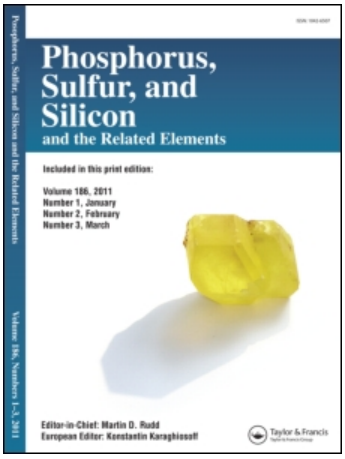

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Utilization of 1,2-Thioalkyl Shifts for Alkaloid Synthesis

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Many structurally diverse alkaloids can be easily accessed via *the domino Pummerer/cycloaddition/*N*-acyliminium ion cyclization cascade.*

Keywords Alkaloid synthesis; cyclization; domino; heterocycles; *N*-acyliminium ion; Pummerer reaction; tandem cascade

INTRODUCTION

Sequential transformations enable the facile synthesis of complex target molecules from simple building blocks in a single preparative step.[1] Their value is amplified if they also create multiple stereogenic centers.[2] A synthetic method that combines transformations of different reaction types significantly broadens the scope of such procedures in synthetic chemistry. Our research program at Emory has recently focused on using new cascade reactions of both *N*-acyliminium and thionium ions for alkaloid synthesis.[3] Our interest in using this domino sequence originated from some earlier work centered on the *Rh(II)-catalyzed cyclization/cycloaddition cascade* of α-diazoimidosulfones.[4] Treatment of α-diazo sulfonylimide **1** with a Rh(II) catalyst first generates an isomünchnone dipole.[5] After the dipolar cycloaddition reaction occurs, the resulting cycloadduct **4** undergoes ready-ring opening with the expulsion of phenyl sulfinic acid, which gives a substituted 3-hydroxy-2(1*H*)-pyridone **5**. The C3-hydroxyl group present in **5** could be transformed into various substituent groups by making use of palladium-catalyzed cross-coupling chemistry.[6] The versatility of the strategy lies in the fact that by appropriate selection of the diazo precursor and dipolarophile, various groups can be introduced into the N-1 and C-4, C-5, and C-6 positions. Among other examples, this procedure was employed in the efficient synthesis of (±)-ipalbidine (**2**),[7] the angiotensin inhibitor (−)-A58365A (**3**),[8] and various β-carbolinines[9] (Scheme 1).

