The Pummerer Reaction: Methodology and Strategy for the Synthesis of Heterocyclic Compounds

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Received September 1, 2003

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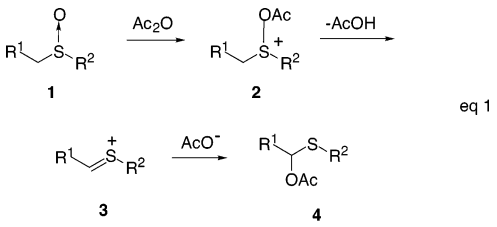
1. Introduction

The use of heteroatom-stabilized carbocations as reactive intermediates represents one of the fundamental tools available for the synthesis of complex molecules. The Pummerer rearrangement, exemplified by the reaction of a sulfoxide, **1**, with an acid anhydride, produces an α-substituted sulfide, **4**, via an elimination/addition mechanism involving thionium ion **3** (eq 1).[1]



The recognition that thionium ion intermediates can act as electrophiles in cyclization reactions has greatly expanded the synthetic utility of this reaction.[2] The Pummerer process generally involves addition of a nucleophile to the thionium ion, and the overall process represents a powerful synthetic method. Examples of both inter- and intramolecular reactions are now widespread, and strategies incorporating heteroatom or carbon nucleophiles have found broad application. As Pummerer chemistry has matured, much effort has focused on novel ways to generate thionium ions to expand the reaction's scope beyond the use of sulfoxide substrates. Concomitantly, new strategies that employ Pummerer-like processes for the synthesis of complex natural and unnatural products have emerged.

Heterocyclic compounds, both naturally produced and synthetically derived, often display important biological activity. In fact, more than 67% of the compounds listed in the Comprehensive Medicinal Chemistry (CMC) database contain heterocyclic rings, and nonaromatic heterocycles are twice as abundant in this database as heteroaromatics.[3] Consequently, the development of new methodology and the strategic deployment of known methods for the synthesis of complex heterocyclic compounds continue to drive synthetic organic chemistry. The rich chemistry of thionium ions has earned the Pummerer reaction an important place in the repertoire of synthetic organic transformations,[2] including reactions that form heterocyclic rings.

Several review papers have outlined recent progress using Pummerer-based chemistry,[2] including the synthesis of nitrogen heterocycles.[4] Since our last

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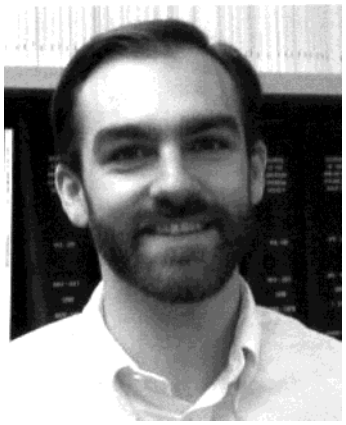
10.1021/cr020090l CCC: $48.50
Published on Web 03/12/2004



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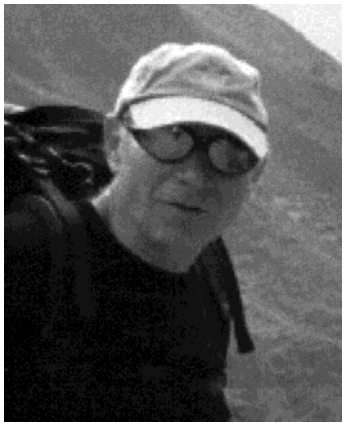
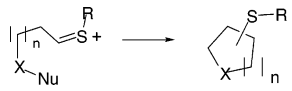


Albert Padwa was born in New York City. He received both his B.A. and Ph.D. degrees from Columbia University. After an NSF postdoctoral position at the University of Wisconsin, he was appointed Assistant Professor of Chemistry at the Ohio State University in 1963. He moved to SUNY Buffalo in 1966 as Associate Professor and was promoted to Professor in 1969. Since 1979, he has been the William Patterson Timmie Professor of Chemistry at Emory University. He has held visiting positions at University Claude Bernard, France, the University of California at Berkeley, the University of Wurzburg, Germany, and the Imperial College of Chemistry, U.K. Professor Padwa has been the recipient of an Alfred P. Sloan Fellowship, a John S. Guggenheim Fellowship, an Alexander von Humboldt Senior Scientist Award, a Fulbright Hays Scholarship, a Senior Award in Heterocyclic Chemistry from the International Society of Heterocyclic Chemists, and an ACS Arthur C. Cope Scholar Award and is the coauthor of more than 600 publications. He served as the Chairman of the Organic Division of the ACS and as President of the International Society of Heterocyclic Chemistry. He has also served as a member of the editorial boards of the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, and *Organic Letters*, has been the volume editor of *Comprehensive Heterocyclic Chemistry, the Synthesis of Science* (Vol. 27), and is currently one of the Associate Editors of the *Journal of Organic Chemistry*. His research interests include heterocyclic chemistry, dipolar cycloadditions, alkaloid synthesis, tandem transformations, organometallic chemistry, and organic photochemistry. Aside from chemistry, his other passion is mountain climbing in various parts of the world.

review detailing the use of Pummerer chemistry to generate heterocycles,[5] additional examples have appeared in the literature in recent years which further define the scope and application of the Pummerer reaction. The focus of this review centers about Pummerer-based transformations for the construction and manipulation of heterocyclic compounds, especially intramolecular Pummerer reactions (e.g., eq 2), and pays particular attention to



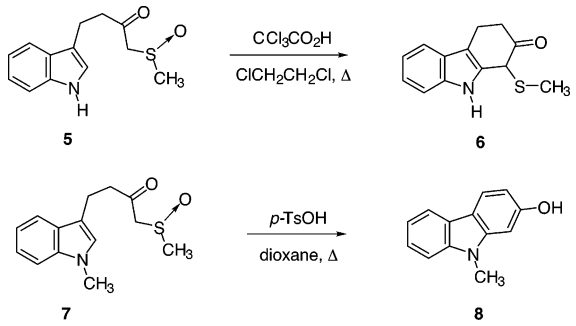
eq 2

recent developments in this area. Attention is given to both new methodology and the application of the Pummerer reaction toward the synthesis of complex natural products. An attempt has been made to show how the Pummerer reaction has been utilized for natural product synthesis. While this review article is primarily organized by ring size, much of the methodology is also useful for the construction of variably sized heterocycles, and these reactions will be presented separately.

2. Modification of Existing Rings

One of the more basic applications of the Pummerer reaction involves the refunctionalization of existing heterocyclic rings. A recent review of thionucleoside chemistry underscores the primary importance of the Pummerer reaction as a way to access complex tetrahydrothiophene derivatives.[6] In addition, electron-rich heterocycles are particularly useful reagents for the trapping of α-acylthionium ions.[7−9] For example, when the *β*-keto sulfoxide-substituted indole **5** was treated with trichloroacetic acid in boiling dichloroethane, the cyclized tricyclic derivative **6** was formed in 68% yield (Scheme 1). This

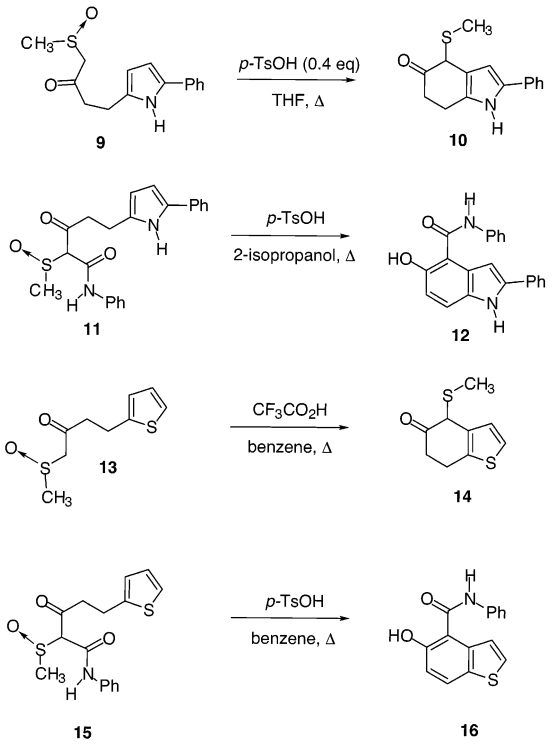
Scheme 1



transformation proceeded by an intramolecular cyclization of the indole ring onto the initially generated α-acylthionium ion. Interestingly, when the related *N*-methylindole derivative **7** was heated with *p*-toluenesulfonic acid (*p*-TsOH) in dioxane at reflux, the carbazole analogue **8** was formed in 54% yield. In this case, the initially formed α-methylthio ketone undergoes aromatization with concomitant elimination of methanethiol.

Pyrrole and thiophene rings also participate in these cyclization reactions. In fact, exposure of sulfoxide **9** to 0.4 equiv of *p*-TsOH produced the tetrahydroindole derivative **10** (Scheme 2). Under harsher conditions, sulfoxide **11** was converted to indole **12** in 91% yield. Benzothiophene-substituted derivatives were also obtained by using the same

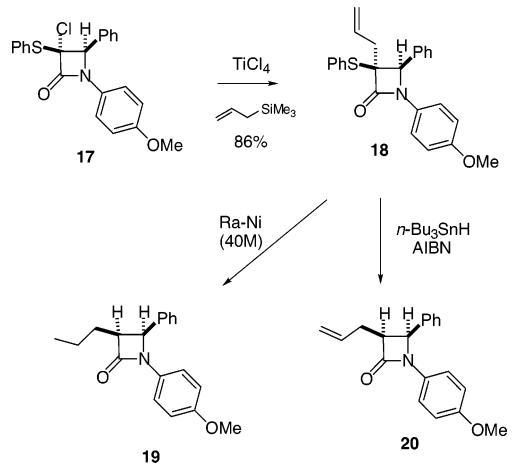
Scheme 2



reaction sequence. Thus, heating β-keto sulfoxide **13** with TFA at reflux in benzene resulted in the isolation of the annulated thiophene **14** in 54% yield. When *p*-TsOH was used as the Pummerer promoter, intramolecular cyclization occurred onto the α-acylthionium ion generated from sulfoxide **15**, and this was followed by aromatization with loss of methanethiol to provide benzothiophene **16** in good yield. These examples demonstrate that the judicious selection of acid and solvent is important for accessing certain heterocyclic compounds.

Bari has used a Pummerer variant to allylate β-lactam derivatives.[10] Exposure of the α-chloro sulfide **17** to a Lewis acid in the presence of allyltrimethylsilane produced **18** as a single diastereomer in 86% yield (Scheme 3). The stereochemistry of the final product arises from addition of the allyl nucleophile to the least hindered side of the rather flat thionium ion intermediate, resulting in a *trans*-

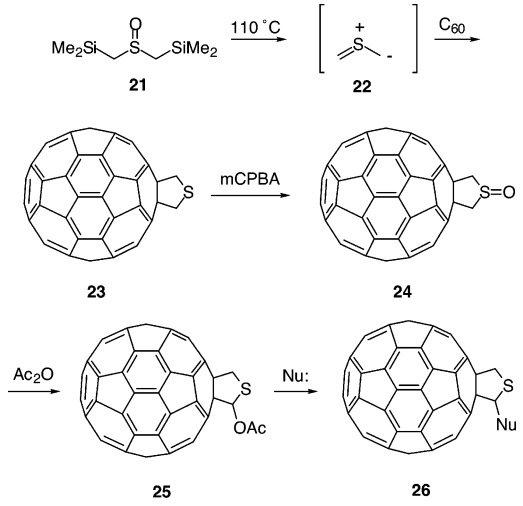
Scheme 3



relationship between the allyl and phenyl substituents. The sulfide moiety was then removed by heating **18** with Raney nickel to stereoselectively provide **19**, in which the olefinic π-bond had also been reduced. Alternatively, heating **18** with tributyltin hydride (Bu_3SnH) in the presence of 2,2′-azobisisobutyronitrile (AIBN) provided **20** as a single diastereomer. The stereoselectivity in these reductions can be explained by the deliverance of hydrogen to the least hindered face (*trans* to the directing phenyl group) of the radical intermediate.

Ohno and Ishida have reported results dealing with the 1,3-dipolar cycloaddition of thiocarbonyl ylide **22**, generated from the thermolysis of **21**, to [60]fullerene, giving rise to tetrahydrothiophene **23** (Scheme 4).[11]

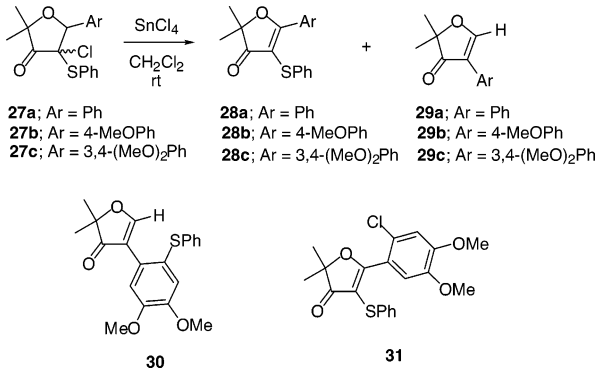
Scheme 4



Oxidation of **23** to sulfoxide **24** by treatment with *m*-chloroperbenzoic acid (*m*-CPBA), followed by an acetic anhydride-mediated Pummerer rearrangement, provided the α-acyloxy derivative **25**. The acyloxy group allows for further derivatization (e.g., **26**) by exposure to either camphorsulfonic acid (CSA) or trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of a nucleophile. Nucleophiles such as alcohols, thiols, allylsilanes, and enol ethers also participate in this reaction.[12]

Although simple substitution reactions are well established, the thionium ion intermediate generated in the Pummerer reaction can evoke unexpected rearrangements when neighboring groups participate. With the intention of using the ionization of α-chloro sulfides **27** to introduce additional functionality on the heterocycle, McCarthy and co-workers observed some interesting rearrangement products (Scheme 5).[13] The distribution of products was found to be dependent upon the nature of the aryl substituent. Exposure of **27a** (Ar = Ph) to a slight excess of $SnCl_4$ in CH_2Cl_2 at room temperature produced the elimination product **28a** in 69% yield. Reaction of **27b** (Ar = 4-MeOPh) under similar conditions, however, produced a mixture of **28b** (12% yield) and **29b** (40% yield). Furanone **27c** (Ar = 3,4-$(MeO)_2$Ph) afforded a mixture of **28c** (7% yield), **30** (35% yield), and **31** (15% yield) when treated with $SnCl_4$. The formation of products **30** and **31** is peculiar in that an aromatic substitution reaction has occurred. Exposure of **27c**

Scheme 5



to $ZnBr_2$ changed the product distribution in that **28c** predominated (49% yield). Chloride **31** was still isolated (11% yield), while **30** was not detected. The formation of **31** suggests that chlorine transfer might be an intramolecular process, but the mechanism could not clearly be delineated on the basis of the experimental data.

3. Formation of Five-Membered Ring Heterocycles

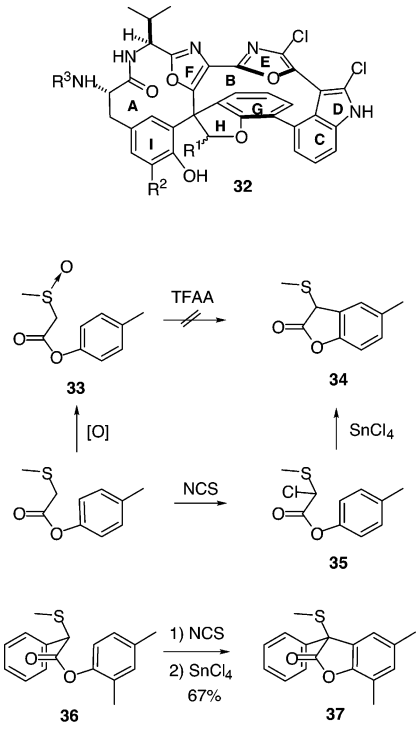
While the refunctionalization of existing heterocycles is certainly an important process, use of the Pummerer reaction as a key strategy in the formation of heterocycles continues to intrigue researchers. The synthesis of numerous complex natural products relies on the intramolecular trapping of nucleophiles by thionium ion intermediates. Research into Pummerer reactions that form five-membered ring heterocycles has been considerable. Often, these heterocycles are transient intermediates in cascade reactions that produce polycyclic arrays. Frequently, however, the Pummerer reaction provides a convenient strategy for forming five-membered ring heterocycles containing functionality that can be leveraged for further manipulation.

3.1. Furan Derivatives

An interesting application of a Pummerer disconnection for the synthesis of the benzofuran core of the diazonamides **32** (Scheme 6) has been reported by Magnus and Kreisberg.[14] Although several examples of constructing oxindoles via an intramolecular Pummerer cyclization are known,[15] no analogous syntheses of benzofuran derivatives had been previously disclosed. A model system was therefore examined. Initial attempts to form the five-membered heterocycle from sulfoxide **33** under normal Pummerer conditions (e.g., trifluoroacetic anhydride) failed to provide **34**. However, exposure of the α-chloro sulfide **35**, derived from the parent α-methylthio ester by treatment with *N*-chlorosuccinimide, to $SnCl_4$ resulted in the formation of **34** in 45% yield. The use of stoichiometric $SnCl_4$ caused significant decomposition, whereas catalytic amounts of this Lewis acid provided a cleaner reaction mixture.

Application of this method to a system that more closely resembles the diazonamide IHG core was also successful. Thus, reaction of **36** with NCS in CCl_4 for

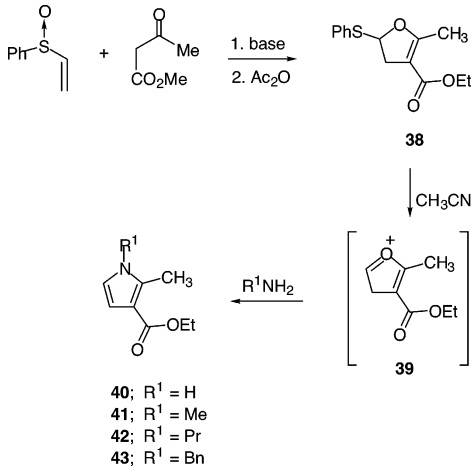
Scheme 6



2 h followed by heating at reflux with catalytic amounts of $SnCl_4$ afforded **37** in 67% yield. Several other examples with varying substitution on the aryl moiety were also reported. This Pummerer strategy allows for use of the methylthio functional group in further transformations that form the bond linking the *F* and *H* rings in the natural product.

A tandem Pummerer cyclization sequence has also been used for a general pyrrole synthesis via the initial formation of a reactive furan derivative (Scheme 7).[16] Dihydrofuran **38** was prepared by Michael

Scheme 7

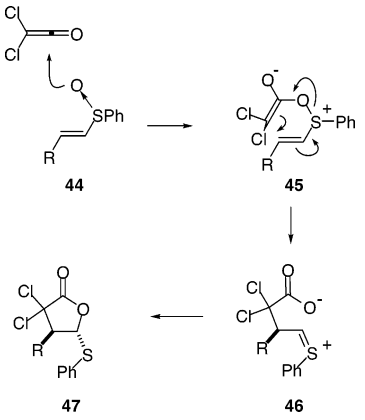


addition of a *β*-keto ester anion to phenyl vinyl sulfoxide followed by a sequential acid-induced Pummerer reaction in which the thionium ion was trapped by the oxygen atom of the enol tautomer. Further reaction of dihydrofuran **38** with $HgCl_2$ induced carbon−sulfur bond cleavage and generation of the oxonium ion intermediate **39**. Reaction of this species with either an ammonium salt or a primary amine

gave rise to the disubstituted pyrroles **40**−**43** in good yields.

The Marino group has developed a novel additive Pummerer reaction (vide infra) that produces γ-butyrolactones by the reaction of dichloroketene with vinyl sulfoxides.[17] In general, the oxygen of a vinyl sulfoxide such as **44** first attacks dichloroketene to produce in situ the salt **45** (Scheme 8). The resulting

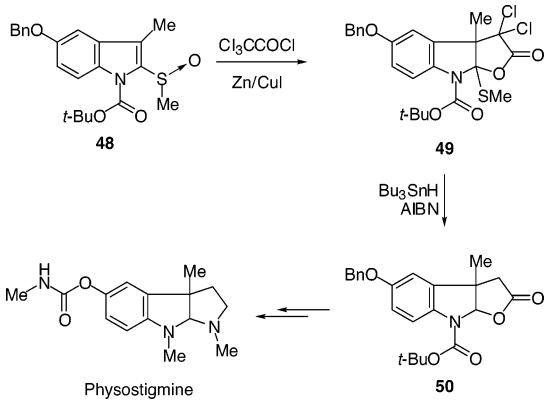
Scheme 8



enolate **45** then undergoes a 3,3-sigmatropic rearrangement to provide thionium ion intermediate **46**. Finally, the resulting carboxylate anion adds to the neighboring thionium ion to furnish butyrolactone **47**, which retains the geometry of the starting olefin. The use of chiral sulfoxides **44** leads to the enantiospecific formation of butyrolactones **47**.[18,19]

An interesting application of this additive Pummerer method was carried out by the Marino group for the synthesis of physostigmine.[20] Addition of indole sulfoxide **48** to a heated solution of zinc dust, CuI, and trichloroacetyl chloride resulted in the isolation of the tricyclic indole derivative **49** in 54% yield (Scheme 9). Dechlorination and dethiomethy-

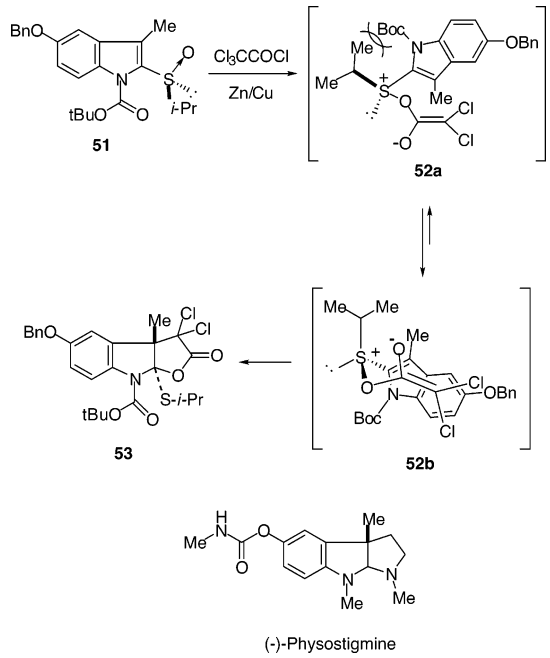
Scheme 9



lation was accomplished in one step using Bu_3SnH/AIBN. Straightforward functional group manipulation of **50** eventually afforded physostigmine.

