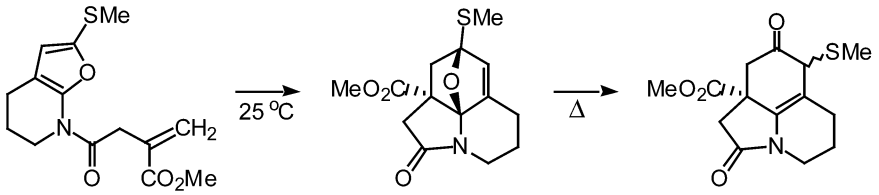
With a satisfactory method for the synthesis of the cycloaddition precursors in place, we examined the Diels–Alder reaction of the *N*-yl-but-3-en-1-one substituted amidofuran **71** (n = 1). Thermolysis of **71** at 110 °C furnished the rearranged hexahydro-pyrroloquinolin-2-one **77** as the only isolable product in 92 % yield as a 3:2-mixture of diastereomers after silica gel chromatography (Scheme 18) [68]. Dethiomethylation occurred smoothly when a sample of **77** was subjected to Raney-Ni reduction in 95 % ethanol producing **78** in 85 % yield. In contrast to the above result, thermolysis



Scheme 18

of the homologous *N*-yl-pent-4-en-1-one amidofuran **72** gave phenol **75** in 82 % yield. In both cases, the initially formed oxo-cycloadducts (i.e., **73** or **74**) could not be isolated, as they readily underwent ring opening to produce the observed products. Furan **72**, 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 **75**. Presumably, the initially formed cycloadduct **74** 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 amidofuran **79** 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 **80** as a single diastereomer in 45 % yield simply by stirring a sample of **79** in benzene at 25 °C (Scheme 19). The structure of **80** 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 [69]. Heating a sample of **80** at 90 °C gave the rearranged hexahydropyrrolo-quinolinone **81** in 78 % yield as a 1:1-mixture of diastereomers.

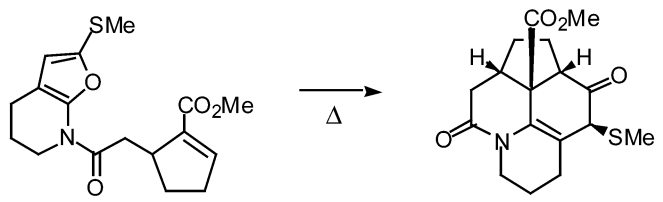


79 **80** **81**

Scheme 19

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 amidofuran **82**. We were gratified to find that heating **82** at 110 °C for 2 h gave the rearranged amide **83** as a single diastereomer in 80 % yield (Scheme 20). 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 [70].

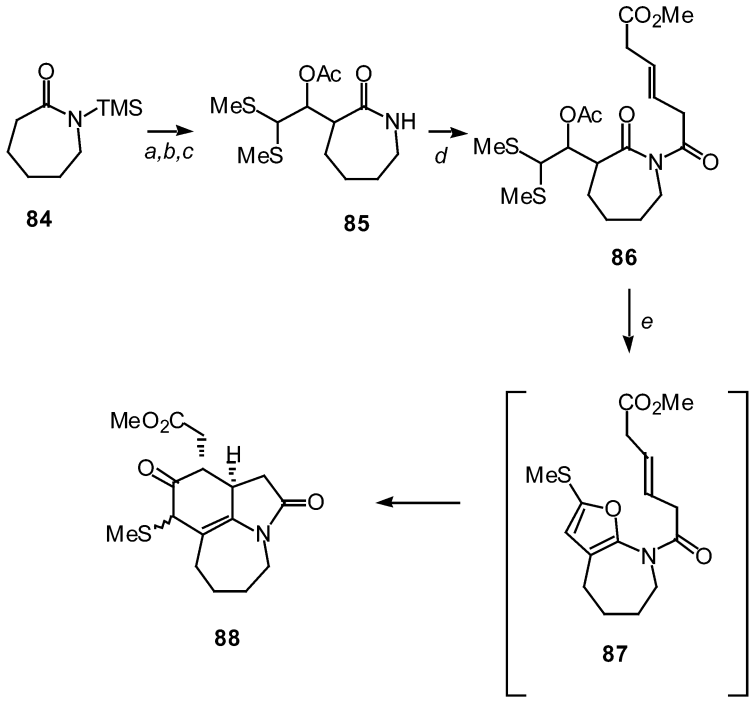


82 **83**

Scheme 20

We have also used the intramolecular Diels–Alder reaction of a 2-amido-5-alkylthio-substituted furan (IMDAF) to create the azepinoindole skeleton present in the alkaloid stenine. The required 2-methylthio-5-amidofuran (**87**) necessary for the intramolecular [4+2]-cycloaddition reaction was prepared by a dimethyl(methylthio)-sulfonium tetrafluoroborate (DMTSF) induced cyclization of