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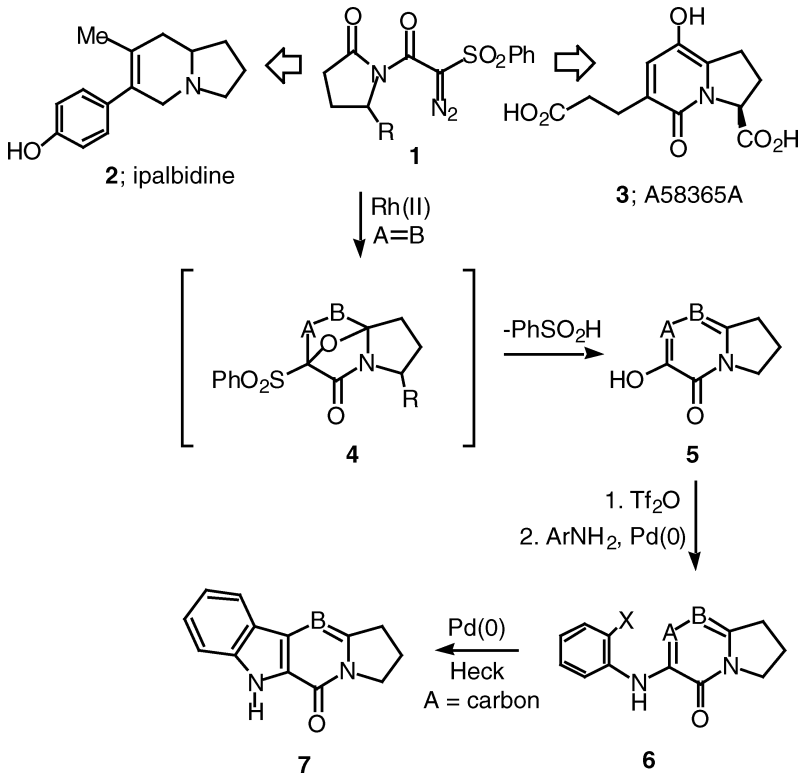
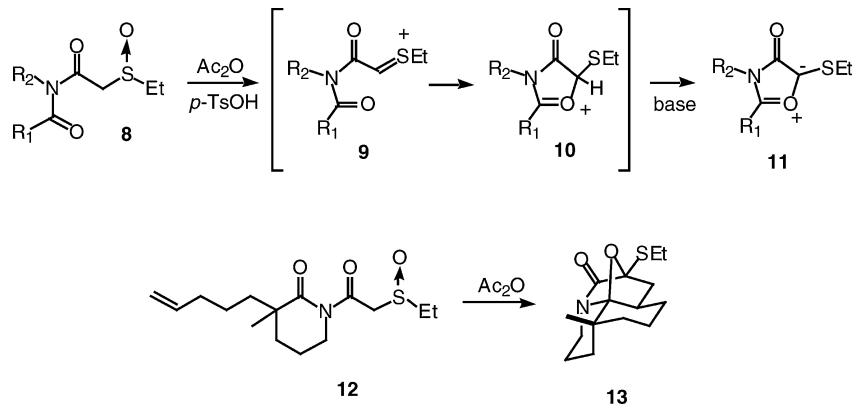