The Pummerer/lactonization procedure was also applied in an asymmetric manner.[20] It was found that only alkyl sulfoxides were capable of generating the lactone ring in an enantiospecific fashion. Apparently, the indolyl α-phenyl sulfoxide derivative was not reactive enough toward dichloroketene to produce the desired product. The low reactivity encountered during this work was eventually solved by using the isopropyl-substituted sulfoxide **51**, which could be lactonized under the standard conditions to give lactone **53**. Treatment of this compound with 2 equiv of Bu_3SnH under radical conditions afforded the dechlorinated lactone in 75% ee (Scheme 10). The

Scheme 10

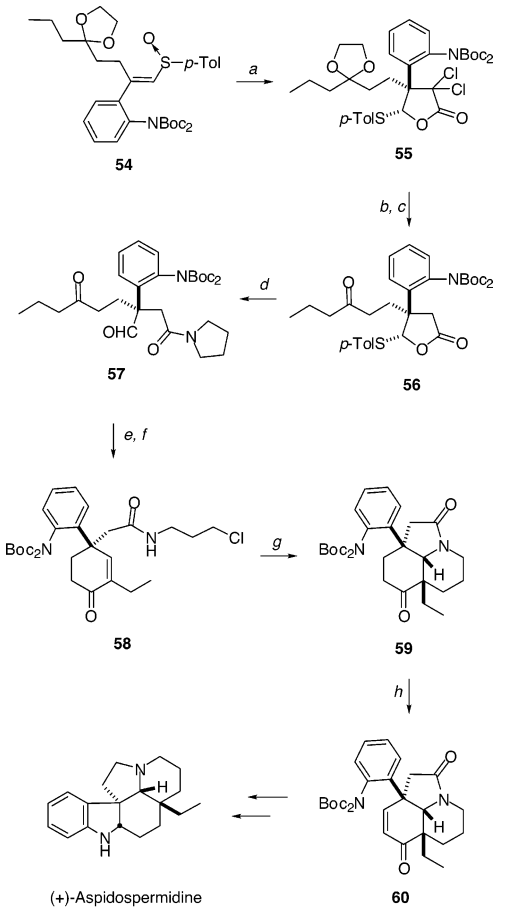


preferred formation of stereoisomer **53** was attributed to the dominance of conformer **52b** of the initially formed intermediate in the equilibrium mixture. Conformation **52a** appears to have a destabilizing $A^{1,2}$-interaction between the Boc protecting group and the isopropyl functionality.

This unique strategy has recently been applied toward the synthesis of (+)-aspidospermidine. In this approach, enantiomerically pure sulfoxide **54** was treated with trichloroacetyl chloride in the presence of zinc−copper couple (Zn−Cu) to enantiospecifically produce lactone **55** in 78% yield (Scheme 11).[21] Subsequent removal of the chloro substituents followed by the deprotection of the ketal afforded **56** in 96% yield. Reaction of **56** with pyrrolidine effected an *O*- to *N*-transacylation with a subsequent elimination of thiolate to give the amido aldehyde **57** in 86% yield. Further exposure of **57** to pyrrolidine in the presence of 33% aqueous AcOH and 2-propanol promoted an intramolecular aldol reaction and simultaneously hydrolyzed the amide group to furnish an intermediate carboxylic acid. Conversion of the carboxylic acid to a mixed anhydride followed by the addition of 3-chloropropylamine gave **58** in 64% yield from **57**. Exposure of **58** to NaH initiated a tandem intramolecular conjugate addition/alkylation to produce **59** in 86% yield. Subjection of the silyl enol ether of **59** to modified Segusa oxidation conditions delivered **60** (85%), which was subsequently carried on to (+)-aspidospermidine.

Another tandem Pummerer/intramolecular oxygen trapping sequence was cleverly used by Burke and

Scheme 11[a]



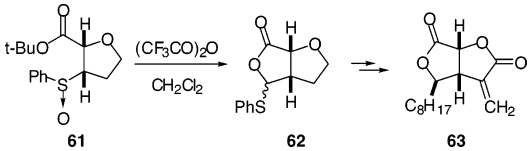
[a] Reagents and conditions: (a) Zn−Cu, Cl_3CCOCl; 78%. (b) Bu_3SnH, Et_3B; 92%. (c) *p*-TsOH, acetone; 96%. (d) Pyrrolidine; 86%. (e) Pyrrolidine, 2-propanol, 33% aqueous AcOH. (f) *i*-BuOCOCl, Et_3N, 3-chloropropylamine·HCl; 64% for two steps. (g) NaH; 86%. (h) KHMDS, TMSCl, then $Pd(OAc)_2/O_2$, DMSO; 80%.

co-workers for the synthesis of avenaciolide (**63**; Scheme 12).[22] Treatment of sulfoxide **61** with TFAA resulted in the formation of a mixture (5:1) of lactones **62** in 84% overall yield. After chromatographic separation, each diastereomer was converted into the 3-normethylene analogue of **63** using standard organic transformations.

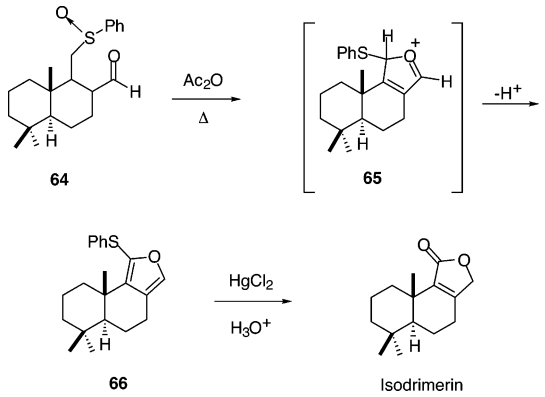
In an early report, de Groot and co-workers established that the Pummerer reaction could be used to construct substituted furans.[23] Thus, treatment of sulfoxide **64** with acetic anhydride gave rise to a transient thionium ion that was attacked by the neighboring aldehydic carbonyl group to produce the oxy-stabilized cation **65** (Scheme 13). The next step involved proton loss to generate 2-phenylthiofuran **66**. Hydrolysis of **66** with $HgCl_2$ ultimately provided isodrimerin.

The method was further extended by de Groot to the regioselective synthesis of several other naturally occurring butenolides. By altering the reaction condi-

Scheme 12

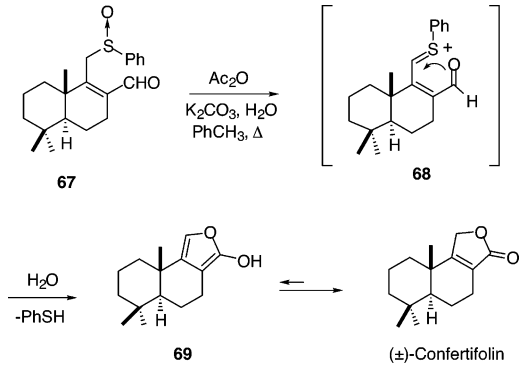


Scheme 13



tions, regioisomeric butenolides could be produced from the same starting vinyl sulfoxide, and this method was applied to the synthesis of (±)-confertifolin (Scheme 14).[24] Under aqueous thermal condi-

Scheme 14

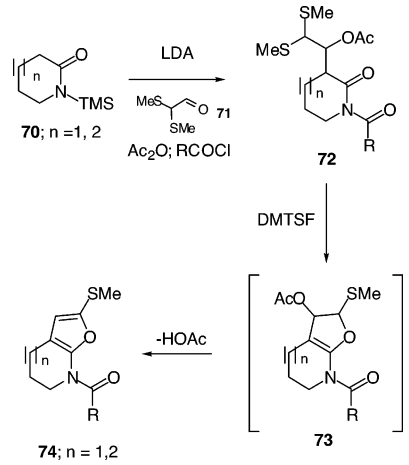


tions, vinyl sulfoxide **67** underwent the Pummerer reaction to form the expected thionium ion. The cationic center present in **68** was attacked by the neighboring hydroxyl group of the hydrated aldehyde. Elimination of thiophenol produced the 2-hydroxyfuran derivative **69**, which spontaneously tautomerized to give (±)-confertifolin.

Our research group at Emory has also made extensive use of this methodology for cascade cyclizations wherein highly reactive furan intermediates undergo Diels−Alder cycloadditions.[25] The lithium enolate of cyclic amides such as **70**, for example, added cleanly to bis(methylsulfanyl)acetaldehyde (**71**) to afford aldol products **72** (Scheme 15).[26] Reaction of **72** with commercially available dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) triggered a Pummerer cascade by first transferring a methylthio group in **72**. This was followed by the elimination of methyl disulfide to produce a reactive thionium ion intermediate that was intercepted by the proximal carbonyl group to furnish the dihydrofuran derivative **73**. Elimination of acetic acid under the reaction conditions gave furans **74** in 70−80% isolated yields.

A variety of 2-methylthio-5-amidofuran systems were prepared that contained a π-bond tethered on the amido nitrogen in a manner that would allow for an intramolecular Diels−Alder reaction.[27] Thus, exposure of imides **75** to DMTSF produced furans **76** in 40−70% yields (Scheme 16). Thermolysis of **76** in

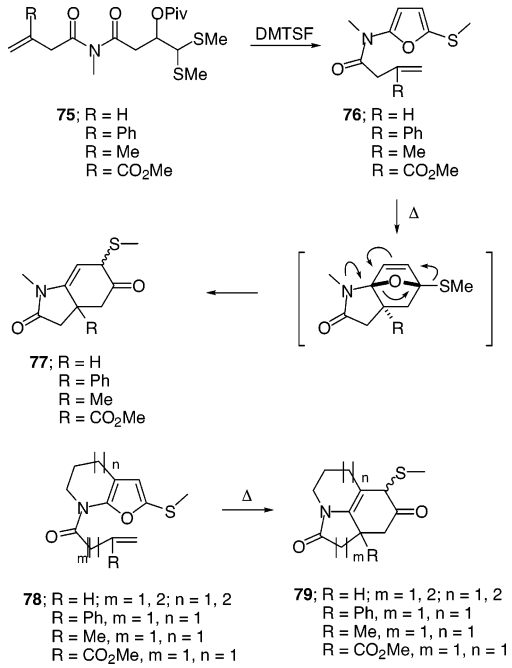
Scheme 15



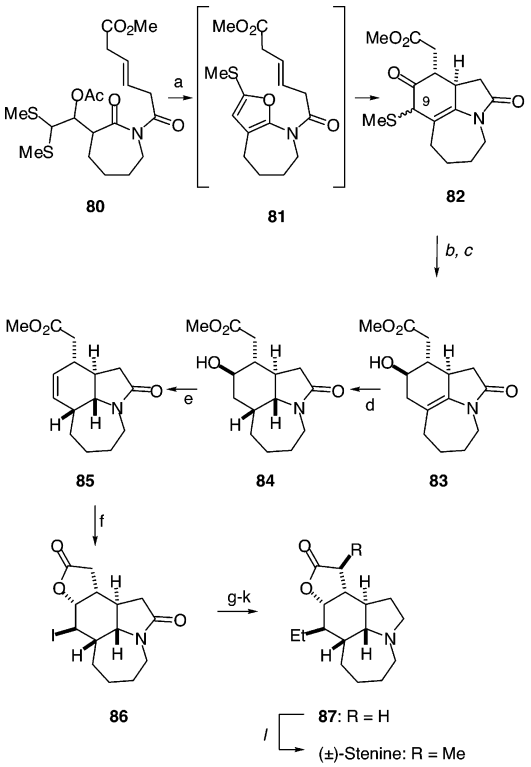
toluene at reflux initiated an intramolecular Diels–Alder reaction (IMDAF) to afford an intermediate oxabicycle. Subsequent fragmentation of the intermediate oxabicycle followed by a 1,2-thio shift provided the bicyclic amides **77** in good yield (ca. 70%). In an analogous manner, the cycloaddition chemistry of furans **78** provided tricyclic products **79**.

Our research group has exploited this thio-substituted furan-forming Pummerer cascade for the synthesis of several natural products. For example, in the total synthesis of (±)-stenine, the reaction of imide **80** with DMTSF provided azapinoindole **82** in 80% yield as a mixture (1:1) of epimers about the C(9) stereocenter (Scheme 17).[28] Interestingly, the intermediate furan **81** could not be isolated as it spontaneously cyclized and rearranged under the DMTSF reaction conditions (<0 °C). Removal of the methylthio moiety followed by reduction of the ketone provided **83** as a single diastereomer. The hydroxyl group was then used to direct the reduction of the enamide π-bond. Hydrogenation of **83** using Crabtree's iridium catalyst[29] provided **84**, setting the

Scheme 16



Scheme 17[a]



[a] Reagents and conditions: (a) DMTSF. (b) Raney Ni. (c) $NaBH_4$, $CeCl_3$. (d) Crabtree's catalyst, H_2. (e) MsCl, TEA; DBU. (f) LiOH; I_2. (g) $CH_2{=}CHCH_2SnBu_3$, AIBN. (h) OsO_4, $NaIO_4$. (i) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$. (j) Lawesson's reagent. (k) Raney Ni. (l) LDA, HMPA, MeI.

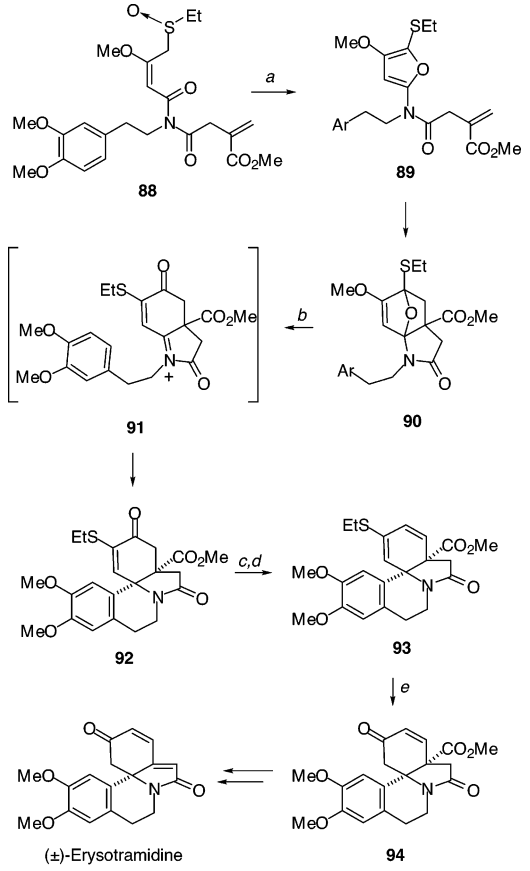
relative stereochemistry of the ring junctions. Conversion of the hydroxyl group to a mesylate followed by elimination using DBU provided the γ,δ-unsaturated ester **85**. Hydrolysis of the ester followed by iodolactonization furnished iodide **86**. Radical-mediated allylation followed by several functional group interconversions eventually afforded **87**. Finally, deprotonation adjacent to the lactone carbonyl group followed by alkylation with methyl iodide gave (±)-stenine.

The formal synthesis of (±)-erysotramidine in the Padwa laboratories represents still another example of this furan-forming Pummerer-initiated cascade reaction as a key strategic disconnection. Imide **88**, when treated with TFAA and Et_3N, was initially converted to furan **89** (Scheme 18).[30,31] Further cyclization to the oxabicycle **90** followed by exposure to $BF_3{\cdot}Et_2O$ produced **92** via a Pictet–Spengler cyclization.

The tetracyclic intermediate **92** was isolated as a single diastereomer in 83% yield from **88**. Conversion of the ketone moiety in **92** to an enol triflate followed by palladium-mediated reduction provided diene **93**. Hydrolysis of the vinyl sulfide present in **93** furnished the known ketone **94**, an intermediate that was pivotal in a previous synthesis of (±)-erysotramidine. A similar approach to erysotrine was also accomplished in our laboratories.[32]

On the basis of the above results, Sarkar and coworkers reported the use of related Pummerer chemistry to generate reactive furo[3,4-*c*]pyridines that undergo a subsequent Diels–Alder reaction to pro-

Scheme 18[a]



[a] Reagents and conditions: (a) TFAA, TEA. (b) $BF_3 \cdot Et_2O$. (c) KH, $PhNTf_2$. (d) $(PPh_3)_2PdCl_2$, TEA, HCO_2H. (e) $TiCl_4$, AcOH, H_2O.

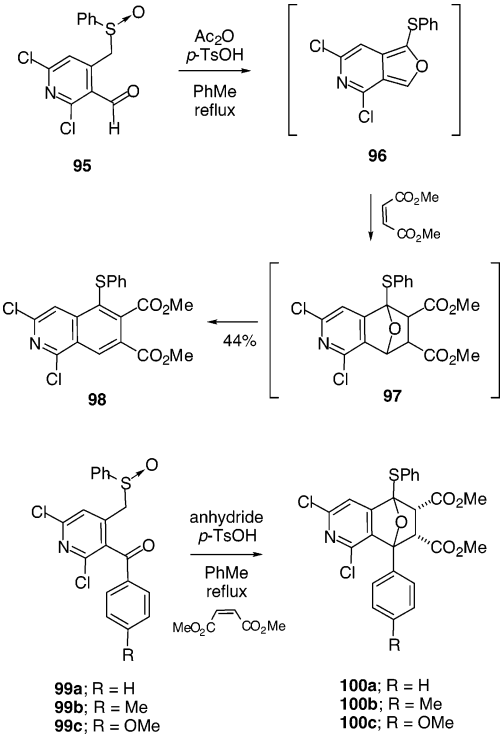
duce isoquinoline derivative.[33] In their study, exposure of sulfoxide **95** to acetic anhydride in the presence of catalytic amounts of *p*-TsOH produced an intermediate pyridofuran derivative **96** that undergoes a subsequent cycloaddition with added dimethyl maleate to afford the polysubstituted isoquinoline **98** in 44% yield (Scheme 19). The intermediate oxabicycle **97** was not isolated.

The use of aryl ketones **99a**−**c** as starting substrates, however, produced oxabicycles **100a**−**c** arising from an *endo* Diels−Alder reaction. The efficiency of furo[3,4-*c*]pyridine formation was found to be sensitive to the conditions employed with these aryl ketones. For example, oxabicycles **100a**−**c** were isolated in 33−40% yield when the transformation was carried out using trifluoroacetic anhydride; yields were lower (17−20% yield) when acetic anhydride was employed. Electron-releasing substituents on the aromatic ring enhanced the overall reaction. Substrate **99a** (R = H) afforded **100a** in 33% yield in the presence of trifluoroacetic anhydride, while compound **99c** (R = OMe) furnished **100c** in 40% yield under the same reaction conditions. Oxabicycles **100a**−**c** underwent fragmentation and subsequent aromatization to give isoquinoline derivatives (e.g., **98**) by the action of DBU in toluene at reflux.

3.2. Pyrrolidine Derivatives

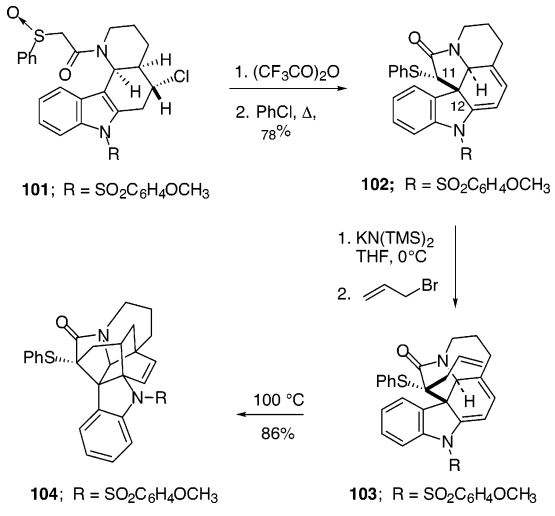
The intramolecular trapping of thionium ions continues to be employed for the synthesis of indole

Scheme 19



alkaloids. The use of Pummerer chemistry as a method to close the five-membered pyrrolidine ring, while forming one of the quaternary centers found in the aspidosperma and strychnos alkaloids, was first studied by Magnus and co-workers.[34] They effectively used this methodology for the synthesis of the kopsane alkaloids.[35] When sulfoxide **101** was exposed to trifluoroacetic anhydride, the homoannular diene **102** was produced in 78% yield (Scheme 20).

Scheme 20

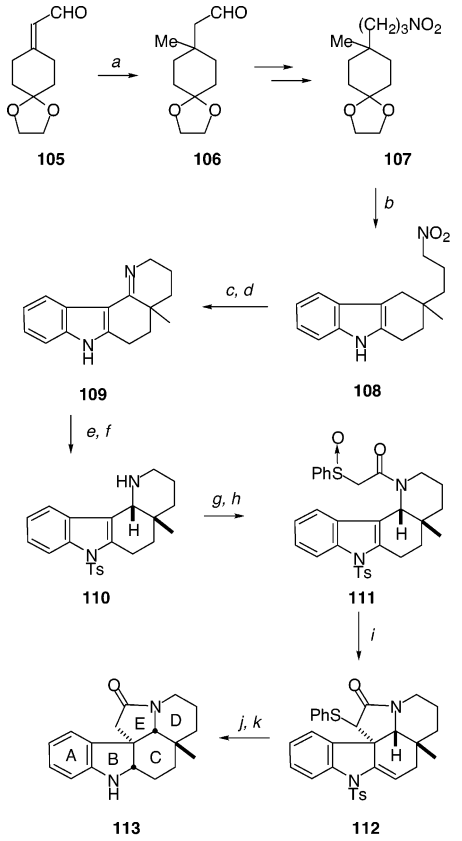


Formation of the C(11)−C(12) bond was proposed to proceed prior to the elimination of HCl, since it was known that the 1,4-dihydrocarbazole system, resulting from elimination of HCl, would readily aromatize under the reaction conditions. Allylation of keto sulfide **102** resulted in the introduction of the allylic tether on the concave face of the diene. Intramolecular [4+2]-cycloaddition of the π-bonds present in **103**

produced the basic kopsane structure **104** in 86% yield.