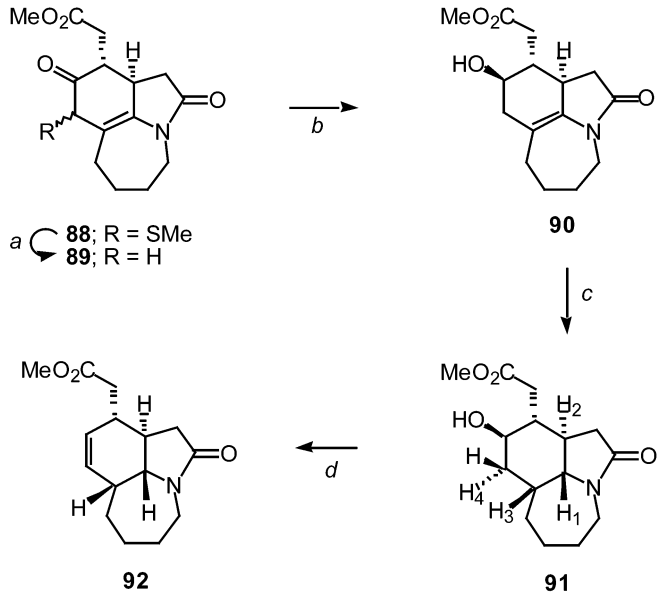
imido dithioacetal **86** (Scheme 21). The synthesis of **86** involved a mixed aldol reaction of *N*-trimethylsilyl ε-caprolactam (**84**) with bis(methylsulfanyl)acetaldehyde followed by quenching with acetic anhydride to give amide **85** in 80 % yield [71]. The resulting lactam was acylated with *trans*-5-chlorocarbonyl-pent-3-enoic acid methyl ester in the presence of 4 Å powdered molecular sieves as a neutral scavenger to furnish imide **86** in 85 % yield as a 4:1-mixture of diastereomers. Methylsulfenylation of one of the methylthio groups of **86** with DMTSF induces a thionium-promoted cyclization and the resulting dihydrofuran readily loses acetic acid to furnish the desired furan. Interestingly, amidofuran **87** could not be isolated under the conditions of its formation, as it rapidly rearranged at room temperature to afford azepinoindole **88** 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 **87** so that it occurs readily at 25 °C [69].



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

Scheme 21

Removal of the methylthio group was easily accomplished by treating **88** with Raney Ni in ethanol which afforded azepinoindole **89** as a single diastereomer in 92 % isolated yield. Subsequent reduction of the keto group under Luche conditions provided alcohol **90** in 77 % isolated yield as a single diastereomer (Scheme 22). The next step involved a controlled hydrogenation of the enamide π-bond. Excellent stereochemical control could be obtained by hydrogenation of **90** with the Crabtree catalyst [72]. 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 **91**. Regiocontrolled dehydration of alcohol **91** to alkene **92** sets the stage for the formation of the butyrolactone ring. Alcohol **91** was converted to the corre-

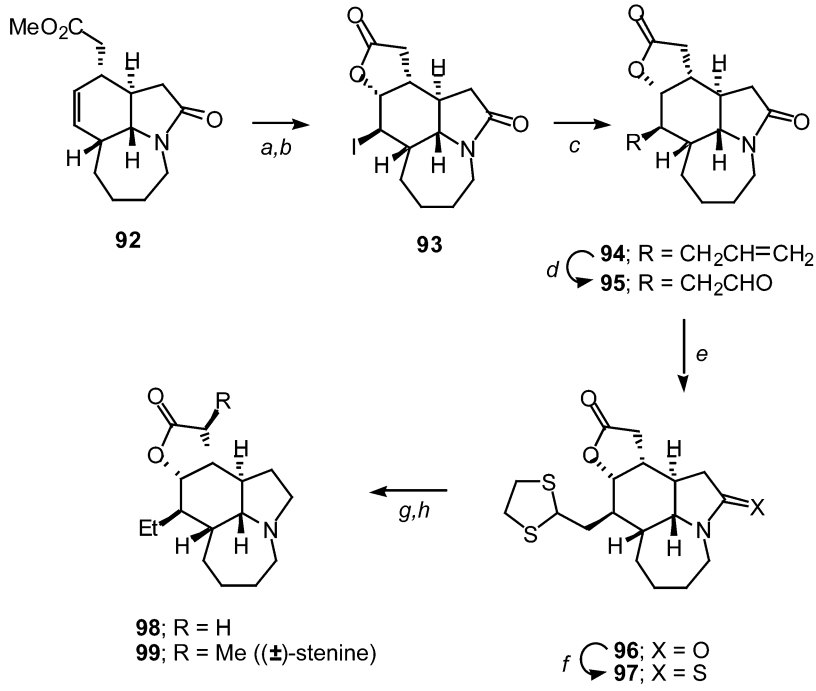


Reagents: (a) Raney-Ni, EtOH; (b) $NaBH_4$, $CeCl_3$, MeOH; (c) Crabtree's catalyst, H_2, CH_2Cl_2; (d) MsCl, NEt_3, DBU, ²

Scheme 22

sponding mesylate and this was followed by treatment with DBU in refluxing toluene to effect elimination providing **92** in 64 % yield.

The conversion of **92** to stenine (**99**) was accomplished using the sequence of reactions outlined in Scheme 23. Thus, hydrolysis of the methyl ester with LiOH followed by treatment with iodine gave iodolactone **93** in 60 % yield. Subsequent Keck allylation with allyltributyl-stannane [73] using the Hart/Wipf protocol74 furnished **94** in 62 % yield and with excellent diastereoselectivity. Johnson–Lemieux oxidation of the allyl group afforded the expected aldehyde **95** which was treated with 1,2-ethanedithiol and $BF_3{\cdot}Et_2O$ to give **96** in 48 % yield for both steps. Conversion of the amide to the corresponding thioamide with Lawesson's reagent provided **97** in 73 % yield. Desulfurization with Raney Ni furnished **98** in 93 % yield. Methylation of the lactone enolate derived by treating **97** with LDA followed by reaction with methyl iodide afforded racemic stenine (**99**) [71].



Reagents: (a) LiOH, H_2O; (b) I_2, MeCN; (c) CH_2=$CHCH_2SnBu_3$, AIBN, (d) OsO_4, $NaIO_4$; (e) $HSCH_2CH_2SH$, $BF_3.Et_2O$; (f) Lawesson's reagent, (g) Raney-Ni (h) LDA, HMPA, MeI

Scheme 23

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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