SCHEME 1

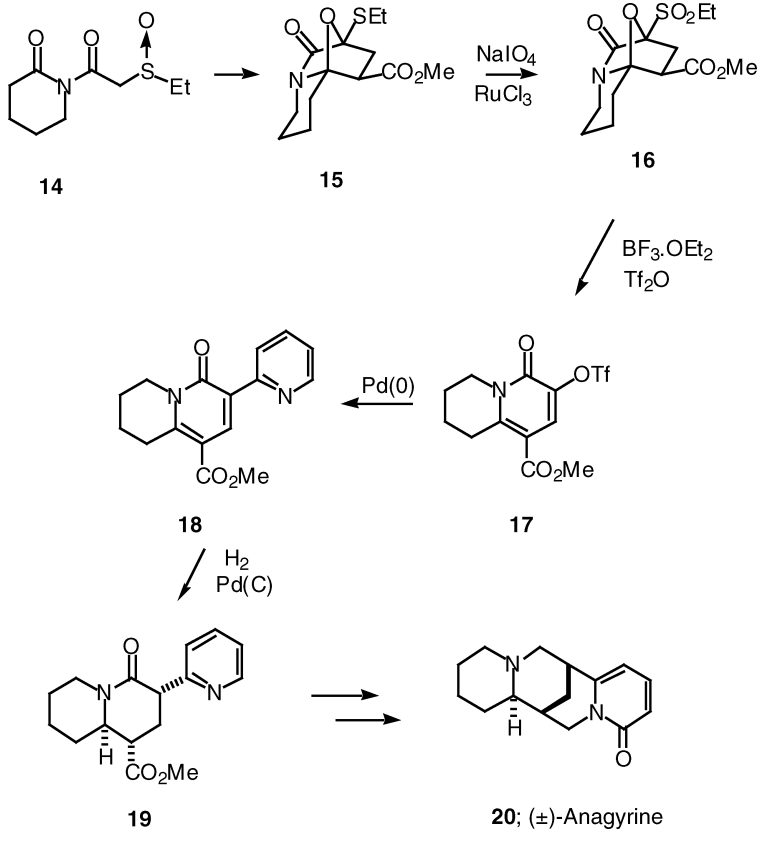
Isomünchnone Di Poles

Subsequent studies in our laboratory showed that a Pummerer reaction could also be employed for the generation of isomünchnone dipoles of type **11**.[10] Thus, the initially formed thionium ion **9** derived from imidosulfoxide **8** was found to undergo rapid cyclization with the neighboring imido group. The resulting oxonium ion **10** readily loses a proton to produce the highly stabilized mesoionic betaine intermediate **11**, which has been further employed for 1,3-dipolar cycloaddition chemistry (Scheme 2). An interesting intramolecular cycloaddition that we studied involved treating imidosulfoxide **12** with acetic anhydride, which afforded the novel polycycle **13** in 73% yield as a single diastereomer.[11]

The oxabicyclic products were used for the synthesis of several alkaloidal natural products. For example, the formal synthesis of (±)-anagyrine **20** involved exposure of imide **14** to a mixture of acetic anhydride and methyl acrylate to provide oxabicycle **15** in 61% yield (Scheme 3). Oxidation of the sulfide group present in **15** with



SCHEME 2

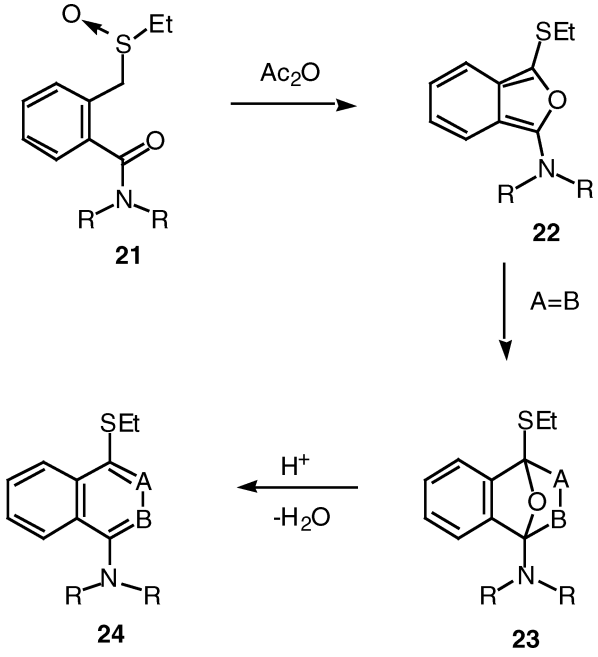


SCHEME 3

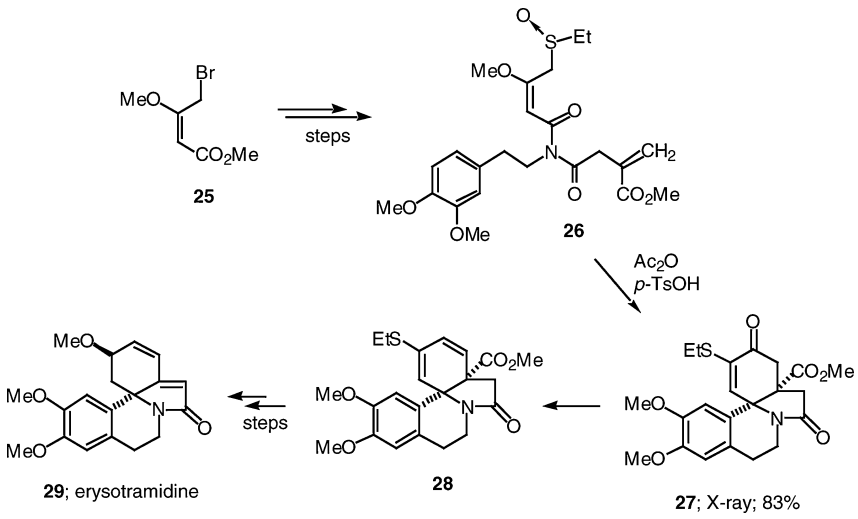
$NaIO_4/RuCl_3$ furnished sulfone **16**. Exposure of **16** to $BF_3{\cdot}OEt_2$ and subsequent reaction with triflic anhydride gave triflate **17** in 80% overall yield. Palladium-catalyzed cross coupling of **17** with 2-(tri-*n*-butylstannyl)pyridine afforded **18** in 70% yield. Catalytic hydrogenation of the pyridone ring in **18** using PtO_2 followed by a base-induced equilibration delivered **19** in 85% yield, which had previously been converted to (±)-anagyrine (**20**).[11]