This approach has also been used for the aspidosperma alkaloids, and was employed by d'Angelo to synthesize (+)-aspidospermidine.[36] More recently, Rodríguez and Urrutia have incorporated this strategy into their synthesis of (±)-18-noraspidospermidine (**113**) as part of an effort to develop useful analogues (Scheme 21).[37] The key transformation in

Scheme 21[a]

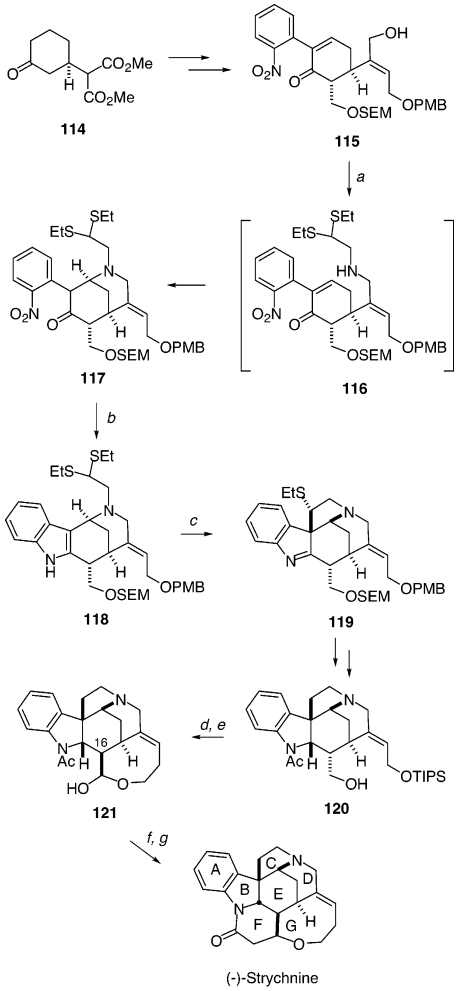


[a] Reagents and conditions: (a) Me_2CuLi,Et_2O; 63%. (b) $PhNHNH_3Cl$; 81%. (c) DDQ; 80%. (d) $NiCl_2{\cdot}6H_2O/NaBH_4/NH_2NH_2{\cdot}H_2O$; 91%. (e) TsCl, NaOH, Bu_4NH_4I; 74%. (f) $LiAlH_4$–$AlCl_3$, toluene/THF (30:1); 93%. (g) $PhSCH_2COCl$; 96%. (h) $NaIO_4$; 72%. (i) TFAA, PhCl; 68%. (j) Raney Ni; 82%. (k) $LiAlH_4$; 50%.

the synthesis involves the conjugate addition of dimethylcuprate to the α,β-unsaturated aldehyde **105** to provide **106** (63% yield), a strategy that allows for the introduction of a variety of angular substituents in the final product. Several functional group manipulations provided access to ketal **107**. The indole ring was subsequently introduced via a Fischer indole reaction to give **108**. Benzylic oxidation followed by nickel boride reduction of the nitro group provided imine **109**. After considerable experimentation, it was found that a mixture of $LiAlH_4/AlCl_3$ could reduce imine **109** to the *cis*-fused amine **110** with modest stereoselectivity (93% yield, 3:1 *cis*/*trans*) in a toluene/THF (30:1) solvent mixture. With amine **110** in hand, the *E* ring was installed by acylation with phenylthioacetyl chloride followed by oxidation of the sulfide to the sulfoxide **111** using $NaIO_4$. Exposure of **111** to trifluoroacetic anhydride effected a Pummerer cyclization to provide **112** in 68% yield. To finish the synthesis, **112** was desulfurized by the action of Raney nickel. Further reaction with $LiAlH_4$ cleaved the tosyl protecting group and stereoselectively reduced the enamine functionality to give the target **113**.

In a recent report, the Shibasaki group described an elegant synthesis of (−)-strychnine that employs a variation on the Magnus approach to form the spirocyclic pyrrolidine moiety.[38] Highlights of the synthesis are depicted in Scheme 22. An asymmetric

Scheme 22[a]

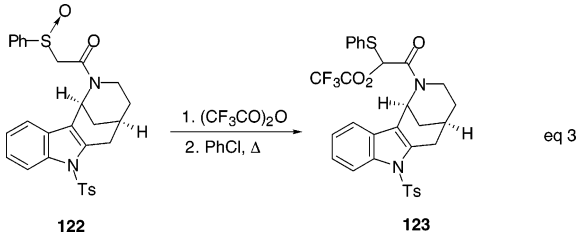


[a] Reagents and conditions: (a) Tf_2O, *i*-Pr_2NEt; 2,2-bis(ethylthio)ethylamine. (b) Zn, MeOH−aqueous NH_4Cl; 77% for two steps. (c) DMTSF; 86%. (d) $SO_3{\cdot}Pyr$, Et_3N, DMSO. (e) $HF{\cdot}Et_3N$, THF; 83% for two steps. (f) NaOMe, MeOH. (g) Malonic acid, NaOAc, Ac_2O, AcOH; 42% for two steps.

Michael addition of dimethyl malonate to cyclohexenone provided enantiomerically pure **114** in 91% yield. In a series of reactions, **114** was transformed into ketone **115**. Conversion of the primary alcohol in **115** to the corresponding triflate, followed by displacement with 2,2-bis(ethylthio)ethylamine afforded bicyclic amine **117** via the intermediacy of **116**. Reduction of the nitro moiety followed by a condensation of the resulting amine with the adjacent carbonyl group provided indole **118** in 77% yield from ketone **115**. Treatment of **118** with DMTSF promoted a Pummerer cyclization to form the spirocyclic C ring of **119** in 86% yield. Protecting group manipulation and removal of the ethylthio moiety furnished pen-

tacycle **120**. Oxidation of the alcohol group in **120**, with concomitant epimerization of the C(16) stereocenter, followed by deprotection of the TIPS ether established the hemiacetal **121** in 83% yield. Removal of the acetyl protecting group followed by exposure to malonic acid under buffered conditions provided (−)-strychnine in 42% yield from **121**.

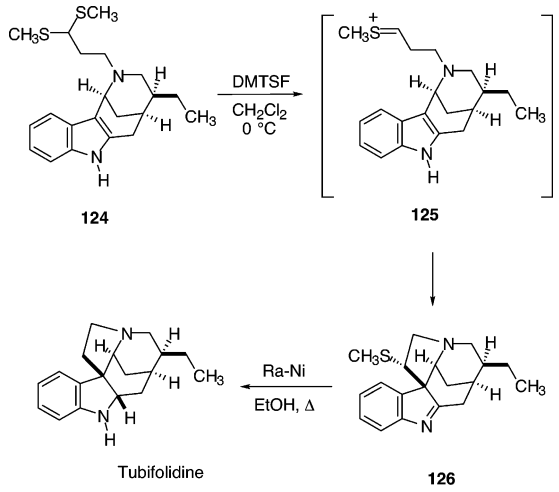
Bosch and co-workers carried out an interesting and novel approach to the pentacyclic ring system present in the strychnos alkaloid family using a tandem Pummerer intramolecular nucleophilic ring closure reaction.[39] Reaction of β-keto sulfoxide **122** with TFAA afforded α-trifluoroacetyl sulfide **123** (90% yield, eq 3). The failure of **122** to cyclize on the



122 **123** eq 3

indole ring was attributed to the fact that cyclization of the thionium ion onto the indole at the 3-position would disturb the planarity of the amide carbonyl group. The ring closure reaction was also expected to be inhibited by the lower conformational flexibility present in the rigid bridged strychnos skeleton.[39a] However, it was possible to overcome these difficulties by preparing the dimethylthioacetal derivative **124** (Scheme 23). Treatment of **124** with DMTSF

Scheme 23

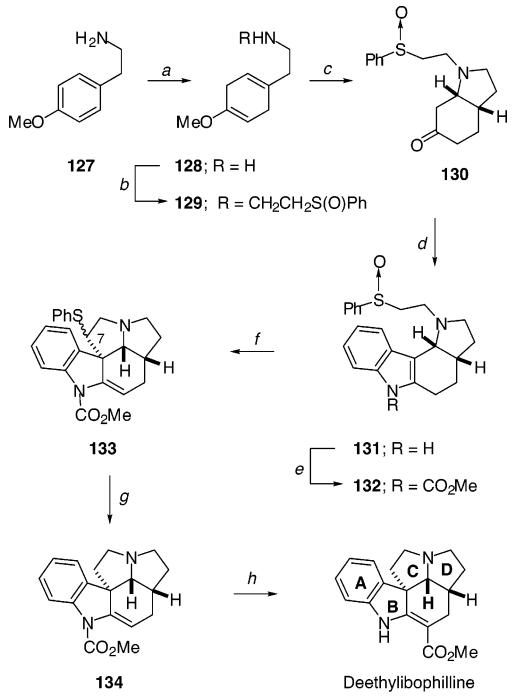


124 **125** **126**

gave rise to the pentacyclic system **126** by an intramolecular ring closure of the indole ring onto thionium ion **125**. Reductive desulfurization with Raney Ni provided tubifolidine in good yield.

The ibophyllidine alkaloids have also been constructed using a ring-closing Pummerer reaction to fashion the C ring. Bosch and co-workers started the synthesis of (±)-deethylibophyllidine by employing a dissolving metal reduction of phenethylamine **127** to provide the dihydrobenzene derivative **128** (Scheme 24).[40] Addition of **128** to phenyl vinyl sufoxide yielded **129**. Heating **129** with 2 N HCl at 90 °C, followed by

Scheme 24[a]



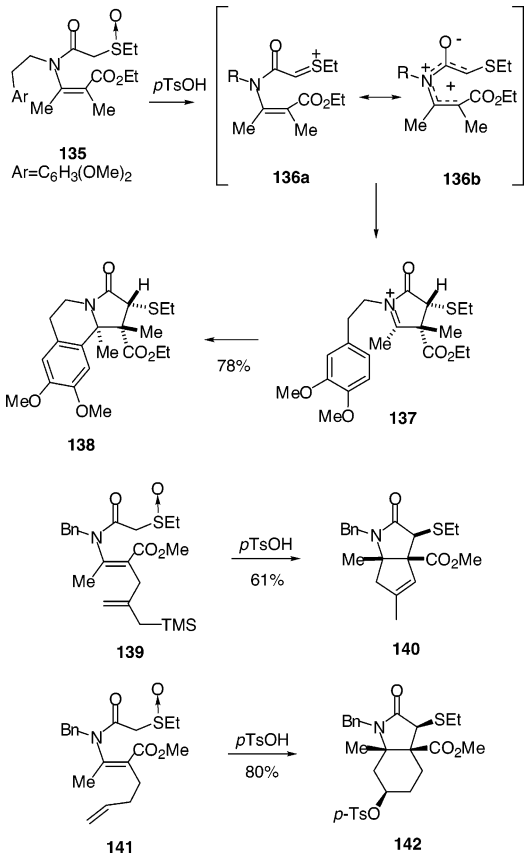
127 **130** **133** **134** Deethylibophilline

[a] Reagents and conditions: (a) Li, NH_3, EtOH, −78 °C. (b) phenyl vinyl sulfoxide, EtOH, rt. (c) 2 N HCl, 90 °C; 54% from **127**. (d) $PhNHNH_2$, EtOH, Δ; then AcOH, 95 °C; 60%. (e) LDA, NC−CO_2Me, THF−HMPA, −78 °C; 76%. (f) TFA (3 equiv), TFAA (3 equiv), 80 °C, 2 h; 63%. (g) Raney Ni, EtOH, Δ; 63%. (h) hν; 50%.

a basic workup, gave the *cis*-ocatahydroindolone **130** in 54% from **127**. A regioselective acid-catalyzed Fischer indole reaction afforded the NH-indole **131** (60% yield), which was protected on the indole nitrogen by treatment with LDA followed by the addition of Mander's reagent to give **132** in 76% yield. It should be noted that neither the hydrolysis of the enol ether nor the Fisher indole reaction, both conducted under acidic conditions, effected a Pummerer reaction of the pendant sulfoxide. This was attributed to the higher stability of sulfoxides lacking an activating group at the α-position, thereby allowing for the early introduction of a sulfur atom at the proper oxidation state. The desired Pummerer cyclization could easily be triggered, however, by exposing **132** to a mixture of TFA and TFAA (3 equiv) at 80 °C for 2 h. Under these conditions, a mixture of pentacyclic isomers (i.e., **133)** epimeric at C(7) was obtained in 63% yield. The now superfluous phenylthio group present in **133** was readily removed by the action of Raney Ni in ethanol at reflux to afford **134** in 63% yield. Irradiation of **134** using a medium-pressure mercury lamp delivered deethylibophyllidine in 50% yield.

In recent years, our research group at Emory has examined the combination of Pummerer-based cyclizations and *N*-acyliminium ion cyclizations in a tandem sequence to form pyrrolidine-containing ring systems. In a typical example, enamide **135** was treated with *p*-TsOH in benzene at reflux temperature to produce thionium ion **136**. A subsequent Nazarov-like ring closure of **136** furnished iminium ion **137**. Finally, interception of this cation by the pendant aromatic ring produced **138** as a single

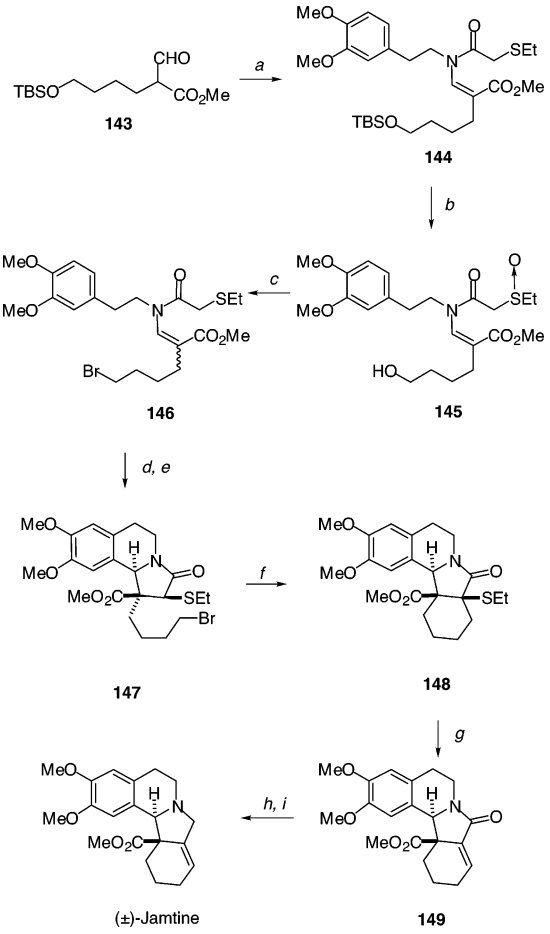
Scheme 25



diastereomer in 78% yield (Scheme 25).[41] The stereochemistry of **138**, established by X-ray crystallographic analysis, suggests a *conrotatory* ring closure. Other π-bonds were also found to efficiently terminate the cascade. For example, allylsilane **139** provided bicycle **140** in 61% yield when heated with *p*-TsOH. The terminal alkene **141** cyclized to give **142** (80% yield), where the resultant secondary carbocation was captured by sulfonate anion. In each case, only one diastereomer was isolated, suggesting that a concerted 4π-electrocyclization reaction results from the intermediate thionium ion.

The Padwa group used this methodology to construct the reported structure of the alkaloid jamtine.[42] The key intermediate was assembled by condensation of aldehyde **143** with 3,4-dimethoxyphenethylamine followed by acylation with (ethylsulfanyl)acetyl chloride to give enamide **144** as a mixture (4:1) of *Z*- and *E*-isomers in which the former predominated (Scheme 26). Exposure of **144** to $NaIO_4$ resulted in oxidation of the sulfide to a sulfoxide with concomitant cleavage of the TBS ether, affording alcohol **145**. This alcohol was converted to the corresponding bromide using CBr_4/PPh_3, providing enamide **146** whereby the sulfoxide functionality had also been reduced. Reoxidation, followed by heating the resulting sulfoxide with CSA, produced several tricyclic products (98% yield) as a mixture (5:2:1:1) of diastereomers in which **147** was isolated as the major diastereomer. The stereochemistry of **147**, secured by X-ray crystallographic analysis, is consistent with a Nazarov-type *conrotatory* 4π-electrocyclization followed by attack of the nucleophilically disposed aromatic ring from the least hindered side

Scheme 26[a]

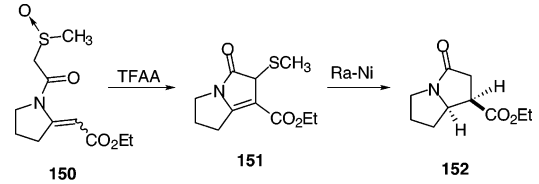


[a] Reagents and conditions: (a) 2,2-Dimethoxyphenethylamine, (ethylsulfanyl)acetyl chloride; 92%. (b) $NaIO_4$, $MeOH/H_2O$; 99%. (c) CBr_4, PPh_3; 83%. (d) $NaIO_4$, $MeOH/H_2O$; 99%. (e) CSA, PhMe, reflux; 98%. (f) NaH, THF, reflux; 99%. (g) $NaIO_4$, $MeOH/H_2O$; heat; 90%. (h) Lawesson's reagent; 99%. (i) Meerwein's salt, $NaBH_4$, MeOH; 61%.

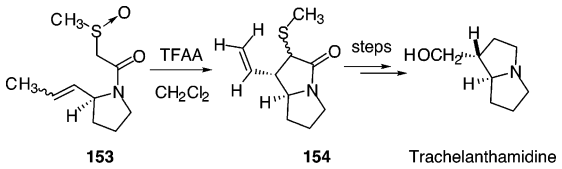
of the intermediate iminium ion. Reaction of α-ethylthio amide **147** with NaH effected an intramolecular alkylation to provide tetracycle **148**. Oxidative elimination of the ethylthio group delivered the required unsaturated amide **149**. Removal of the now superfluous carbonyl group was accomplished by first converting **149** to a thioamide followed by a subsequent reduction using methyl Meerwein's salt and $NaBH_4$ to complete the synthesis of (±)-jamtine.

Preparation of the skeletal framework of the pyrrolizidine alkaloid family was carried out by Ishibashi using amido sulfoxide **150**.[43] The Pummerer reaction of **150** provided the bicyclic lactam **151** in 31% yield (Scheme 27). Conversion of **151** to **152** was accomplished by reducing the thiomethyl group with Raney Ni. Intermediate **152** was subsequently converted into both (±)-isoretronecanol and (±)-trachelanthamidine.

Scheme 27



Scheme 28

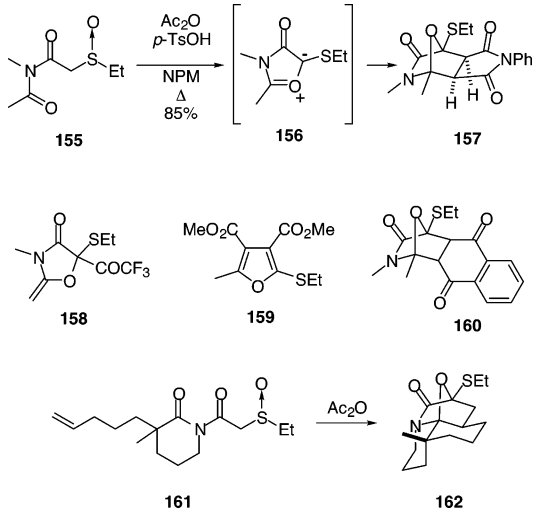


A related method was employed as the key step for the synthesis of (−)-trachelanthamidine (Scheme 28).[44] Sulfoxide **153** was treated with TFAA, and lactam **154** was isolated in 87% yield. This bicyclic lactam was then converted into trachelanthamidine in several additional steps.

3.3. Mesoionic Betaines

In a series of papers, Padwa and co-workers examined the use of a Pummerer-initiated cascade reaction to generate isomünchnones, a class of mesoionic betaines,[45−47] and further studied their ability to participate in 1,3-dipolar cycloaddition chemistry. For example, treatment of sulfoxide **155** with acetic anhydride resulted in the formation of a reactive thionium ion that engaged the distal amide carbonyl group to produce isomünchnone **156** (Scheme 29).[46]

Scheme 29

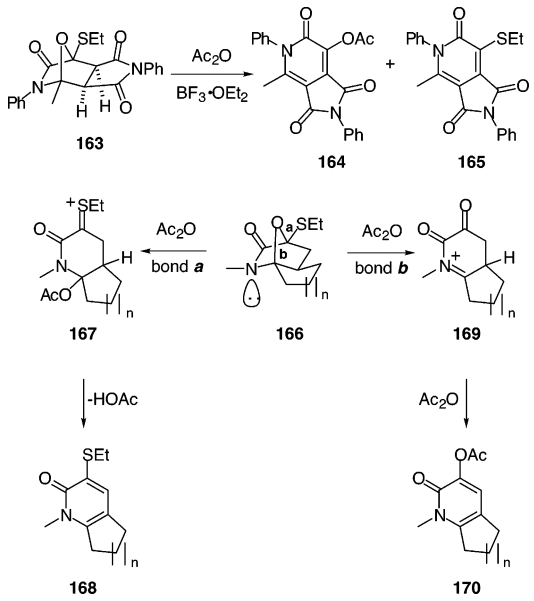


Further exposure of **156** to a dipolarophile, such as *N*-phenylmaleimide (NPM), induced a 1,3-dipolar cycloaddition and gave **157** as a single diastereomer in 85% yield.

The specific conditions required to successfully effect this transformation were important and warrant comment. The initial attempts to form the intermediate isomünchnone employed TFAA to promote the cyclization and Et_3N to form the dipole from the oxonium ion intermediate. These conditions, however, failed to produce a viable dipole. Rather, cyclic ketene acetal **158**, in which the transient dipole first reacted with excess TFAA followed by deprotonation, was obtained. After considerable experimentation, it was discovered that the slow addition of **155** to a mixture of acetic anhydride, a catalytic amount of *p*-TsOH, and the appropriate dipolarophile at the reflux temperature of toluene gave consistently good yields of the 1,3-cycloadduct. Several different dipolarophiles were found to participate in these cycloadditions. When **156** was allowed to react with DMAD, the initially formed oxabicycle underwent a rapid fragmentation reaction to produce furan **159** (41% yield) and methyl isocyanate. The reaction of isomünchnone **156** with 1,4-naphthoquinone produced **160** in 73% yield. Other dipolarophiles that were used included vinyl sulfones, maleic anhydride, and acrylate derivatives. Unactivated olefins also participated in the cycloaddition when they were tethered to the isomünchnone dipole. For example, when sulfoxide **161** was treated with acetic anhydride, polycyclic **162** was isolated as a single diastereomer in 73% yield.

The oxabicyclic products could be further transformed into highly substituted pyridones. Thus, exposure of cycloadduct **163** to a mixture of acetic anhydride and $BF_3{\cdot}OEt_2$ produced a mixture (5:1) of pyridones **164** and **165** in 96% combined yield (Scheme 30). In experiments with related cycloadducts, the

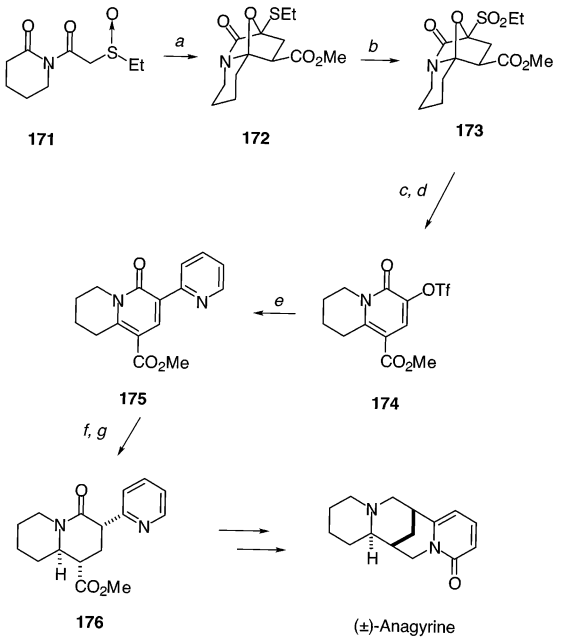
Scheme 30



preferential formation of either the acetoxy (e.g., **164**) or ethylthio (e.g., **165**) substituted pyridone was found to be substrate dependent. The products arise from differential cleavage of the bridging bond in either the *N*,*O*-acetal (bond *a*) or *S*,*O*-acetal (bond *b*). Accordingly, when bond a in oxabicycle **166** is ruptured, loss of acetic acid and further tautomerization of thionium ion **167** produces the ethylthio-substituted pyridone **168**. Alternatively, fragmentation of bond *b* produces iminium ion **169**. Deprotonation followed by acylation of the resulting carbonyl group gives **170**. The preference for pyridone **170** is thought to hinge upon the ability of the amide nitrogen to assist in the breaking of bond *b*. Thus, cycloadducts with geometries in which the nitrogen's lone pair of electrons are *anti*-periplanar to the nucleofuge provide greater quantities of the acetoxy-substituted product **170**.

The above Pummerer-initiated cycloaddition/cascade strategy was used for the synthesis of several alkaloid natural products. For example, the formal synthesis of (±)-anagyrine involved exposure of imide **171** to a mixture of acetic anhydride and methyl

Scheme 31[a]

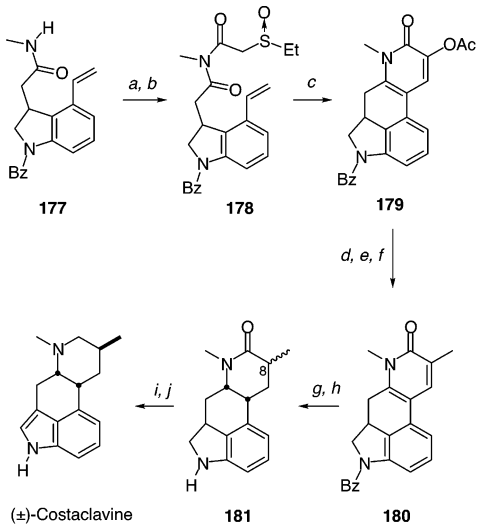


[a] Reagents and conditions: (a) Ac_2O, methyl acrylate; 61%. (b) $NaIO_4$–$RuCl_3$; 91%. (c) $BF_3{\cdot}OEt_2$. (d) $(Tf)_2NPh$, Et_3N; 80% for two steps. (e) 2-(tri-*n*-butylstannyl)pyridine, $Pd_2(dba)_3$, TFP; 70%. (f) H_2, PtO_2. (g) NaOMe, MeOH; 85% for two steps.

acrylate to provide oxabicycle **172** in 61% yield (Scheme 31).[47] Oxidation of the sulfide group present in **172** with $NaIO_4/RuCl_3$ furnished sulfone **173** (91% yield). Exposure of **173** to $BF_3{\cdot}OEt_2$ and subsequent reaction with Comins' reagent gave triflate **174** in 80% overall yield. Palladium-catalyzed cross coupling of **174** with 2-(tri-*n*-butylstannyl)pyridine afforded **175** in 70% yield. Catalytic hydrogenation of the pyridone ring in **175** using PtO_2 followed by a base-induced equilibration delivered **176** (85% overall yield), a compound previously converted to (±)-anagyrine.

Another example that makes use of this strategy for natural product chemistry involves the synthesis of (±)-costaclavine (Scheme 32).[47] The methyl amide functionality present in **177** was acylated with (ethylsulfanyl)acetyl chloride, and subsequent oxidation of the sulfide with $NaIO_4$ provided sulfoxide **178**. The key tandem Pummerer cyclization/cycloaddition cascade was initiated by exposing **178** to acetic anhydride and a trace of *p*-TsOH, which gave tetracycle **179** in 64% yield. A sequence of functional group interconversions (hydrolysis of the acetate, conversion to the vinyl triflate, and a Stille coupling for installation of a methyl group) provided **180** in 59% overall yield. Platinum oxide-mediated hydrogenation of the pyridone moiety present in **180** followed by removal of the benzoyl group under acidic conditions furnished **181** as a separable mixture (4:1) of epimers about the C(8) methyl group in 85% overall yield. The amido group of the major diastereomer of **181** was reduced with $LiAlH_4$, and subsequent manganese dioxide oxidation of the dihydroindole delivered (±)-costaclavine in 12 steps with an overall yield of 17%. The synthesis of several other alkaloids, including onychine, dielsquinone, (±)-lupinine, and pumiliotoxin C, were also described by the Padwa group.[47]

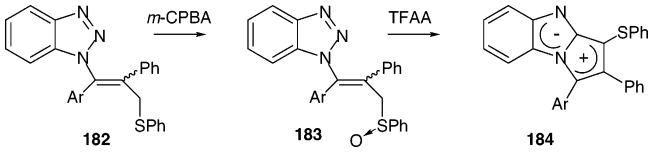
Scheme 32[a]



[a] Reagents and conditions: (a) (Ethylsulfanyl)acetyl chloride, Δ. (b) $NaIO_4$. (c) Ac_2O, *p*-TsOH (trace); 64%. (d) K_2CO_3, MeOH. (e) *N*-(5-chloro-2-pyridyl)triflimide, Et_3N. (f) $Pd(Ph_3)_2Cl_2$, Me_4Sn, LiCl; 59% over three steps. (g) H_2, PtO_2. (h) HCl, H_2O; 45% for two steps. (i) $LiAlH_4$. (j) MnO_2.

In a somewhat related study, Kim and Park have reported the use of the Pummerer reaction as a key step for the synthesis of triazapentalenes, another class of mesoionic betaines.[48] In this example, the benzotriazole-substituted allyl sulfide **182** (Ar = 4-$MeOC_6H_4$) was first oxidized to sulfoxide **183** in 94% yield using *m*-CPBA (Scheme 33). Treatment of

Scheme 33



183 with TFAA at room temperature provided triazapentalene **184** in 91% yield. The Pummerer-initiated cyclization worked equally well on stereochemically pure samples of either the (*E*)- or (*Z*)-allyl sulfoxides **183**. A variety of other aryl substituents on the olefin were studied, and yields of the corresponding triazapentalenes ranged from 34% to 91%, with the typical yield being near 80%.

4. Formation of Six-Membered Ring Heterocycles

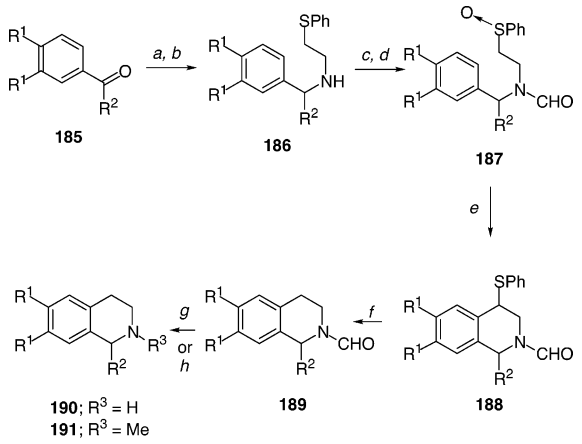
As seen from some of the above schemes, reactive five-membered ring heterocycles are often involved as intermediates for the generation of six-membered ring products. Pummerer cyclizations can also be used to access these structures directly. Many natural products feature nitrogenous and oxygenated six-membered rings that are fused to aromatic rings. For these compounds, Pummerer cyclizations are frequently employed. In contrast to thionium ion cyclizations that produce five-membered rings, products that arise from C−S bond formation often accompany the desired six-membered ring closure adducts.

4.1. Isoquinoline Derivatives

The formation of isoquinoline derivatives via Pummerer-induced cyclizations has been studied by sev-

eral research groups, including those of Tamura and Craig.[15a,49] Sano and co-workers have also employed this strategy to construct a series of tetrahydroisoquinoline alkaloids that are thought to be involved in the pathogenesis of Parkinson's disease. Their synthesis began with a Ti(*i*-PrO)$_4$-mediated condensation of benzyl ketones **185** (R^1 = H, OMe; R^2 = Me, Ph, Bn) with 2-phenylthioethylamine followed by reduction of the resulting imine with $NaBH_4$ to provide amines **186** (Scheme 34).[50] In previous studies by Shinohara,[51a] it was found that *N*-formyl derivatives provided the best yields in the Pummerer cyclization. Accordingly, formylation of the amino group present in **186** and subsequent oxidation of the sulfide moiety with $NaIO_4$ afforded substrates **187** for the Pummerer cyclization. Reaction of **187** (R^1 = OMe) with TFAA in benzene at 25 °C provided **188** (R^1 = OMe) in quantitative yield. For Pummerer cyclizations onto aromatic rings that are devoid of activating groups, the addition of BF_3·OEt_2 was found to be critical for the success of the cyclization. Thus, after exposure of **187** (R^1 = H, Me) to TFAA in benzene for 1 h, BF_3·OEt_2 was added to effect the desired cyclization, furnishing **188** in 94−97% yields. Compounds **188** were desulfurized using a nickel boride-mediated reductive elimination to give **189**. The formyl group in **189** could be either hydrolyzed (HCl or NaOH) to the secondary amines **190** or reduced with $LiAlH_4$ to deliver the *N*-methyl derivatives **191**. This method, employing TFAA and BF_3·OEt_2, for making these isoquinoline derivatives has a distinct advantage over other methods such as the Pictet−Spengler, Bischler−Napierelski, or Pomeranz−Fritsch approaches, because it allows for the synthesis of isoquinolines, such as **188** (R^1 = H, Me), that are devoid of activating groups, in high yield (94−97%).

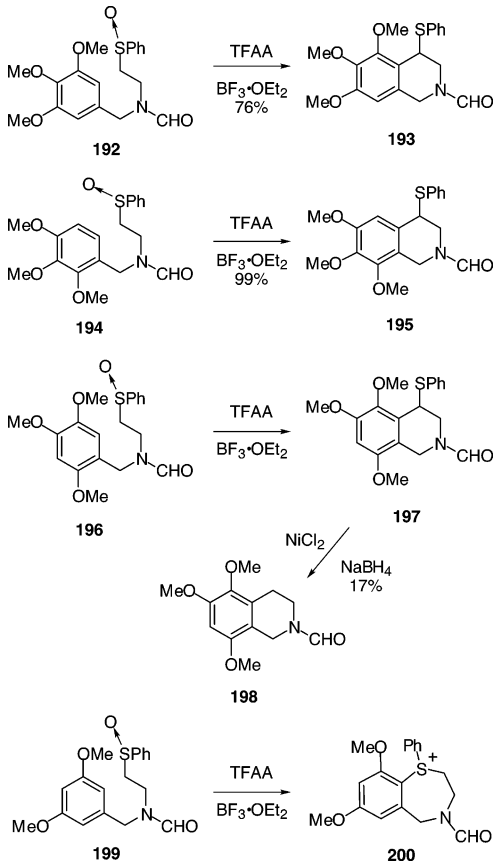
Scheme 34[a]



[a] Reagents and conditions: (a) 2-Phenylthioethylamine, Ti(*i*-PrO)$_4$. (b) $NaBH_4$. (c) HCO_2H, Ac_2O. (d) $NaIO_4$. (e) TFAA, BF_3·OEt_2 ($R^1 \neq$ OMe). (f) $NiCl_2$–$NaBH_4$. (g) NaOH or HCl. (h) $LiAlH_4$.

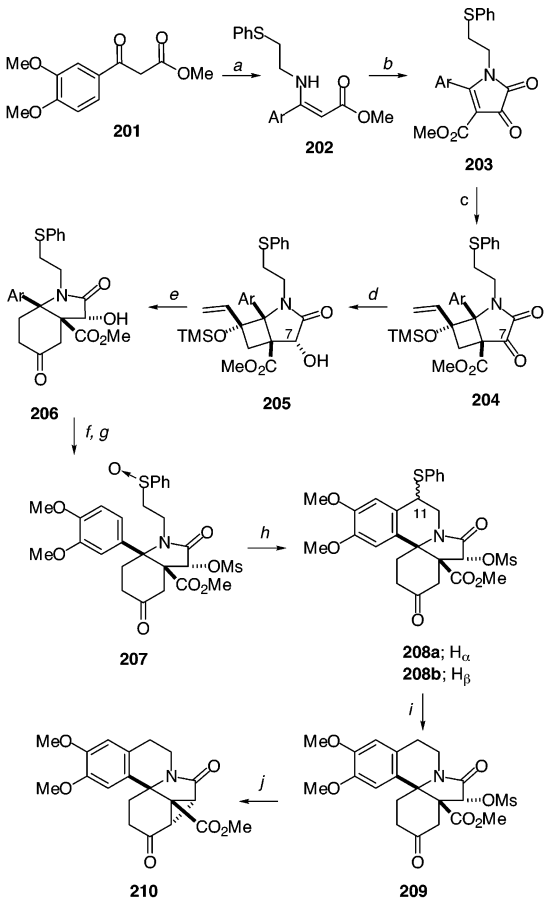
Further studies by Sano and co-workers revealed some interesting electronic effects when three methoxy groups were present on the aromatic cyclization partner. Thus, when compound **192** was treated with TFAA followed by exposure to BF_3·OEt_2, tetrahydroisoquinoline **193** was produced in 76% yield (Scheme 35).[51b] Although the reaction proceeded without BF_3·OEt_2, the addition of this Lewis acid to the reaction medium greatly accelerated the rate of the cyclization. Similarly, when **194** was subjected to similar conditions, **195** was formed in 99% yield.[52] Upon treatment with TFAA and BF_3·OEt_2, however, **196** only produced **197** in low yields. After the crude reaction mixture containing **197** was subjected to the nickel boride reduction conditions, the isoquinoline derivative **198** was isolated in only 17% yield. Interestingly, when the dimethoxy-substituted aromatic **199** was treated with the TFAA/BF_3·OEt_2 mixture, compound **200**, arising from C−S bond formation, was isolated as the major product.

Scheme 35



The isoquinoline ring system is found in several families of natural products, including the erythrina alkaloids. With this target class in mind, the Sano group has applied the Pummerer methodology toward the preparation of a key erythrina alkaloid intermediate. In this approach, *β*-keto ester **201** was condensed with 2-phenylthioethylamine to give vinylogous amide **202** (Scheme 36).[53] Treatment of **202** with oxalyl chloride produced dioxopyrroline **203** in 81% overall yield. Photolysis of **203** and 2-trimethylsilyloxybutadiene afforded cyclobutane **204** as a single diastereomer in 79% yield. The stereochemistry of **204** was established by comparison of its NMR spectral data to those of a similar photoadduct whose structure had been secured by X-ray analysis. Reduction of the C(7) carbonyl group with $NaBH_4$ afforded **205** (93%), which underwent a 1,3-sigmatropic rearrangement upon exposure to TBAF to deliver the ring-expanded product **206** in 99% yield. Mesylation of the C(7) hydroxyl group in **206** followed by oxida-

Scheme 36[a]



[a] Reagents and conditions: (a) 2-Phenylthioethylamine; 90%. (b) $(COCl)_2$; 90%. (c) 2-TMSO-butadiene, hν, 79%. (d) $NaBH_4$; 93%. (e) TBAF, −30 °C; then rt; 99%. (f) MsCl, pyridine. (g) $NaIO_4$; 97% over two steps. (h) TFAA, CH_2Cl_2, rt; 88%. (i) Bu_3SnH, AIBN, toluene, Δ; 77% (**208b**), 59% (**208a**). (j) DBU; 60%.

tion of the sulfide moiety with $NaIO_4$ gave the Pummerer cyclization precursor **207** in 97% overall yield. The TFAA-promoted thionium ion cyclization of sulfoxide **207** produced **208a** and **208b** as a mixture (1:87) of epimers about the C(11) stereocenter in 88% combined yield. Radical reduction of the major diastereomer **208b** afforded **209** in 77% yield, while **208a** also gave **209** in 59% yield under the same conditions. Exposure of **209** to DBU afforded cycloerythrinan **210**, which has been employed as a key intermediate in the syntheses of several natural products.

The relative stereochemistry of compounds **208a**,**b** was established by comparison of their ^{1}H NMR spectra to those of similar compounds of known stereochemistry. The preferential formation of **208b** (H_β) was rationalized in terms of steric interactions in the corresponding transition states. Transition state **A**, leading to **208a**, suffers from an unfavorable steric interaction between the phenylthio group and the angular methoxycarbonyl substituent (Figure 1). This interaction is relieved in transition state **B**, which leads to structure **208b**.

A Pummerer cyclization approach was also employed as a key strategic disconnection by Desmaële and Jousse in their synthesis of the erythrinan alkaloid skeleton.[54] In this investigation, nitro enoate

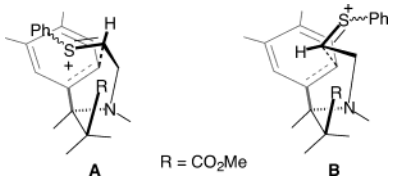
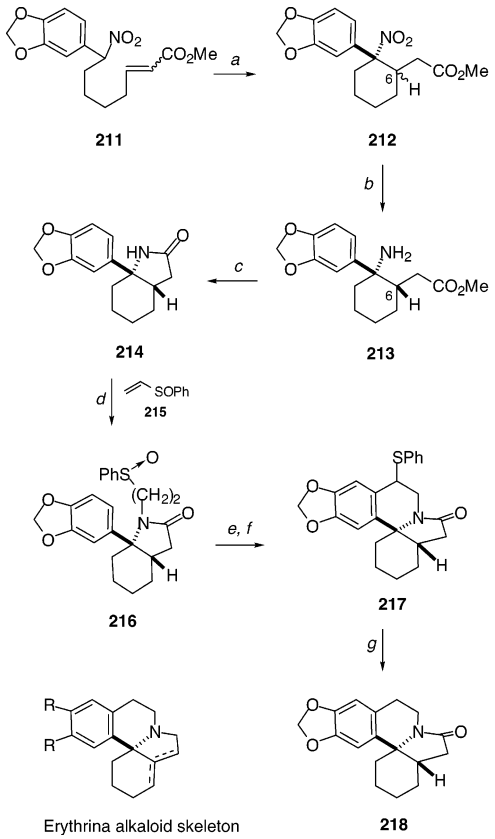


Figure 1. Transition states leading to **208a**,**b**.

211 was cyclized via an intramolecular Michael addition to afford ester **212** (68%) as a separable mixture (1:1) of diastereomers about the C(6) stereocenter (Scheme 37). Other bases were also examined,

Scheme 37[a]



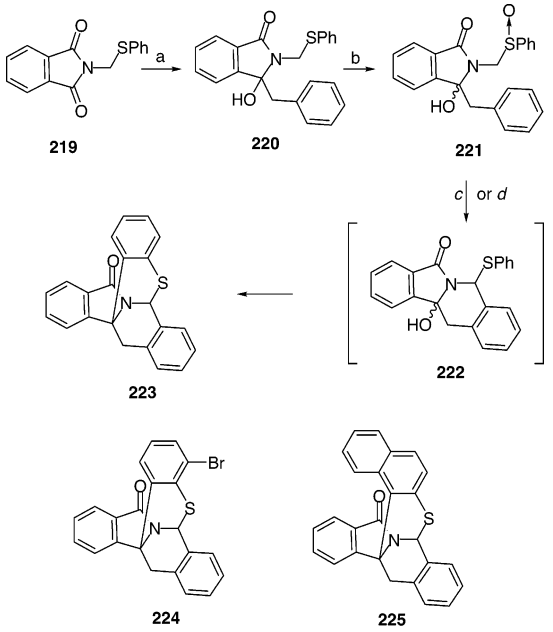
[a] Reagents and conditions: (a) TBAF, THF, rt, 18 h; 68%. (b) Raney Ni. (c) Toluene, Δ, 1 h; 42% over two steps. (d) NaHMDs, THF/HMPA, −78 °C, then **215**; 55%. (e) Ac_2O, Δ. (f) $SnCl_4$, CH_2Cl_2, 0 °C; 56%. (g) Bu_4SnH, AlBN, toluene, Δ; 75%.

but they resulted in lower yields of the desired product along with other structures in which the nitro group had been oxidatively hydrolyzed to the corresponding aryl ketone. It should be noted that the C(6) center is generally sp^2 hybridized in most of the erythrina alkaloid targets (e.g., erysotramidine, Scheme 18), so both diastereomers can be employed in the remainder of the synthetic sequence. For clarity, however, only the α-isomer with respect to the C(6) substituent is shown in the reaction scheme. Reduction of the nitro group in **212** by exposure to Raney nickel provided **213**. Although it was expected that a spontaneous *O*- to *N*-transacylation would occur to give **214**, it was discovered that thermal activation was required. Heating a sample of **213** in toluene at reflux provided **214**. Reaction of **214** with vinyl sulfoxide **215** afforded the 1,4-addition product **216**. After some experimentation, it was ultimately

discovered that a stepwise ring closure provided the best results for the conversion of **216** to **217**. Thus, heating **216** with acetic anhydride followed by exposure to $SnCl_4$ at 0 °C delivered **217** in 56% yield. The phenylthio moiety present in **217** was removed under radical reducing conditions to furnish the erythrina skeleton **218**.

As part of their investigations into *N,S*-fused polycyclic ring systems, Daich and co-workers have reported a tandem Pummerer/*N*-acyliminium ion cyclization that was used to construct interesting isoquinolinone structures.[55] Addition of benzylmagnesium bromide to **219** provided **220** in 51% yield (Scheme 38). Oxidation of the sulfide functionality

Scheme 38[a]



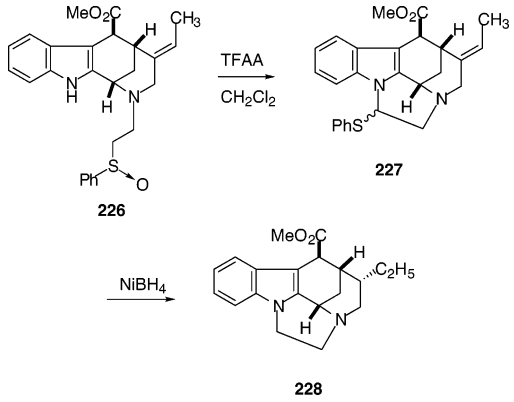
[a] Reagents and conditions: (a) BnMgBr; 51%. (b) *m*-CPBA, 0 °C, 1−3 min; −100%. (c) TFAA, CH_2Cl_2, rt, 8 h; TFA, rt, 12 h; 42%. (d) TFAA, pyridine; 56%.

to the corresponding sulfoxide was accomplished by exposure of **220** to *m*-CPBA for short periods of time (1−2 min) to furnish **221** as a mixture of diastereomers. Treatment of sulfoxide **221** with TFAA in CH_2Cl_2 at room temperature for 8 h followed by the addition of TFA produced **223** in 42% yield through the intermediacy of **222**. If the reaction was carried out under buffered conditions (TFAA, pyridine), compound **222** could be isolated in 56% yield. An *N*-acyliminium ion intermediate could then be generated by treating **222** with neat TFA. Subsequent cyclization of the iminium ion gave **223** in 58% yield. Other arylthio groups were also examined, with compounds **224** and **225** being obtained from the TFAA/TFA conditions in 62% and 41% yield, respectively.