Domino Cyclization Cascade

As part of our studies in this area, we became interested in another type of Pummerer cascade, which we refer to as the *domino Pummerer/cycloaddition/N-acyliminium ion cyclization cascade*.[12] Many structurally diverse heterocyclic compounds can be easily accessed *via* this method. We found that the α-thiocarbocation derived from the Pummerer reaction of **21** can be readily intercepted by the adjacent amido group to produce isobenzofuran **22** as a transient intermediate. This reactive species undergoes a subsequent Diels–Alder cycloaddition with an added dipolarophile.[13] The resulting cycloadduct **23** was readily converted to representatives of several types of amino-substituted naphthalene lignans **24** (Scheme 4).[14]



SCHEME 4



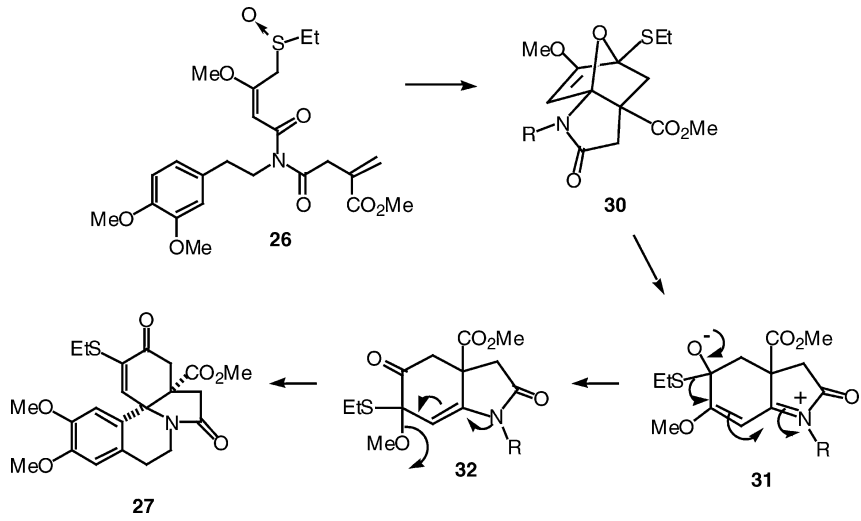
SCHEME 5

A variation of this cascade was used to synthesize the erythrina alkaloid erysotramidine **29**.[15] Formation of the required preassembled sulfoxide-amide **26** involved a number of straightforward steps. When treated with a Pummerer promoter, a series of events occurred that culminated in the formation of the ring system of the Erythrina family. The resultant fused heterocycle was transformed into the known target (**27** → **28** → **29**) (Scheme 5). An X-ray crystal structure analysis established the correct stereochemical relationship among the groups.[16]

From a mechanistic point of view, this transformation is quite interesting (Scheme 6). Treatment of the starting sulfoxide **26** with a Pummerer promoter first generates a thionium ion, which then undergoes cyclization to give the desired 2-amidofuran. A subsequent Diels–Alder reaction produces the oxa-bicyclic ring **30**. Subsequent Grob fragmentation of the bicyclic system leads to a transient zwitterion **31**, which undergoes a 1,2-thio shift, perhaps *via* a bridged sulfonium ion, to give **32**. Lewis acid-promoted loss of methoxide generates an iminium ion, which then undergoes the desired Pictet–Spengler reaction to give **27**.