4.2. Indole Alkaloids

Intramolecular addition of nitrogen nucleophiles onto thionium ions derived from Pummerer reactions have also been used for the formation of the C(6)−C(7) bond in an attempted synthesis of the akuammiline family of alkaloids. For example, treatment

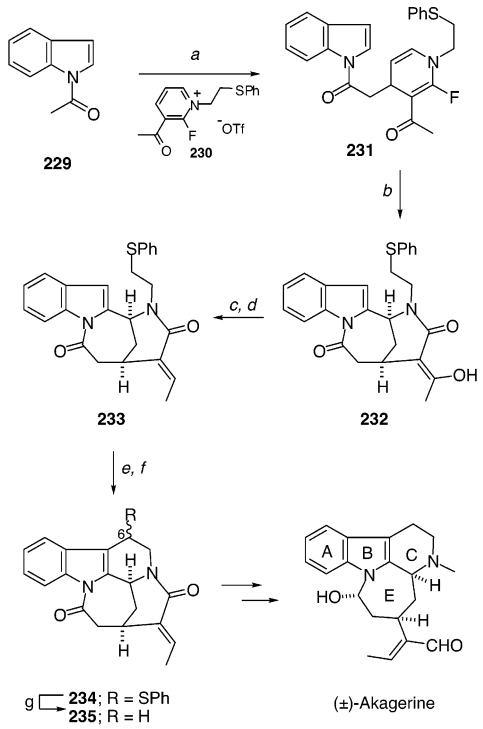
Scheme 39



of sulfoxide **226** with TFAA produced the novel heterocycle **227** in 24% yield (Scheme 39).[56,57] Reduction of the sulfide linkage using $NiBH_4$ afforded indole **228**. Compound **227** arises from intramolecular trapping of the initially generated thionium ion onto the indole nitrogen atom.

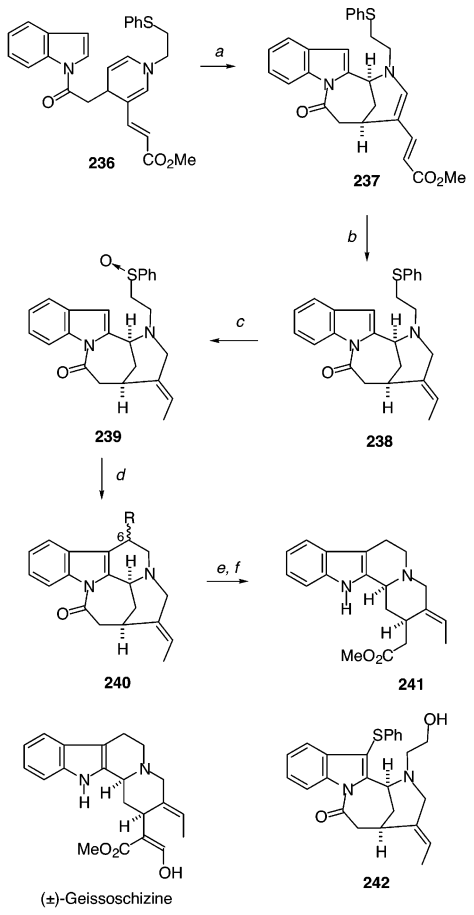
The construction of the indolo[2,3-*a*]quinolizidine system[56b] and the pentacyclic ring system of apogeissoschizine[56c] by formation of the C(6)−C(7) bond has also been reported. In this context, an interesting application of the Pummerer cyclization to fashion the C ring of the corynanthean alkaloid (±)-akagerine was reported by Bennasar and Bosch.[58] As outlined in Scheme 40, their approach involves the addition of the enolate derived from 1-acetylindole (**229**) onto pyridinium triflate **230** to provide **231** in 25% yield. Exposure of **231** to *p*-TsOH and LiI effected cycliza-

Scheme 40[a]



[a] Reagents and conditions: (a) LDA, THF, −30 °C; then **230**; 25%. (b) *p*-TsOH, LiI, MeOH/C_6H_6; 58%. (c) Tf_2O, 1,8-bis(dimethylamino)naphthalene, −30 to −10 °C. (d) Bu_3SnH, $Pd(PPh_3)_4$, LiCl; 45% over two steps. (e) *m*-CPBA, −70 °C. (f) TFAA, 2,6-di(*tert*-butyl)pyridine, rt, 30 min; then Δ; 71% over two steps. (g) Bu_3SnH, AIBN, C_6H_6, reflux; 72%.

Scheme 41[a]



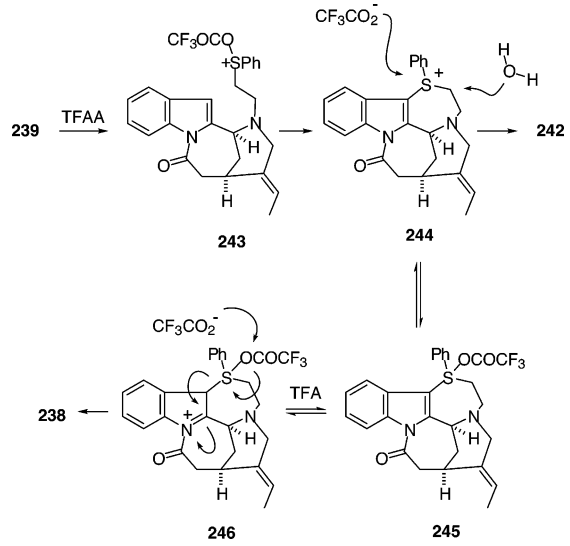
[a] Reagents and conditions: (a) *p*-TsOH, C_6H_6, LiI; 22%. (b) 2.5 N HCl, MeOH, Δ; then $NaBH_4$, 0 °C; 33%. (c) TFA, CH_2Cl_2, 0 °C; then *m*-CPBA, −78 °C; 80%. (d) TMS−OTf, i-Pr_2NEt, CH_2Cl_2, rt; 64%. (e) NaOMe, MeOH, rt. (f) Bu_3SnH, AIBN, C_6H_6, Δ; 52% over two steps.

tion of the dihydropyridine residue onto the indole with concomitant loss of fluoride to furnish **232** in 58% yield. The enol functionality in **232** was reduced to alkene **233** in 45% overall yield by first converting **232** to the corresponding enol triflate followed by a palladium-mediated reduction with Bu_3SnH. In preparation for the Pummerer cyclization, the sulfide group in **233** was oxidized with *m*-CPBA. Subjection of the resulting sulfoxide to buffered Pummerer conditions gave pentacycle **234** in 71% yield as a mixture of epimers about the C(6) stereocenter. The extraneous phenylthio group in **234** was then removed by a radical reduction procedure to deliver **235** (72% yield), a known intermediate used in the synthesis of akagerine.

In a more detailed account of the investigations that led to akagerine, a formal total synthesis of geissoschizine was also presented.[59] In this sequence, the enolate of acetylindole was added to a pyridinium salt which lacked the fluoro substituent and instead contained an acrylate substituent, to give dihydropyridine **236** in 22% yield (Scheme 41). Acid-induced cyclization provided tetracyclic amine **237** in 50% yield. Heating **237** in aqueous HCl followed by the addition of $NaBH_4$ stereoselectively produced the (*E*)-ethylidenepiperidine **238** in 33% yield. To chemoselectively oxidize the sulfide functionality, the basic nitrogen atom was first protonated with TFA before reaction with *m*-CPBA to deliver the Pummerer cyclization precursor **239** in 80% yield. Initial attempts to effect the cyclization by heating **239** with a mixture of TFAA and TFA in CH_2Cl_2 at reflux failed to produce **240**. Rather, a mixture of **238** and **242** was isolated (vide infra). However, exposure of **239** to TMSOTf and Hünig's base did effect the desired cyclization. Adduct **240** was isolated as a mixture of epimers about the C(6) stereocenter in 64% yield. Opening of the lactone ring with subsequent desulfurization by a radical pathway provided **241**, a known intermediate in the synthesis of geissoschizine.

The product distribution of the above Pummerer cyclization attempts using TFAA/TFA deserves some comment. As was seen from Sano's studies (Scheme 35),[53] formation of a C−S bond (i.e., **200**) can compete with C−C bond formation. The reduction of **239** to **238** and the generation of **242** both arise from the nucleophilic addition of the indole π-bond to the acyloxysulfonium ion **243** to give intermediate **244** (Scheme 42).[60] Hydrolytic cleavage of the C−S bond

Scheme 42

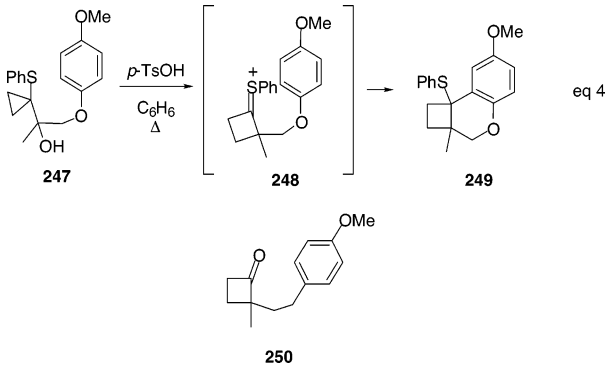


then provides **242**. Capture of the sulfonium ion by trifluoroacetate, however, affords a tetravalent sulfur compound, **245**. Subsequent protonation of the indole ring by TFA produces the iminium ion **246**. Trifluoroacetate anion effects rupture of the O−S bond with subsequent breaking of the C−S bond to regenerate **238** and trifluoroacetyl peroxide. Although this C−S bond formation represents an undesired pathway for the syntheses of akagerine and geissoschizine, this "interrupted Pummerer" reaction has been further exploited for heterocyclic synthesis by other investigators (vide infra).

4.3. Chromene Derivatives

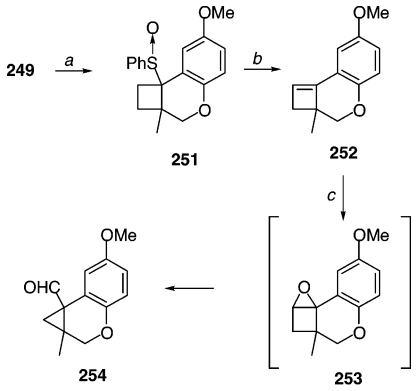
A recent report by Bernard, Piras, and co-workers describes an interesting Wagner−Merwein-type rearrangement that was used to trigger a subsequent Pummerer cyclization.[61] For example, when phenylsulfanylcyclopropane **247** was heated with *p*-TsOH in dry benzene at reflux, ionization of the hydroxyl group occurred with concomitant ring expansion to

give the transient thionium **248** ion that was subsequently captured by the pendant aryl group to furnish **249** in 77% yield (eq 4). Other aryl groups, such as those containing a *p*-Me or *p*-Cl substituent also participated in this reaction, as did the unsubstituted analogue (67−80% yield). Interestingly, if the ether linkage in the tether was removed, only cyclobutanone **250** was isolated in 80% yield.



These phenylsulfanylcyclobutane derivatives have high potential as synthetic intermediates. In the report detailing this methodology, chromene **249** was converted to the core structure of the radulanins.[61] For example, the treatment of **249** with *m*-CPBA produced sulfoxide **251** in 70% yield (Scheme 43).

Scheme 43[a]



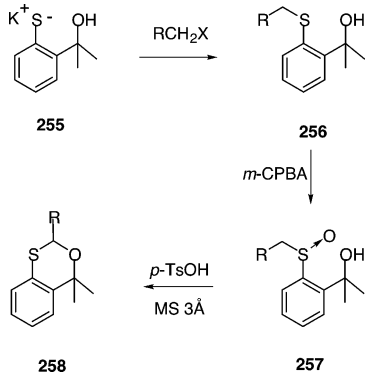
[a] Reagents and conditions: (a) *m*-CPBA, −20 °C, CH_2Cl_2; 70%. (b) Toluene, Δ; 83%. (c) *m*-CPBA, 0 °C, CH_2Cl_2; 46%.

Thermolysis of **251** in toluene resulted in elimination of PhSOH to give **252** in 83% yield. Exposure of **252** to *m*-CPBA induced a ring contraction reaction, presumably through the intermediacy of epoxide **253**, providing **254** whose carbon skeleton is found in the radulanin family of natural products.

4.4. 1,3-Oxathianes

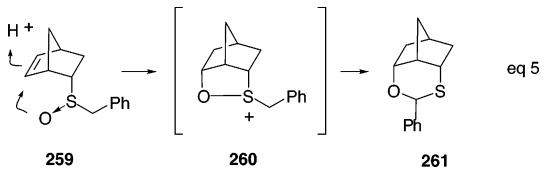
Formation of the 1,3-oxathiane ring has been achieved through a Pummerer cascade. Alkylation of potassium thiolate **255** with a variety of alkyl halides (R = Me, Et, Bn, $PhCOCH_2-$, $HOCH_2CH_2-$) gave sulfides **256** in high yield (85−96%; Scheme 44).[62a] Subsequent oxidation of **256** with *m*-CPBA produced the corresponding sulfoxides **257**. Reaction of these sulfoxides with *p*-TsOH in the presence of 3 Å molecular sieves provided 1,3-oxathianes **258** in 50−95% yields. Because *S*,*O*-acetals are easily removed

Scheme 44



masks for carbonyl functional groups, this methodology is useful for the synthesis of protected aldehydes from derived alkyl halides. The range of alkyl halides successfully used suggests that this procedure may be quite useful for the synthesis of protected aldehydes that are more complex.

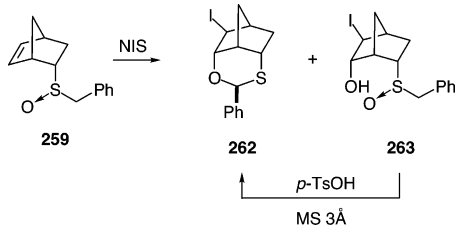
In earlier studies, Abe and Harayama demonstrated the facility with which 1,3-oxathianes **261** are formed by exposing γ,δ-unsaturated sulfinyl compounds of type **259** to *p*-TsOH (eq 5).[62b,c] The sulfo-



nium salt **260** was postulated as a reaction intermediate.

These authors recognized that electrophilic reagents other than protic acids could effect the same transformation, and the use of an iodonium ion was examined. The initial studies employed molecular iodine and *N*-iodosuccinimide (NIS) as the electrophilic source of iodine. When sulfoxide **259** was treated with NIS or I_2, the expected Pummerer product **262** was isolated in only 23% yield (Scheme 45).[63] One of the byproducts corresponded to the

Scheme 45

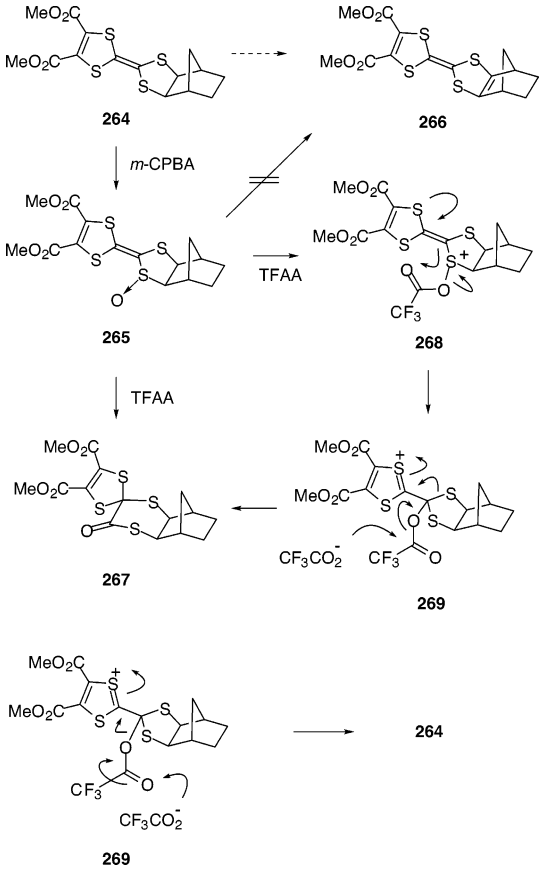


iodohydrin **263**. Conditions were then optimized for the formation of this byproduct, and **263** could eventually be generated in 80% yield by using NIS at −78 °C. Subsequent exposure of **263** to *p*-TsOH in the presence of 3 Å molecular sieves furnished **262** in 63% yield as a mixture (10:1) of diastereomers about the *S*,*O*-acetal.

4.5. Rearrangements

The isolation of C−S bonded products such as **200** (Scheme 35) and **242** (Schemes 41 and 42) demon-

Scheme 46



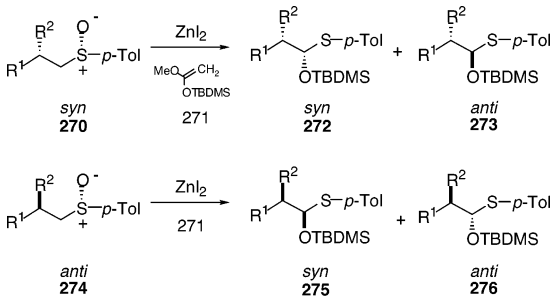
strates that some sulfoxides act unexpectedly in Pummerer-induced reactions.[64,65] Aitken and coworkers also observed a rather unusual rearrangement when they examined the behavior of dihydrotetrathiofulvalene under Pummerer conditions.[64] Oxidation of **264** with *m*-CPBA delivered the thionium ion precursor **265** (Scheme 46). Reaction of **265** with TFAA was expected to deliver compound **266**. Unexpectedly, however, products **264** and **267** were isolated in 38% and 42% yield, respectively. The rearrangement product **267** was thought to originate from a mechanism wherein a sulfur-assisted 1,2-acyl shift of the intermediate sulfonium salt **268** produces **269**. Cleavage of the trifluoroacetate triggered a subsequent ring expansion, affording 1,4-dithiane **267** and TFAA. The reduction product **264** arises from a nucleophilic displacement of the trifluoroacetyl group where the oxygen atom acts as the electrophile to produce **264** as well as trifluoroacetyl peroxide. This reduction is closely related to the reduction previously described in Scheme 42 where **239** was reduced to **238**.

5. Generation of Other Heterocyclic Ring Systems

5.1. *β*-Lactam Formation

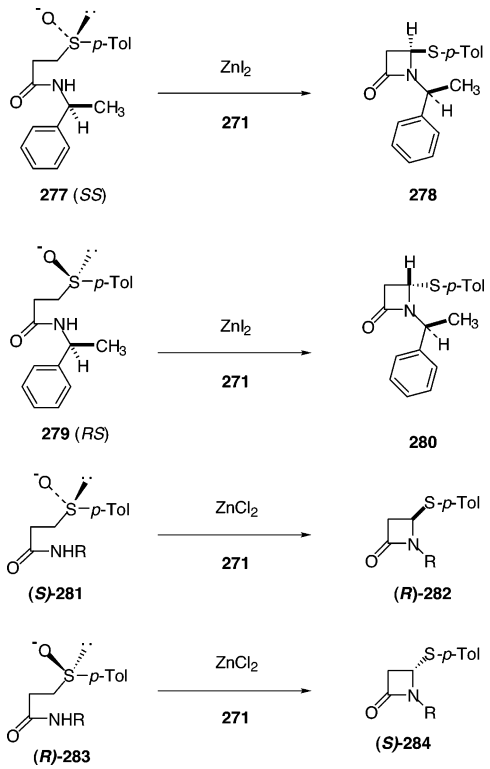
There have been several reports in the literature dealing with the asymmetric conversion of chiral *β*-amido sulfoxides into *β*-lactams using an intramolecular Pummerer cyclization process.[66−70] Kita demonstrated that a highly asymmetric Pummerer reaction of acyclic sulfoxides can be induced using an *O*-silylated ketene acetal.[69,70] The reaction of sulfoxide **270** with silyloxy ketene acetal **271** in the presence of a catalytic amount of ZnI_2 in CH_3CN provided a mixture (88:12) of the *syn*- and *anti*-α-silyloxy sulfides **272** and **273** in 75% yield (Scheme 47). Various *syn* and *anti* *β*-substituted sulfoxides were treated with the *O*-silylated ketene acetal under similar reaction conditions to give high yields of the corresponding α-silyloxy sulfides. Although the exact mechanistic details of this process are unclear, the transformation appears to involve silylation of the chiral sulfoxide followed by proton removal at the α-carbon from the face opposite the sulfoxide group by the ester enolate. The siloxy group then migrates to the α-position by one of the following possibilities: (i) an intimate ion pair mechanism, (ii) a radical dissociation−recombination mechanism, or (iii) direct carbanion attack.[64]

Scheme 47

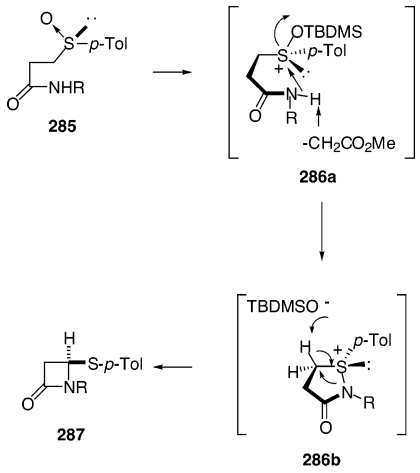


Kita has used this asymmetric Pummerer to construct enantiomerically enriched *β*-lactams **278** and **280** starting from the chiral, nonracemic *β*-amido sulfoxides **277** and **279** (Scheme 48).[70−72] The chiral sulfoxides **277** and **279** were prepared from the

Scheme 48



Scheme 49



known chiral carboxylic acids by condensation with (*S*)-phenethylamine in the presence of 1,3-dicyclohexylcarbodiimide (DCC) using DMF as the solvent. Treatment of the pure (*S*)-sulfoxide **277** under standard Pummerer conditions (ZnI_2, CH_3CN, **271**) gave the (*R*)-*β*-lactam **278** in 75% yield and in 60% enantiomeric excess. Changing the reaction conditions to $ZnCl_2$ in CH_2Cl_2 improved the ee to 80−85%. *N*-Benzyl amides (*S*)-**281** and (*R*)-**283** produced (*R*)-**282** and (*S*)-**284** in 54% yield with 80% and 82% ee, respectively.

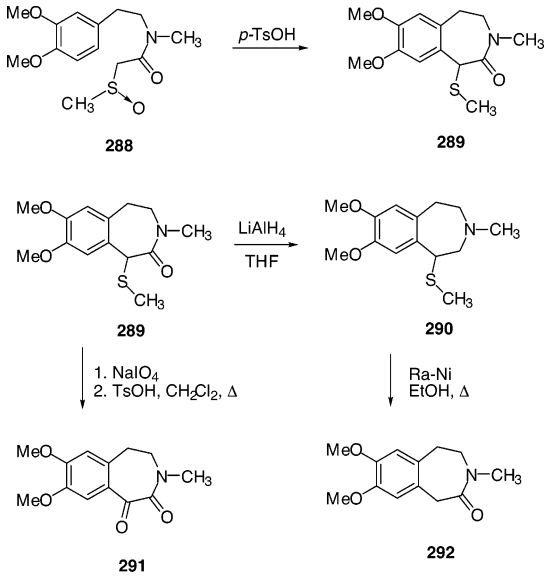
The proposed mechanism involves silylation of the sulfoxide to give intermediate **286a** that is subsequently attacked by the amide nitrogen atom to produce the chiral isothiazolone **286b** (Scheme 49). This transient species undergoes preferential 1,2-rearrangement from the α-face to provide *β*-lactam **287**.[71]

5.2. Benzazepine Derivatives

While the generation of five-membered ring heterocycles using the Pummerer reaction is clearly an efficient process, the isolation of C−S bonded and rearranged products often accompanies formation of six-membered rings. Although relatively few investigations into the synthesis of larger ring sizes have been reported, it would appear as though the Pummerer-promoted cyclization leading to these larger systems is less efficient than for the corresponding six-membered rings. Nevertheless, several larger ring heterocyclic compounds that are difficult to synthesize in other ways have been prepared using Pummerer cyclizations.

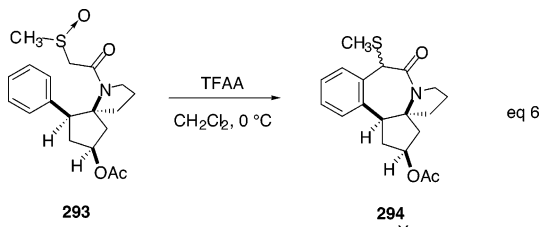
As previously noted (cf. Schemes 1 and 2), Pummerer cyclizations onto aromatic rings are quite general. Several research groups have leveraged Pummerer methodology to construct benzazepine derivatives. Ishibashi, for example, employed the method toward the synthesis of 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one, a pharmacologically important target.[73] When the phenethylamido sulfoxide derivative **288** was exposed to TFAA or *p*-TsOH, an intramolecular Friedel−Crafts cyclization onto the α-acylthionium intermediate occurred to furnish tetrahydro-2*H*-3-benzazepin-2-one **289** in modest yield

Scheme 50



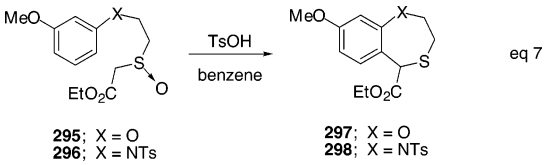
(Scheme 50). A number of structurally related analogues (**290**, **291**, and **292**) were accessed from substrate **289**. Reduction of **289** with $LiAlH_4$ provided tetrahydro[3]benzazepine-2(2*H*)-one **290**. Further reaction with Raney Ni gave **292**. Sodium periodate oxidation of the thiomethyl ether group present in **289** followed by a Pummerer reaction afforded the dicarbonyl derivative **291** in 35% yield.

An interesting application of the Pummerer/Friedel−Crafts alkylation methodology for the preparation of a seven-membered heterocycle was described by Ishibashi in an approach toward (±)-cephalotaxine (eq 6).[74] The key step in the synthesis



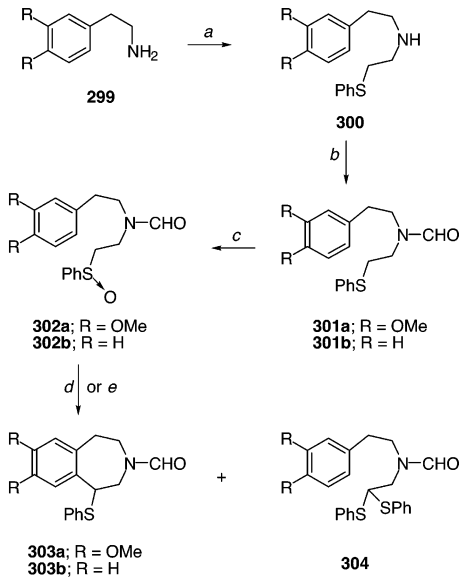
involved the ring closure of sulfoxide **293** by means of a TFAA-initiated α-acylthionium ion cyclization to give the seven-membered lactam **294** that was subsequently converted to cephalotaxine by standard synthetic transformations. Ishibashi and co-workers have used this same strategy for the synthesis of related benzazepines.[74−76]

Similarly, 1,4-benzoxathiepins **297** and **298** were synthesized from sulfoxides **295** and **296** in 53% and 55% yield, respectively (eq 7).[77]



As an extension of their earlier work with isoquinolines (Schemes 34 and 35), Sano and co-workers have applied their BF_3·OEt_2-assisted Pummerer cy-

Scheme 51[a]

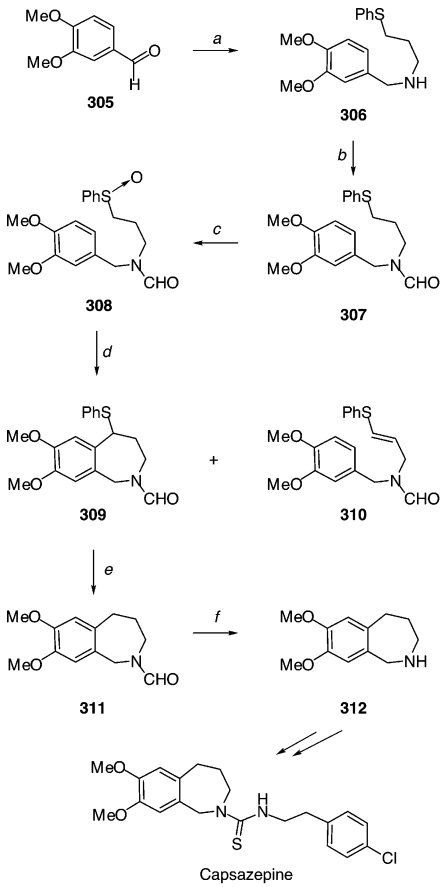


[a] Reagents and conditions: (a) 2-Chloroethyl phenyl sulfide, Na_2CO_3, NaI, Bu_4NBr, dioxane, Δ. (b) HCO_2H-Ac_2O, 70 °C. (c) $NaIO_4$, $MeOH-H_2O$. (d) TFAA, C_6H_6, rt; 80%. (e) TFAA, $BF_3{\cdot}OEt_2$, C_6H_6, rt; 47%.

clization strategy toward the synthesis of several benzazepine derivatives. In this study, phenethylamine **299** (R = H or OMe) was alkylated with 2-chloroethylphenyl sulfide to furnish **300** (Scheme 51).[78] Amine **300** was then protected by exposing it to a mixture of formic acid and acetic anhydride to give **301**, which was oxidized to sulfoxide **302** using $NaIO_4$. When **302a** was treated with TFAA in benzene at 25 °C, the Pummerer cyclization product **303a** was isolated in 80% yield. As was encountered in previous work,[50] however, these conditions failed to produce cyclized products when the nucleophilic aryl group lacked electron-donating groups. Thus, when **302b** was subjected to the same conditions that produced **303a**, only bissulfide **304** was formed in 38% yield. Addition of $BF_3{\cdot}OEt_2$ to the mixture of **302b** and TFAA, however, afforded **303b** in 47% yield along with traces of **304** and sulfide **301b**. As with the isoquinoline synthesis, this Pummerer methodology is remarkable in its ability to generate benzazepine derivatives that lack activating groups on the aryl moiety. This reaction sequence, however, is not as efficient as the formation of the isoquinoline derivatives described in Scheme 34.

More recently, Sano and co-workers have applied this methodology to the formal synthesis of capsazepine, an antagonist of the sensory neuron excitants capsaicin and resinferatoxin.[79] Reductive amination of aldehyde **305** with 3-phenylthiopropylamine and AcOH/$NaBH_4$ provided amine **306** in 74% yield (Scheme 52). Treatment of **306** with a mixture of formic acid and acetic anhydride furnished formamide **307** (quantitative yield), which was subsequently oxidized to sulfoxide **308** in 84% yield using $NaIO_4$. Although exposure of **308** to TFAA in benzene at 25 °C produced the desired cyclization product **309** in 56% yield, vinyl sulfide **310** was also simultaneously formed in 31% yield. By adding $BF_3{\cdot}OEt_2$ to the mixture of TFAA and **308**, the yield of **309** was

Scheme 52[a]

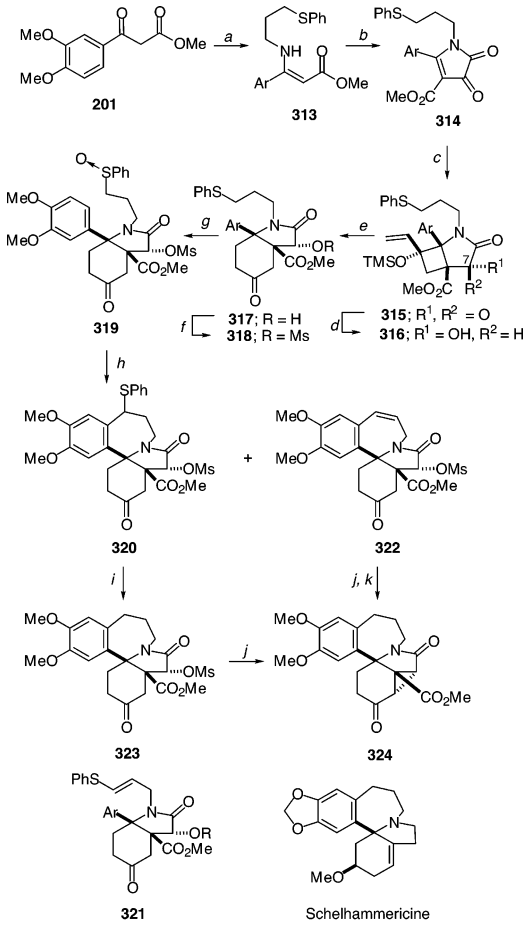


[a] Reagents and conditions: (a) 3-Phenylthiopropylamine, AcOH, EtOH, Δ, 23 h; then $NaBH_4$, 0 °C; 74%. (b) Ac_2O, HCO_2H, 70 °C; quantitative. (c) $NaIO_4$, $MeOH-H_2O$, rt; 84%. (d) TFAA, C_6H_6, rt, 30 min; then $BF_3{\cdot}OEt_2$, rt, 45 min; 66%. (e) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH−THF, 0 °C, 80%. (f) aqueous NaOH, EtOH, Δ; 98%.

increased to 66%. Concomitantly, the amount of **310** produced under these conditions was reduced to 5%. Reductive elimination of the sulfide group in **309** under nickel boride conditions gave **311** in 80% yield. Removal of the formyl protecting group under aqueous base conditions delivered **312**, which is a known intermediate in the synthesis of capsazepine.

Use of the Pummerer reaction for the synthesis of naturally occurring seven-membered ring derivatives of the erythrina alkaloids, the homoerythrinans, has also been reported. The Sano group has applied the Pummerer reaction toward the synthesis of an advanced intermediate for these alkaloids.[53] Following a similar reaction sequence that was used for constructing cycloerythrinan (Scheme 36), *β*-keto ester **201** was condensed with 3-phenylthiopropylamine to give the vinylogous amide **313** in 82% yield. Subsequent reaction of **313** with oxalyl chloride provided dioxopyrroline **314** in 96% yield (Scheme 53).[80] A [2+2]-photocycloaddition of **314** and 2-trimethylsilyloxybutadiene afforded cyclobutane **315** as a single diastereomer in 83% yield. Reduction of the C(7) carbonyl group with $NaBH_4$ gave **316** (89%), which underwent an anionic 1,3-sigmatropic rearrangement to afford **317** (86%) upon exposure to TBAF. The C(7) hydroxyl group was converted to the corresponding mesylate **318** in 89% yield, and this was followed by

Scheme 53[a]



[a] Reagents and conditions: (a) 3-Phenylthiopropylamine; 82%. (b) $(COCl)_2$; 96%. (c) 2-TMSO-butadiene, *hν*; 83%. (d) $NaBH_4$; 89%. (e) TBAF, THF; 86%. (f) MsCl, pyridine; 89%. (g) $NaIO_4$; 91%. (h) TFAA, CH_2Cl_2, 80 °C, 48 h; 51% (**320**) or 120 h; 67% (**320**). (i) Bu_3SnH, AIBN; 61%. (j) DBU; 52%. (k) H_2, 10% Pd−C; 53% from **320**.

reaction of the sulfide functionality in **318** with $NaIO_4$ to provide sulfoxide **319** in 91% yield. When the reaction of **319** with TFAA was carried out at 25 °C, the desired benzazepine **320** was only isolated in 16% yield together with the elimination product **321** (41%). The yield of **320** could be improved by conducting the reaction at higher temperatures and for longer reaction times, presumably because of the establishment of an equilibrium between the initially formed **321** and the reactive thionium ion present in the acidic media. By heating a mixture of **319**, TFAA, and CH_2Cl_2 in a sealed tube at 80 °C for 48 h, compound **320** could be isolated in 51% yield together with small amounts of **322**. Extended reaction times (120 h) resulted in the exclusive formation of **322** in 67% yield. The thiophenyl group in **320** could be removed by the action of Bu_3SnH and AIBN to provide **323** in 61% yield. Exposure of **323** to DBU effected the desired cyclopropanation to deliver **324** in 52% yield. Alternatively, **322** could be converted to **324** in 53% overall yield by first forming the cyclopropane ring using DBU followed by palladium-mediated hydrogenation of the olefinic π-bond. A similar compound, which contains a methylenedioxy substitution pattern on the aryl group, had been previously converted to alkaloids such as schelhammericine.

5.3. Indole Alkaloids

One of the main advantages of using the Pummerer cyclization for the formation of six- and seven-membered rings that are fused to aromatic rings is that the high reactivity of thionium ions permits the use of unactivated aromatics as nucleophiles. Bennasar and Bosch have taken advantage of the inherently higher reactivity of thionium ions to generate an eight-membered ring in their synthesis of secoakuammilan alkaloids.[81] The akuammilan alkaloids, of which cathafoline is an example (Figure 2), belong

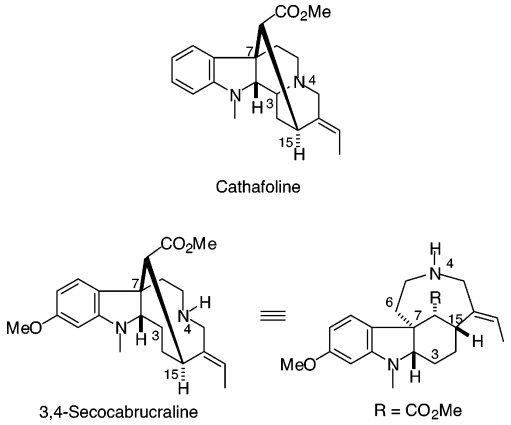
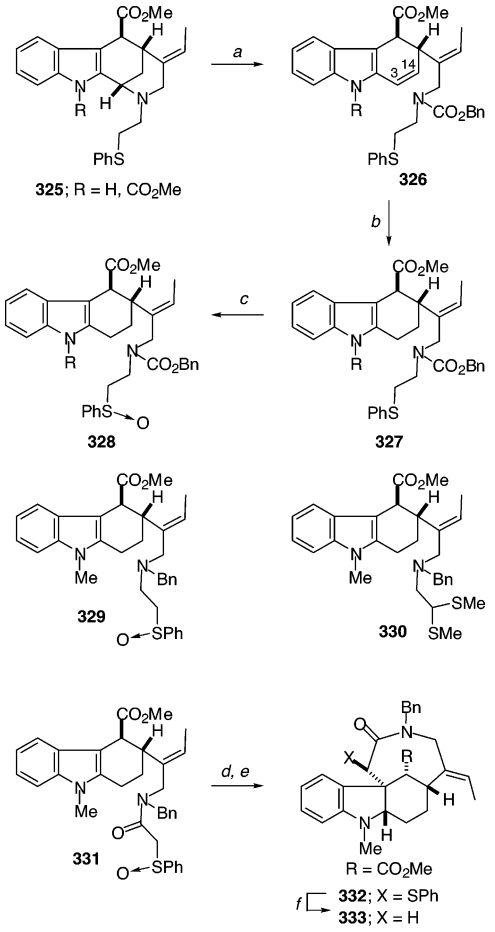


Figure 2. Akuammiline-type alkaloids.

to the coryanthean family and are characterized by an additional C(7)−C(15) bonded ring. The secoakuamillan alkaloids, such as 3,4-secocabrucraline, differ from the akuamillan series in that they lack a bond between the C(3) and N(4) centers. Formation of the C(6)−C(7) bond to establish the quaternary center at a late stage of the synthesis was considered to be an efficient strategy for the synthesis of this family of alkaloids.

Construction of the key sulfoxide intermediate commenced with the exposure of amine **325**[56] to benzyl chloroformate, which resulted in a fragmentation reaction that produced **326** (Scheme 54).[82] Reduction of the C(3)−C(14) olefinic π-bond in **326** via the action of Et_3SiH and TFA gave sulfide **327** in 65% yield from **325**. The thiophenyl group in **327** was then oxidized using *m*-CPBA to provide sulfoxide **328**. When sulfoxide **328** was subjected to the Pummerer conditions (TFAA in CH_2Cl_2 at 0 °C for 15 min) followed by $NaCNBH_3$ reduction, only sulfide **327** was obtained. Similarly, the related sulfoxide **329** also failed to cyclize under a variety of reaction conditions. Moreover, the cyclization of dithioacetal **330** did not take place when it was treated with DMTSF. The high degree of conformational flexibility present with these cyclization substrates (i.e., **328**, **329**, and **330**) was thought to be problematic. Accordingly, substrate **331**, which contained a conformationally more restrictive amido tether, was constructed. When **331** was treated with TFAA in CH_2Cl_2 at 0 °C followed by exposure to $NaCNBH_3$, the desired tetracycle **332** was isolated in 23% yield as a single diastereomer whose stereochemistry was

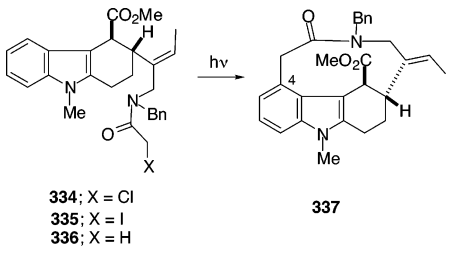
Scheme 54[a]



[a] Reagents and conditions: (a) $BnCO_2Cl$, toluene, Δ. (b) Et_3SiH, TFA; 65% for two steps. (c) *m*-CPBA; 83%. (d) TFAA, CH_2Cl_2, 0 °C. (e) $NaCNBH_3$; 23% over two steps. (f) Raney Ni; 80%.

based upon extensive NMR spectroscopy. Small amounts of the corresponding sulfide were also detected. Removal of the thiophenyl group in **332** was accomplished using Raney nickel to deliver the 3,4-secoakuammilan derivative **333** in 80% yield.

It should be noted although that the yield in the key cyclization step was only 23%. Attempts to effect similar cyclizations, using substrates such as **334** and **335** under radical conditions, failed to occur (eq 8).



eq 8

Thus, the irradiation of indole **334** produced the novel compound **337** in which the tethered radical intermediate cyclized onto the C(4) position of the indole ring. Heating a mixture of iodide **335** and $Bu_3Sn-SnBu_3$ in toluene produced the reduced product **336**. This observation demonstrates the relative merits of using a Pummerer cyclization as a key bond disconnection for the synthesis of complex natural products. The successful cyclization of **317**, when compared to the failure of compounds **328**−**330** to produce the desired tetracycle, underscores the subtle conformational effects that can influence the course of these larger sized ring forming reactions.

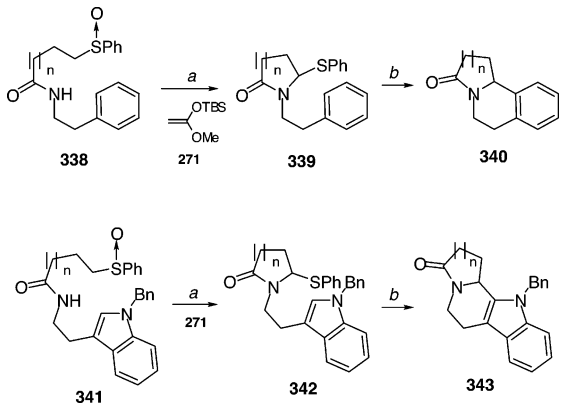
6. General Methods for the Formation of Five- and Six-Membered Rings

Although many methodologies have been developed that specifically form five-membered rings (vide supra), Pummerer reactions that produce a variety of heterocyclic ring sizes are becoming increasingly important. A strategy similar to that used by Sano to construct isoquinoline derivatives (Schemes 34 and 35) has also been employed to form benzazepine analogues (Schemes 50 and 51). Bennasar and Bosch used the same synthetic strategy for appending a six-membered ring onto an indole core (Schemes 39 and 40) as they did for eight-membered ring annulation (Scheme 54).

6.1. Pummerer/*N*-Acyliminium Ion Cascades

In several examples, Kita and co-workers reported an efficient Pummerer cyclization wherein the initially generated thionium ion was intercepted by a pendant secondary amide to produce an *S*,*N*-acetal.[70−72,83] Because of our long-standing interest in tandem processes,[4,25] our research group at Emory carried out a related study using α-thiophenyl amides as precursors for the formation of *N*-acyliminium ions, which were then employed as intermediates for subsequent cyclization chemistry. A typical example involves the treatment of amido sulfoxide **338** with silyl ketene acetal **271** in the presence of ZnI_2 to give lactam **339** in excellent yield (>90%; Scheme 55).[84]

Scheme 55[a]

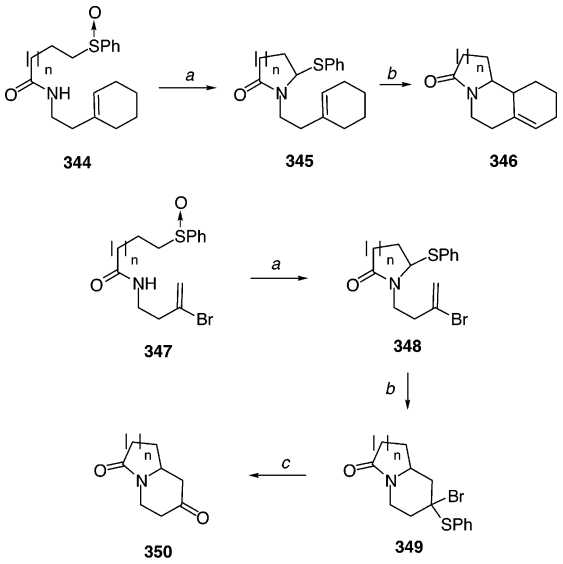


[a] Reagents and conditions: (a) ZnI_2, (b) BF_3·2AcOH.