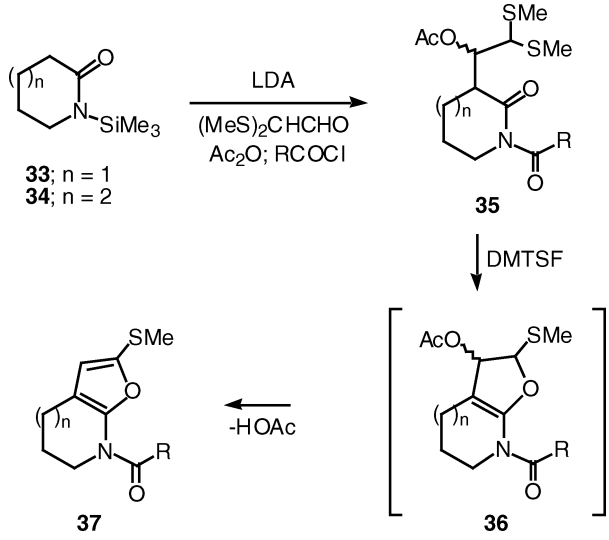
Cycloaddition of 5-Thio-z-Amido-Furans

More recently, we developed a method for preparing cyclic 5-thio-2-amido-furans because functionalized furans of this sort allow for the ready access to a variety of novel azapolycyclic ring systems.[17] The method consists of a Pummerer-induced cyclization of imido



SCHEME 6

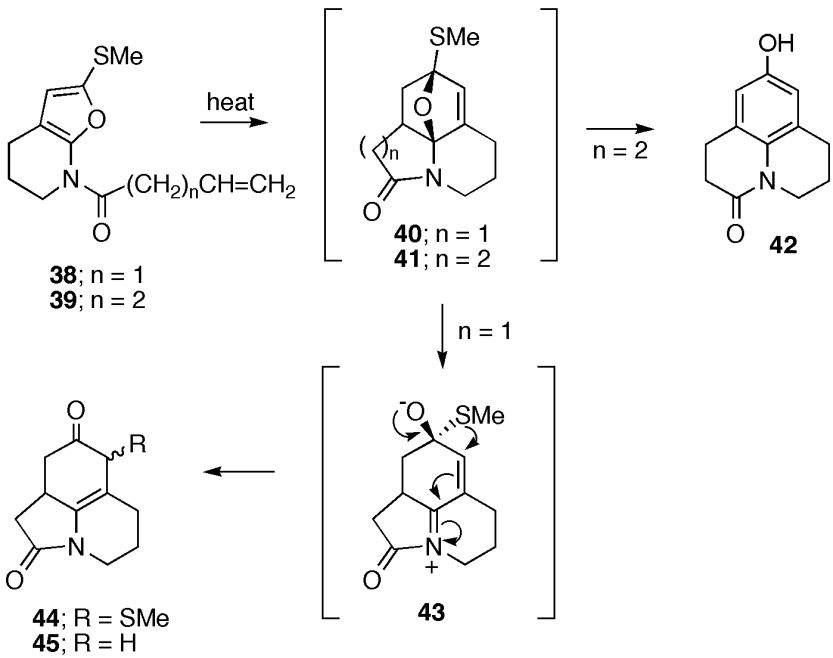
dithioacetals of type **35** (Scheme 7). The starting substrates were prepared by the mixed aldol reaction of the *N*-trimethylsilyl-protected δ-valerolactam **33** (or ε-caprolactam **34**) with *bis*-(methylsulfanyl)-acetaldehyde. Quenching the reaction with acetic anhydride followed by aqueous workup provided the expected aldol product in high yield as a 4:1 mixture of diastereomers. The cyclic lactams were acylated



SCHEME 7

with various acid chlorides using powdered 4A° molecular sieves as a neutral acid scavenger to provide the corresponding imides **35** 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.[18] The initially formed alkylthiosulfonium ion easily dissociates to produce a thionium ion and methyl sulfide.[19] Cyclization of the Pummerer intermediate onto the amide carbonyl group first affords dihydrofuran **36**, which undergoes a subsequent elimination of acetic acid to give the cyclic 2-thio-amido-furan system **37** in high overall yield.