The action of BF_3·2AcOH on **339** led to further ionization of the phenylthio group, and cyclization of the resultant iminium ion onto the aromatic ring furnished **340** in 98% ($n = 1$) and 79% ($n = 2$) yield, respectively. In a similar manner, the indole-substituted amido sulfoxide **341** furnished **343** via the intermediacy of **342** in good overall yield, when subjected to the same sequence of reaction conditions.

During the course of our work in this area, we noted that nonaromatic π-systems also acted as nucleophiles in the iminium ion cyclization step. For

Scheme 56[a]

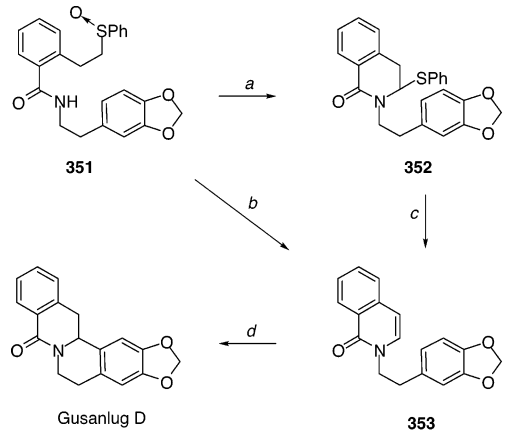


[a] Reagents and conditions: (a) ZnI_2, **271**. (b) BF_3·2AcOH. (c) $Hg(OAc)_2$, AcOH.

example, the reaction of **271** with ZnI_2 and the cyclohexene-substituted amido sulfoxide **344** afforded **345** in 76% (n = 1) and 54% (n = 2) yield. Lactam **345** delivered compound **346** in 54% (n = 1) and 52% (n = 2) yield when treated with BF_3·2AcOH (Scheme 56).[84] In an analogous manner, treatment of vinyl bromide **347** with a mixture of ZnI_2 and **271** produced lactam **348** in 80% (n = 1) and 72% (n = 2) yield. Interestingly, when **348** was exposed to BF_3·2AcOH, the subsequent Mannich-like cyclization was terminated by the addition of phenylthiolate, rather than by a deprotonation event, to furnish **349**. This bromo- and phenylthio-substituted indolizidine was subsequently converted to ketolactam **250** in 64% (n = 1) and 58% (n = 2) yield by reaction with $Hg(OAc)_2$ in acetic acid.

Using this sequential Pummerer/Mannich cyclization methodology, the Padwa group reported a rapid synthesis of the protoberberine alkaloid gusanlung D. Accordingly, the Pummerer cyclization of **351** was promoted by reaction with TMSOTf and Et_3N to provide α-phenylthio lactam **352** in 64% yield (Scheme 57).[85] When amido sulfoxide **351** was treated with

Scheme 57[a]

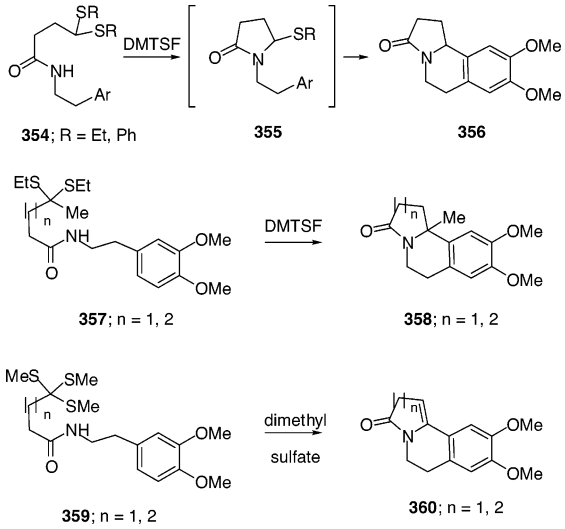


[a] Reagents and conditions: (a) TMSOTf, Et_3N; 64%. (b) **271**, ZnI_2; 85%. (c) ZnI_2. (d) Concentrated HCl; 55%.

silyl ketene acetal **271** and ZnI_2, however, pyridone **353** was produced in 85% yield. The Lewis acid-induced elimination of thiophenol from the initially formed *S*,*N*-acetal **352** appears to be facilitated by the generation of the aromatic 2-pyridone. This result contrasts with other Pummerer cyclizations conducted under similar conditions but which lack the aromatic moiety in the tethered sulfoxide (e.g., Schemes 55 and 56). *S*,*N*-Acetal **352** was easily converted to **353** by exposure to ZnI_2, thereby supporting the role of this Lewis acid in the direct tranformation from **351** to **353**. Stirring a sample of pyridone **353** with concentrated HCl provided the protoberberine alkaloid gusanlung D in 55% yield.

Dithioacetals were also found to undergo the Pummerer/Mannich cascade. Thus, exposure of **354** (R = Et) to DMTSF in CH_2Cl_2 at 25 °C produced **356** directly in 98% yield (Scheme 58).[85] The suspected

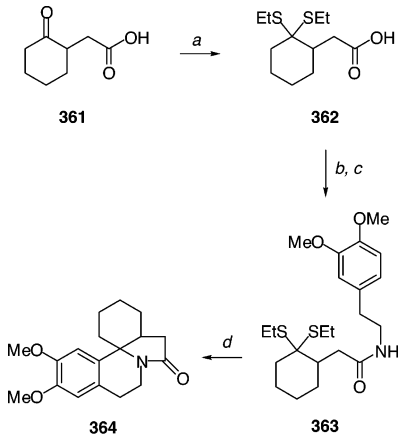
Scheme 58



intermediate lactone **355** was not detected in the crude reaction mixture. It is interesting to note that the use of the phenyl thioacetal **354** (R = Ph) gave **356** in only 64% yield. Because generation of the intermediate thionium ion depends on the transfer of a methylthio group to one of the acetal sulfur atoms, the difference in reactivity between the phenyl thio- and the alkyl thioacetals is presumably due to the less nucleophilic nature of the aromatic-substituted sulfur atom.

Thioketals and ortho esters were also found to undergo the Pummerer/Mannich reaction cascade. For example, exposure of **357** to DMTSF furnished bicyclic lactam **358**, which interestingly contains a quaternary carbon next to the nitrogen atom.[85] For this transformation to proceed, the reaction mixture needed to be heated at reflux in CH_2Cl_2. The tertiary thionium ion generated from the reaction of **357** with DMTSF is more stable and therefore less reactive than the secondary thionium ion obtained from thioacetals, and this lower reactivity seemingly accounts for the thermal requirement. The reaction of thio ortho ester **359** with DMTSF failed to provide cyclization products, but exposure of **359** to dimethyl

Scheme 59[a]



[a] Reagents and conditions: (a) EtSH, HCl. (b) CDI, CH_2Cl_2. (c) 3,4-Dimethoxyyphenethylamine. (d) DMTSF, CH_2Cl_2, Δ; 71%.

sulfate produced **360** in 46% ($n = 1$) and 71% ($n = 2$) yield.

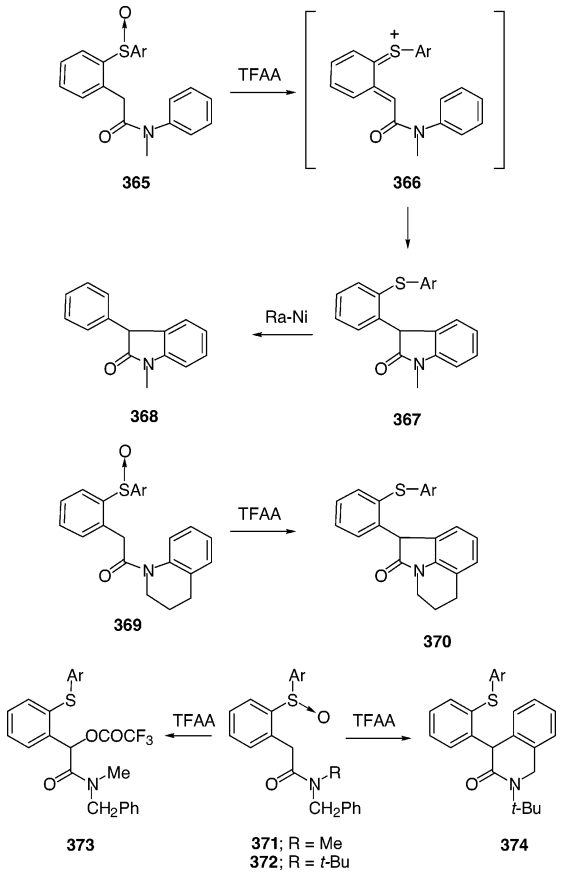
The above tandem Pummerer/Mannich cyclization cascade was also applied to a rapid and efficient synthesis of the erythrina alkaloid core.[85] Keto acid **361** was transformed into the thioketal **362** (Scheme 59). Coupling of **362** with 3,4-dimethoxyphenethylamine using carbonyldiimidazole (CDI) produced **363**. Further, treatment of **363** with DMTSF in CH_2Cl_2 at reflux temperature delivered the indoloisoquinoline **364** in 71% yield.

6.2. Vinylogous Pummerer Reaction

The two other known modes of Pummerer cyclization (i.e., the additive (Schemes 8−11) and vinylogous Pummerer reactions) have recently been studied by the Padwa group. In the vinylogous Pummerer process, a vinyl sulfoxide is activated by an anhydride to generate a β,γ-unsaturated thionium ion that is subsequently trapped at the γ-position by a nucleophile in the reaction medium. For example, treatment of amido sulfoxide **365** with TFAA in CH_2Cl_2 at 25 °C generated vinyl thionium ion **366** (Scheme 60).[86] Subsequent cyclization onto the aryl ring produced oxindole **367** in 91% yield. The pendant arylthio group could be removed with Raney nickel to deliver **368**. Likewise, the quinoline derivative **369** furnished oxindole **370** in 85% yield under the same conditions. When an attempt was made to generate a six-membered ring by exposing *N*-methylbenzamide **371** to TFAA, however, only the normal-mode Pummerer reaction occurred to produce **373**. Interestingly, when the methyl group was replaced with a *tert*-butyl substituent, the reaction proceeded as expected. Thus, the TFAA-mediated vinylogous Pummerer cyclization of **372** delivered **374** in 85% yield.

The explanation offered for this substantial difference in reactivity is related to the rotational barrier about the acyl carbon−nitrogen bond.[87] With a methyl substituent on the nitrogen, the preferred conformation of **371** places the methyl group *trans* to the amide carbonyl group. The preferred conformation of **372**, however, contains a *cis*-relationship between the amide carbonyl group and the *tert*-butyl substituent. Presumably, rotation about the acyl carbon−

Scheme 60



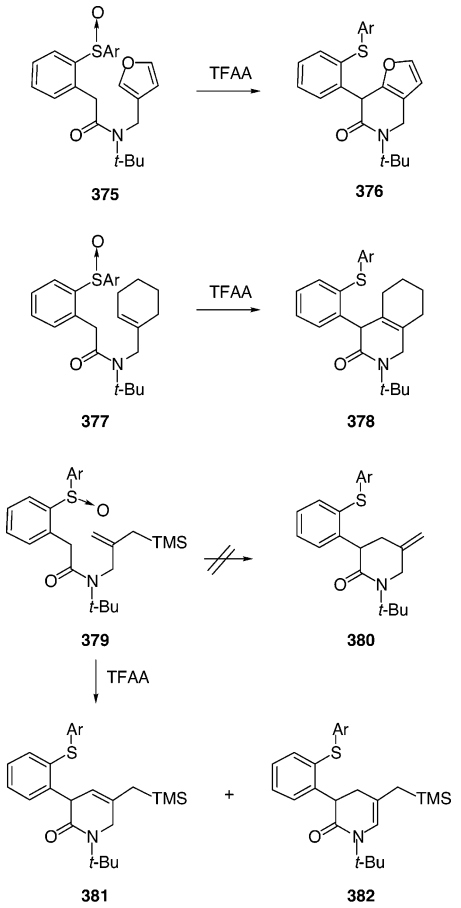
nitrogen bond is slow when compared to the rate of cyclization and the lifetime of the thionium ion. Therefore, the preferred *cis*-conformation of **372**, where the pendant nucleophile is disposed toward cyclization, can lead to a cyclized product, whereas amide **371** cannot.

Other π-systems have been found to successfully engage vinyl thionium ions. Thus, furan **375** reacted with TFAA to give **376** in 68% yield, while cyclohexene **377** furnished dihydropyridone **378** in 67% yield under similar conditions (Scheme 61).[86] Suprisingly, the vinylogous Pummerer cyclization of allylsilane **379** did not produce the expected endocyclic methylene compound **380**. Rather, a separable mixture (1:1) of allylsilanes **381** and **382** was isolated in 90% combined yield. Evidently, the trifluoroacetoxy anion generated under the reaction conditions is not nucleophilic enough to displace the trimethylsilane group, so only deprotonation products are encountered.

6.3. Additive Pummerer Reaction

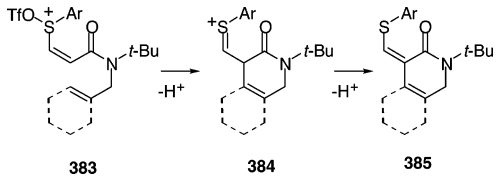
As was pointed out earlier (see Scheme 8), an additive Pummerer reaction occurs when a nucleophile can displace the acyloxy leaving group of a vinylsulfonium ion through an S_N2' mechanism. Our group at Emory has studied a variant of the additive Pummerer process wherein the generalized sulfonium salt **383** undergoes cyclization to produce **384** after the loss of a proton (Scheme 62).[86] A second deprotonation of the resultant thionium ion would then deliver vinyl sulfide **385**. To explore this se-

Scheme 61

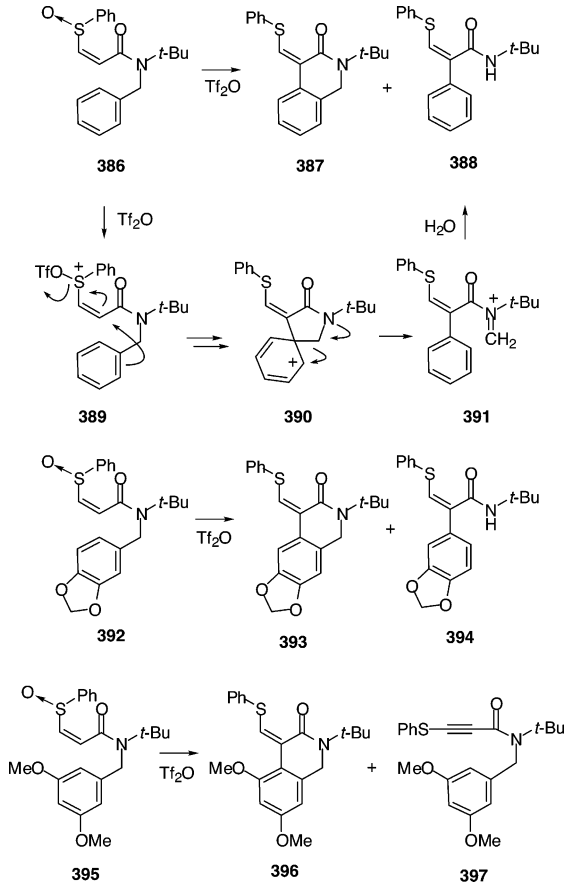


quence of events, sulfoxide **386** was treated with triflic anhydride (Tf_2O), and it was found that a mixture of **387** (32%) and the rearranged product **388** (45%) was formed (Scheme 63). The mechanism that is responsible for the formation of **388** probably involves S_N2' displacement of the triflate in **389** by the *ipso* carbon of the pendant aryl group to afford the spirocyclic intermediate **390**. Subsequent fragmentation of **390** provides iminium ion **391** that is subsequently hydrolyzed to give **388**. The distribution of cyclization and rearranged product was found to be dependent upon the electronic nature of the displacing nucleophile. When sulfoxide **392**, in which the nucleophilic aryl ring contains a methylenedioxy substitution pattern that activates both the *ipso* and the *ortho* positions, was treated with Tf_2O, a mixture of the cyclized product **393** (15%) and rearranged product **394** (60%) was formed. In contrast, sulfoxide **395**, which contains two *m*-methoxy groups that inhibit addition by the *ipso* position, produced the expected cyclization product **396** in 63% yield along with a small amount (8%) of the elimination product **397**.

Scheme 62



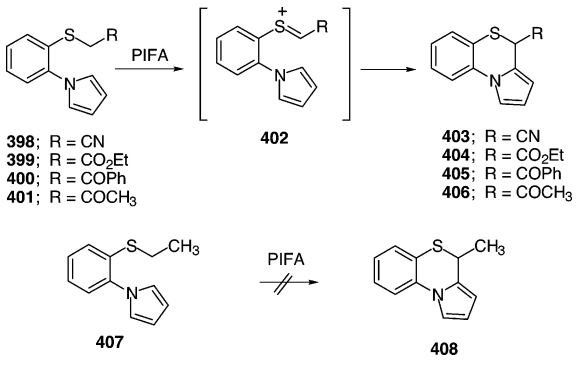
Scheme 63



6.4. Hypervalent Iodine-Promoted Cyclizations

Hypervalent iodine reagents have also been employed to promote Pummerer reactions, but using sulfides rather than sulfoxides as the starting substrates.[88] Several reports in the literature have demonstrated that Pummerer cascades terminated by pyrroles can lead to the formation of some novel *N*,*S*-heterocycles. Under standard Pummerer conditions, sulfoxides in which the alkyl side chain of the sulfur atom contained an electron-withdrawing group (i.e., sulfoxides derived from **398**−**401**), the Pummerer-derived compounds **403**−**406** were formed (Scheme 64).[89−94] Phenyl iodine(III) bis(trifluoroacetate) (PIFA) was found to be a particularly good initiator for the Pummerer reaction of sulfides **398**−**401**.[93,94] Of particular interest was the observation

Scheme 64[a]

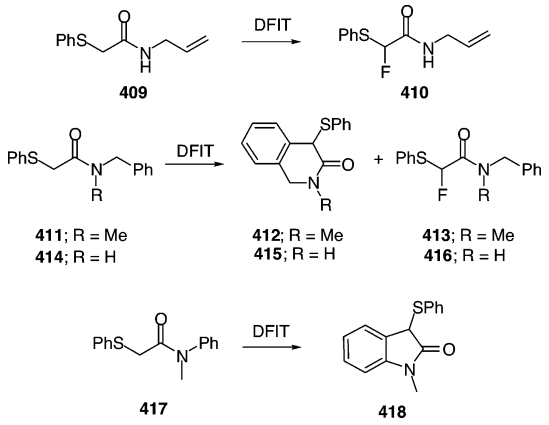


[a] PIFA = phenyl iodine(III) bis(trifluoroacetate).

that sulfoxides possessing a simple ethyl group, such as **407**, produced five-membered ring sulfenylation products rather than the desired six-membered ring heterocycle **408** (vide infra). The desired cyclization could, however, be promoted by treating the corresponding sulfoxide with a mixture of TFAA and TFA.

Recently, Motherwell and co-workers have examined the use of difluoroiodotoluene (DFIT) as a reagent to induce α-fluorination of α-phenylsulfanyl acetate derivatives via a Pummerer-type process. For example, when **409** was heated in CH_2Cl_2 at reflux with DFIT, the fluorinated derivative **410** was isolated in 71% yield (Scheme 65).[95] Replacing the allyl

Scheme 65



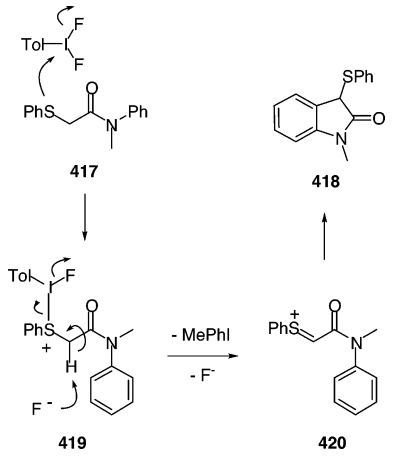
group in **409** with a benzyl group, however, changed the course of the reaction. Thus, subjection of **411** to the same conditions that produced **410** resulted in cyclization to give **412** in 47% yield together with a smaller amount of the expected fluorinated product **413** (25%). Interestingly, when the secondary amide **414** was treated with DFIT, the product distribution again shifted, producing some cyclized material, **415** (11%), as well as the fluorinated product **416**, which now predominated in 35% yield. Treatment of **417** with DFIT delivered the oxindole derivative **418** as the sole product in 59% yield. The difference in reactivity between the secondary amide **414** and the tertiary amide **411** can be explained by the relatively slow rate of rotation about the acyl carbon−nitrogen bond when compared to the rates of cyclization and fluorination (see **371** vs **372**, Scheme 60).

The mechanism associated with these Pummerer-like reactions can be attributed to nucleophilic displacement of a fluorine atom in the hypervalent iodine reagent by the sulfur atom so as to generate a sulfonium salt, **419** (Scheme 66). The displaced fluoride then acts as a base to eliminate iodotoluene as well as a second fluoride ion from the resulting sulfonium salt **419**, thereby affording an intermediate thionium ion, **420**. In the case of **420**, cyclization to give oxindole **418** is much faster than capture of fluoride to quench the thionium ion.

7. Related Processes

Although the normal Pummerer reaction involves addition of a nucleophile to the electrophilic carbon atom of a thionium ion, the addition of nucleophiles to the sulfur atom of the intermediate sulfonium salt

Scheme 66

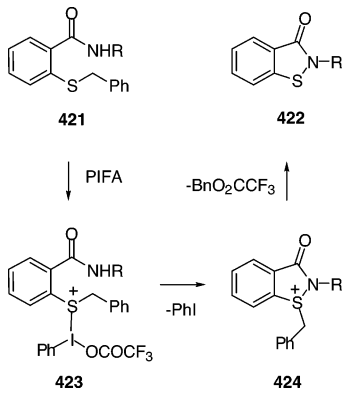


represents a competitive process. Often referred to as the "interrupted" Pummerer reaction, this nucleophilic attack at sulfur has been leveraged for the preparation of some interesting sulfur-containing heterocycles. In addition, reactions involving thionium ions have also been developed that employ pathways which proceed by alternate mechanisms.