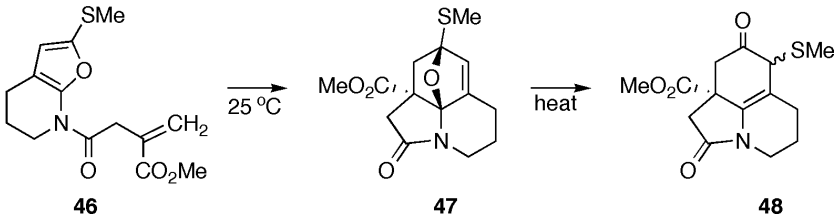
With a satisfactory method for the synthesis of the cycloaddition precursors in place, we examined the Diels–Alder reaction of the *N*-yl-but-3-en-1-one substituted amido-furan **38** (n = 1). Thermolysis of **38** at 110°C furnished the rearranged hexahydro-pyrroloquinolin-2-one **44** as the only isolable product in 92% yield as a 3:2 mixture of diastereomers after silica gel chromatography (Scheme 8).[20] Dethiomethylation occurred smoothly when a sample of **44** was subjected to Raney-nickel reduction in 95% ethanol, producing **45** in 85% yield. In contrast to the above result, thermolysis of the homologous *N*-yl-pent-4-en-1-one



SCHEME 8

amido-furan **39** gave phenol **42** in 82% yield. In both cases, the initially formed oxo-bridged cycloadducts (*i.e.*, **40** or **41**) could not be isolated, as they readily underwent ring opening to produce the observed products. Furan **39**, 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 **42**. Presumably, the initially formed cycloadduct **41** 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 **46** 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 **47** as a single diastereomer in 45% yield by simply stirring a sample of **46** in benzene at 25°C (Scheme 9). The structure of **47** 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 that show a large ground state energy difference between the two diastereomers.[21] Heating a sample of **47** at 90°C gave the rearranged hexahydropyrrolo-quinolinone **48** in 78% yield as a 1:1 mixture of diastereomers.

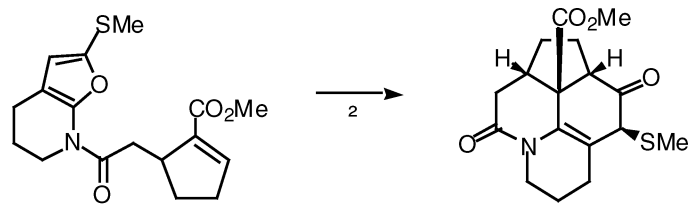


46 **47** **48**

SCHEME 9

Utilization of Thio-Substituted Furans for the Synthesis of Polyazacycles

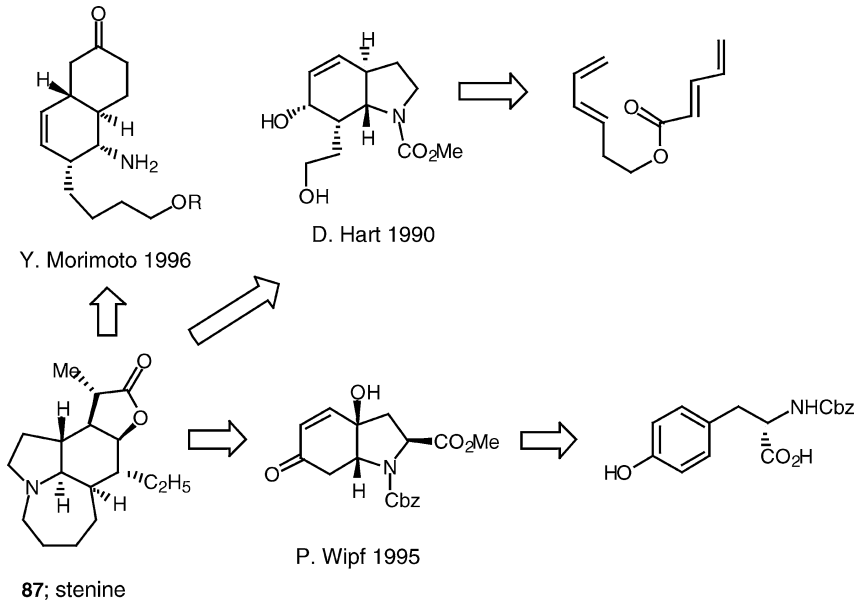
To further illustrate the viability of this sequence as a practical strategy for the synthesis of complex polyazacyclic systems, we studied the cycloaddition behavior of the related amido-furan **49**. We were gratified to find that heating **49** at 110°C for 2 h gave the rearranged amide **50** as a single diastereomer in 80% yield (Scheme 10). The 1,2-thiomethyl shift that occurs from the transient Diels–Alder cycloadduct probably proceeds *via* an episulfonium ion and consequently only one diastereomer



49 **50**

SCHEME 10

would be expected.[22] Application of this methodology toward the total synthesis of the azepinoindole alkaloid stenine **51** has also been carried out (Scheme 11).[23] Although stenine has been previously synthesized, all of the published routes to this alkaloid have required construction of the seven-membered nitrogen ring after all of the other rings have been assembled.[24]

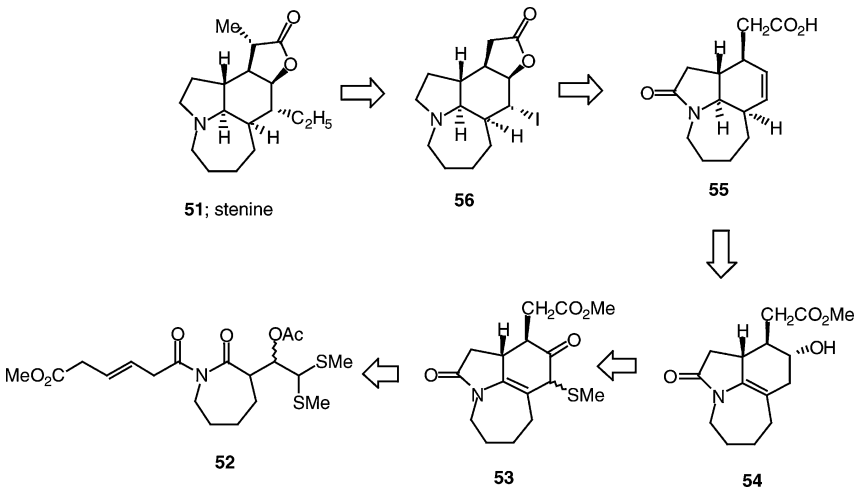


87; stenine

SCHEME 11

Synthesis of Stenine

Our approach to this azepino-indole alkaloid (Scheme 12) starts off with a preassembled seven-membered lactam (**52**). As before, aldol



SCHEME 12

condensation with the dithiomethyl-substituted aldehyde and subsequent *N*-acylation at nitrogen yielded the required Pummerer precursor. After the furan ring was constructed by treatment with the DMTSF reagent, the cycloaddition rearrangement proceeded at room temperature in 80% yield to give **53**. The thiomethyl group was quantitatively removed using Raney-nickel. A bulky hydride reagent was found to induce reduction of the carbonyl group from the less crowded *beta* face to furnish alcohol **54** with the stereochemistry shown in Scheme 12. Hydrogenation of the double bond using Crabtree's catalyst[25] provided the correct stereochemical array of hydrogens as evidenced by X-ray analysis. *trans*-Elimination of the alcohol gave **55** and this was followed by iodolactonization to furnish the stenine precursor **56**. Further conversion of this intermediate into the target molecule has been accomplished in several additional steps.

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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