7.1. Interrupted Pummerer Reactions

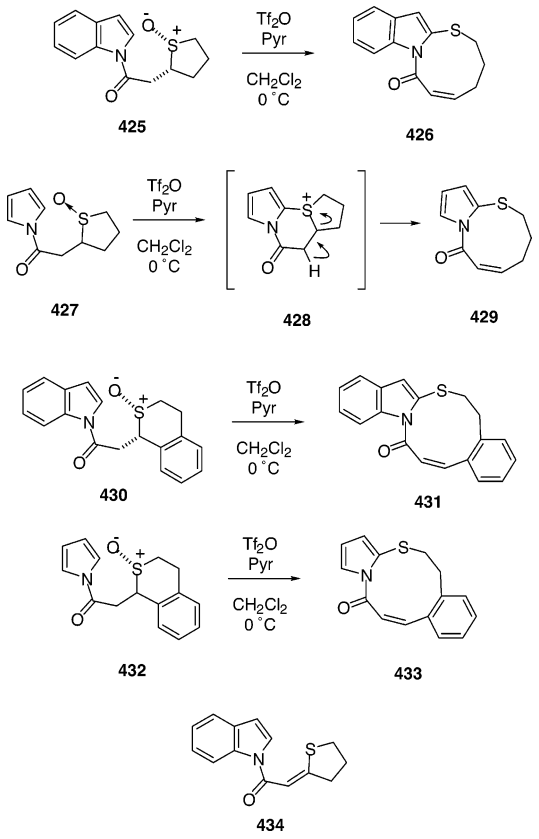
In their continuing studies of Pummerer reactions that are promoted by hypervalent iodine reagents,[93,94] Chen and co-workers used the interrupted Pummerer reaction to generate benzisothiazole derivatives, a class of compounds that have antifungal properties. For example, exposure of **421** to PIFA and TFA in CH_2Cl_2 gave rise to compound **422** (Scheme 67).[96]

Scheme 67



This reaction probably proceeds by a mechanism involving nucleophilic displacement of the trifluoroacetate group from the iodine atom by the sulfur atom to produce a transient sulfonium ion intermediate, **423**. Without the presence of an electron-withdrawing group at the carbon atom adjacent to the sulfonium salt, trifluoroacetate is not a sufficiently strong enough base to effect the elimination of the iodo group so as to generate a thionium ion. Instead, displacement of the iodo group by the internally disposed nucleophile is the preferential path which results in the formation of sulfonium salt **424**. Nucleophilic displacement of the benzyl group present on the sulfonium salt ultimately produces **422** and benzyl trifluoroacetate. According to this

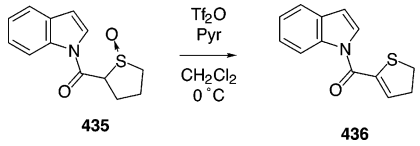
Scheme 68



mechanism, it is understandable why electron-releasing substituents on the nitrogen atom facilitate this reaction. Thus, amide **421** (R = 3,5-dimethoxyphenyl), when treated with PIFA in the presence of TFAA, afforded **422** (R = 3,5-dimethoxyphenyl) in 80% yield. In contrast, when a nitro group is present on the aromatic ring (i.e., R = *p*-nitrophenyl), this system fails to furnish **422**.

The interrupted Pummerer reaction, sometimes referred to as the "sulfoxide electrophilic sulfenylation (SES) process" has been studied in some detail by Bates and co-workers.[97] Recently, a cascade that forms large-ring *N*,*S*-heterocycles from sulfoxides tethered to electron-rich aromatic compounds was reported. The reaction of indole sulfoxide **425** with Tf_2O and pyridine in CH_2Cl_2 at 0 °C afforded the novel heterocycle **426** in 65% yield (Scheme 68).[98] Similarly, the pyrrole-containing sulfoxide **427** furnished the related pyrrole **429** in 60% yield. The mechanism of this reaction presumably involves addition of the adjacent aromatic π-bond onto the intermediate sulfonium salt so as to produce a new sulfonium salt, **428**. Deprotonation at the carbon β to the sulfonium ion induces a Grob-type fragmentation, delivering the ring-expanded product **429**. Larger macrocycles were obtained by starting with sulfoxides that are connected to six-membered rings. Thus, sulfoxide **430** was reacted with Tf_2O to provide the 10-membered ring **431** in 42% yield, and the related pyrrole **432** was transformed into **433** in 80% yield. Interestingly, it was discovered that only the sulfoxide diastereomer wherein the tether and the sulfoxide oxygen were *syn* to one another underwent clean reaction to produce the ring-expanded products. Subjection of the *trans*-diastereomer of **425** to the same reaction conditions gave rise to a complex reaction mixture that did not appear to contain compound **426**. When less reactive acylating reagents were used, products derived from deprotonation of an intermediate thionium ion were isolated. Thus, treatment of **425** with TFAA and pyridine cleanly led to the elimination product **434**.

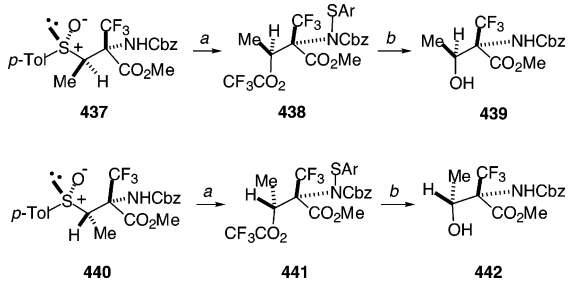
The acidity of the proton adjacent to the intermediate sulfonium ion was also shown to be an important factor for these Pummerer-like processes. For example, when indole **435**, which possesses an electron-withdrawing carbonyl group that can assist in the deprotonation/elimination reaction of the sulfonium salt, was exposed to the Tf_2O conditions, only the typical elimination product **436** was isolated in 72% yield (eq 9).



eq 9

The mechanism generally invoked for rationalizing products derived from an interrupted Pummerer reaction often includes the formation of a second sulfonium salt (such as **424** and **428**) when a nucleophilic partner is present.[99] In one example, Zanda and Bravo have published an interesting, stereospecific interrupted Pummerer reaction where they observe an intermediate σ-sulfurane intermediate rather than a sulfonium salt.[100] Thus, when **437** was exposed to TFAA and collidine, sulfenamide **438** was produced (Scheme 69). Addition of $NaBH_4$ to the

Scheme 69[a]

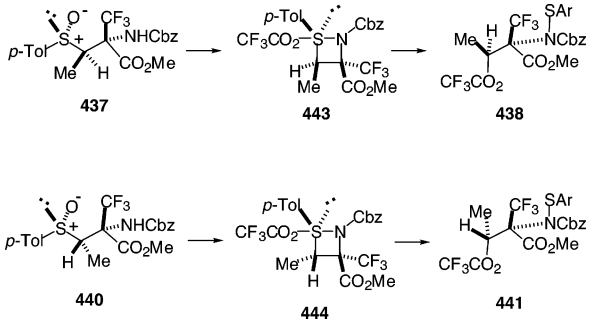


[a] Reagents and conditions: (a) TFAA, collidine, 0 °C, CH_3CN. (b) $NaBH_4$, H_2O.

reaction mixture provided β-hydroxyamine **439** as the only diastereomer in 87% yield. Similarly, reaction of **440** under related conditions furnished **442** (70%), again as a single diastereomer via the intermediacy of **441**.[101]

The rearrangement of **437** to **438** was nearly instantaneous when **437** was treated with TFAA and collidine, whereas the conversion of **440** to **441** required 40 min.[101] The lower rate of conversion with **440** allowed these workers the opportunity to study the reaction spectroscopically. The observations made during the spectroscopic analysis of the reaction led to the proposal of σ-sulfuranes **443** and **444** (Scheme 70),[102] arising from an interrupted Pummerer cyclization of **437** and **440**, respectively. When a mixture of **440**, collidine, and CD_3CN was treated

Scheme 70

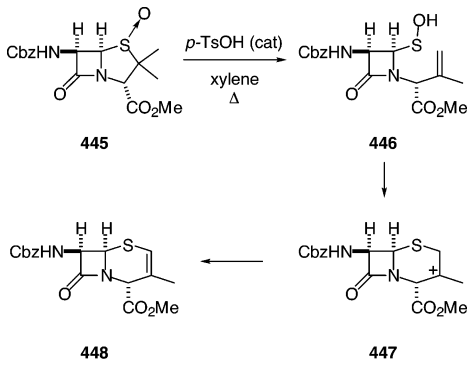


with TFAA in an NMR tube, intermediate **444** was immediately observed. Specifically, the signals in the ^{1}H NMR spectrum of **444** at 8.18 ppm (*o*-tolyl H) and 5.82 ppm (C(4) methyne H) were shifted downfield by 0.47 and 1.47 ppm, respectively, in comparison to the signals present in the spectrum of **440**. This was attributed to electronic effects caused by the increased valency of the sulfur atom. In addition, competition experiments were carried out wherein **437** was exposed to TFAA and an excess of potassium cyanide, rather than collidine, as the base and was found to lead to only **438**. No cyano-substituted product was observed in the reaction. This result is consistent with an intramolecular S_N2 displacement of the sulfur atom by the much less nucleophilic trifluoroactetate and provides additional support for the mechanistic hypothesis that the intermediate in this interrupted Pummerer reaction is an σ-sulfurane and not an ion-paired sulfonium salt.

7.2. Morin Processes

Another process that has occasionally been observed to occur under Pummerer reaction conditions is the Morin rearrangement.[103] This rearrangement involves activation of the sulfoxide **445** under typical Pummerer conditions (Scheme 71). The initially

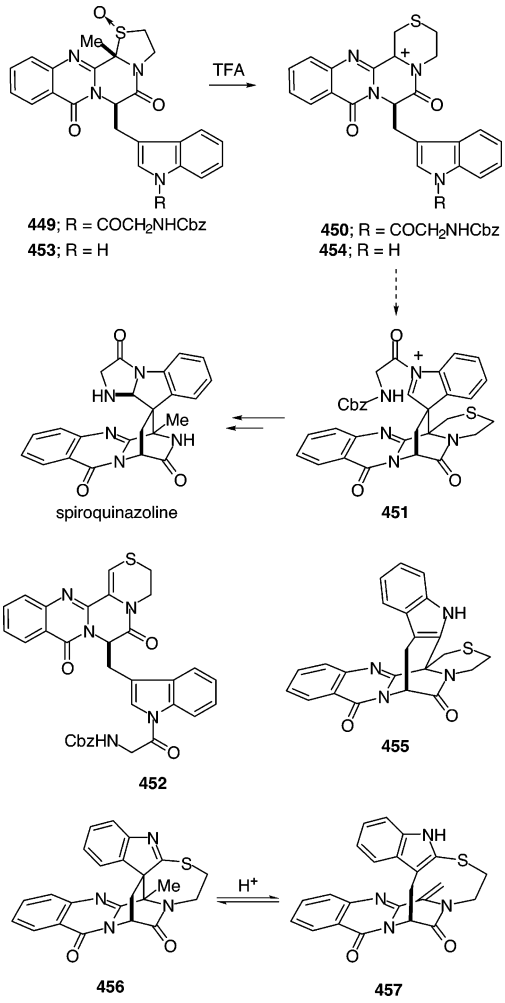
Scheme 71



formed sulfonium salt, however, decomposes via the elimination of a sulfenic acid moeity to produce the ring-opened sulfinic acid **446**. Further protonation of the sulfenic acid followed by cyclization with the adjacent π-bond leads to the cationic intermediate **447**, which eventually loses a proton to afford the rearranged product **448**.

While studying synthetic routes to spiroquinazoline, Hart and co-workers further investigated trapping of the cationic intermediate **450** derived from

Scheme 72

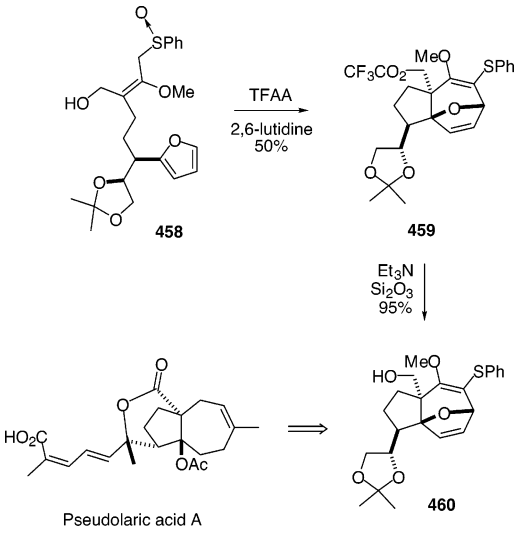


the Morin rearrangement of **449** (Scheme 72).[104] Ideally, the pendant indole would intercept the transient cation to produce **451** and thereby furnish the skeleton of spiroquinazoline. However, only the Morin rearrangement product **452** was isolated in 80% yield. Because the acyl group on the indole nitrogen decreases the nucleophilicity of the indole, it was thought that an indole lacking the acyl group would better be able to trap the cationic intermediate. With this in mind, the reaction of sulfoxide **453** with TFA was studied and was found to give **455** (35%), in which the 2-position of the indole had formally intercepted the cation. Spirocycle **456** (25%) and alkene **457** (21%) were isolated, and their formation was rationalized in terms of the sulfenic acid moiety adding to the indole ring. Interestingly, compounds **456** and **457** were found to equilibrate (2:1) in the presence of acid.

7.3. [4+3]-Cycloadditions

In addition to the additive and vinylogous Pummerer reactions (cf. Schemes 8, 60, and 63), vinyl thionium ions are also known to participate in intramolecular [4+3]-cycloadditions. On the basis of earlier studies of the Harmata group's earlier work using alkoxyallyl sulfone[105] and vinyl sulfoxide[106] substrates, Bai and co-workers have examined the application of an intramolecular [4+3]-cycloaddition

Scheme 73



reaction toward the synthesis of pseudolaric acid A (Scheme 73).[107] In their studies, sulfoxide **458** was allowed to react with TFAA in the presence of 2,6-lutidine to afford cycloadduct **459** in 50% yield and with remarkably high diastereoselectivity (>95% de). Hydrolysis of the trifluoroacetyl group delivered an advanced intermediate, **460**, that was used for the synthesis of pseudolaric acid A.

8. Conclusion

Deployment of the Pummerer reaction as a key strategic connection for the synthesis of heterocycles continues to be an active area of interest. Formation of five-membered heterocyclic ring systems by this method represents a particularly efficient process. While the formation of larger sized rings is often accompanied by interrupted Pummerer byproducts, the Pummerer reaction has been extensively employed to form heterocycles that are difficult to synthesize by other means. With the formation of larger sized ring systems, the product distribution between interrupted and normal Pummerer processes is often influenced by several structural features. Changing the acidity of the proton α to the intermediate sulfoxide salt by incorporating a carbonyl group can shift the course of the reaction from an interrupted to a normal Pummerer reaction (Scheme 68 and eq 9). The nucleophilicity of the reaction partner can also change the nature of the products isolated. More electron rich nucleophiles often cause the rate of the interrupted Pummerer reaction to become competitive with the deprotonation that ultimately leads to thionium ions (see **200**, Scheme 35). The nature of the nucleofuge used in the elimination reaction that leads to thionium ions can also have an impact on the chemoselectivity of the Pummerer reaction. Promotion of the Pummerer reaction of **425** by, for example, TFAA led to a normal Pummerer reaction producing **434**, whereas the use of Tf_2O effected an interrupted Pummerer cyclization to give **426** (Scheme 68).

These structural features often work in concert and can change the course of the reaction. For example, the use of hypervalent iodine reagents produces normal Pummerer cyclization products when the generation of the intermediate thionium ion is assisted by a carbonyl group β to the sulfonium salt (Schemes 64 and 65). On the other hand, when the proton α to the sulfonium salt is less acidic, interrupted Pummerer cyclization products are obtained (see Scheme 67). The combination of an electron-rich nucleophile and a weakly acidic α-proton led to the generation of an interrupted Pummerer product (Scheme 42).

Processes such as additive and vinylogous variants continue to expand the utility of the Pummerer reaction for synthesis. Reactions that generate thionium ions in novel ways, such as the Wagner−Merwein-type rearrangement (see eq 4), also enhance the scope of this reaction. The use of thionium ion-containing arrays that undergo chemistry other than nucleophilic additions, including Nazarov-type cyclizations (Schemes 24−26) and the [4+3]-cycloaddition (Scheme 73), have also broadened the application of the Pummerer reaction as well. Undoubtedly, many important applications of the Pummerer reaction remain undiscovered. The use of Pummerer chemistry as a key bond-forming strategy will continue to greatly expand its utility in organic synthesis. The incorporation of Pummerer reactions into cascade sequences will certainly continue to play an important role in the construction of complex heterocyclic ring systems. As researchers develop a better understanding of the subtle electronic and conformational effects that influence the course of Pummerer-initiated cyclization reactions, larger sized heterocyclic rings may be formed more efficiently. It is clear, however, that the Pummerer cyclization is, and will continue to be, an important method for the synthesis of a wide assortment of heterocyclic compounds.

9. Acknowledgment

We gratefully thank the National Science Foundation and the National Institutes of Health for generous support of our work dealing with various aspects of Pummerer chemistry. We also acknowledge the contributions of the graduate and postdoctoral students who participated in this research area. Their names are given in the literature references from our group.

10. References

(1) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282.

(2) (a) Russell, G. A.; Mikol, G. J. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1968; Vol. 1, pp 157−207. (b) DeLucchi, O.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley: New York, 1991; Chapter 3, pp 157−184. (c) Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 6, pp 909−947. (d) Kennedy, M.; McKervey, M. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, pp 193−216. (e) Oae, S.; Numata, T. The Pummerer Type of Reactions. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. E., Eds.; Elsevier: New York, 1980; Vol. 5, Chapter 2. (f) Oae, S.; Numata, T.; Yoshimura, T. Heterosulphonium Salts. In *The Chemistry of the Sulphonium Group*; Stirling, C. J., Patia, S., Eds.; John Wiley: New York, 1981. (g) Marino, J. P. In *Topics in Sulfur Chemistry*; Senning, A., Ed.; George Thieme: Stuttgart, Germany, 1976; Vol. 1, p 1.

(3) (a) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55. (b) Xu, J.; Stevenson, J. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1177.
(4) (a) Padwa, A. *Phosphorus, Sulfur, Silicon* **1999**, *153*, 23. (b) Padwa, A.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *J. Braz. Chem. Soc.* **2001**, *12*, 571. (c) Padwa, A.; Bur, S. K.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *Synlett* **2002**, 851.
(5) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.
(6) For a recent review of thionucleoside manipulation, see: Yokoyama, M. *Synthesis* **2000**, 1637.
(7) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118.
(8) Oikawa, Y.; Yonemitsu, O. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1479.
(9) Oikawa, Y.; Yonemitsu, O. *Heterocycles* **1976**, *5*, 233.
(10) Bari, S. S.; Venugopalan, P.; Arora, R. *Tetrahedron Lett.* **2003**, *44*, 895.
(11) Ishida, H.; Ohno, M. *Tetrahedron Lett.* **1999**, *40*, 1543.
(12) Ishida, H.; Itoh, K.; Ohno, M. *Tetrahedron* **2001**, *57*, 1737.
(13) McCarthy, D. G.; Collins, C. C.; O'Driscoll, J. P.; Lawrence, S. E. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 3667.
(14) Magnus, P.; Kreisberg, J. D. *Tetrahedron Lett.* **1999**, *40*, 451.
(15) (a) Tamura, Y.; Uenishi, J.-I.; Maeda, H.; Choi, H.-D.; Ishibashi, H. *Synthesis* **1981**, 534. (b) Tamura, Y.; Uenishi, J.-I.; Choi, H.-D.; Haruta, J.-i.; Ishibashi, H. *Chem. Pharm. Bull.* **1984**, *32*, 1995. (c) In a recent report, α-sulfanyl-*N*-arylacetamides attached to a resin via the sulfur atom were found to undergo an efficient Pummerer cyclization to give oxindoles. The cyclized products were cleaved from the resin in a traceless manner using samarium(II) iodide; see: McAllister, L. A.; Brand, S.; Gentile, R.; Procter, D. J. *Chem. Commun.* **2003**, 2380.
(16) Chan, W. H.; Lee, A. W. M.; Lee, K. M.; Lee, T. Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2355.
(17) Marino, J. P.; Neisser, M. *J. Am. Chem. Soc.* **1981**, *103*, 7687.
(18) (a) Marino, J. P.; Perez, A. D. *J. Am. Chem. Soc.* **1984**, *106*, 7643. (b) Marino, J. P.; de la Pradilla, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381. (c) Marino, J. P.; de la Pradilla, R. F.; Laborde, E. *Synthesis* **1987**, 1088. (d) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 641.
(19) See also (a) Posner, G. H.; Asirvatham, E.; Ali, S. F. *J. Chem. Soc., Chem. Commun.* **1985**, 542. (b) Burke, S. D.; Shankaran, K.; Helber, M. J. *Tetrahedron Lett.* **1991**, *32*, 4655. (c) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409. (d) Bravo, P.; Arnone, A.; Bandiera, P.; Bruchè, L.; Ohashi, Y.; Ono, T.; Sekine, A.; Zanda, M. *Eur. J. Org. Chem.* **1999**, *111*, 1.
(20) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566.
(21) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398.
(22) Burke, S. D.; Jung, K. W.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 5841.
(23) de Groot, A.; Jansen, B. M. J. *J. Org. Chem.* **1984**, *49*, 2034.
(24) Jansen, B. J. M.; Bouwmann, C. T.; de Groot, A. *Tetrahedron Lett.* **1994**, *35*, 2977.
(25) (a) Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 3495. (b) Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60*, 3938. (c) Padwa, A.; Cochran, J. E.; Kappe, C. O. *J. Org. Chem.* **1996**, *61*, 3706. (d) Kappe, C. O.; Padwa, A. *J. Org. Chem.* **1996**, *61*, 6166.
(26) Ginn, J. D.; Lynch, S. M.; Padwa, A. *Tetrahedron Lett.* **2000**, *41*, 9387.
(27) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412.
(28) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.
(29) Crabtree, R. H.; Felkin, H.; Fellebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1971**, *168*, 183.
(30) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144.
(31) See also Padwa, A.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1996**, *61*, 4888.
(32) Padwa, A.; Eidell, C. K.; Lynch, S. M. *Heterocycles* **2002**, *58*, 227.
(33) Sarkar, T. K.; Basak, S.; Panda, N. *Tetrahedron Lett.* **2002**, *43*, 1341.
(34) (a) Magnus, P.; Gallagher, T. *J. Am. Chem. Soc.* **1982**, *104*, 1140. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. (c) Ladlow, M.; Cairns, P.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1986**, 1756. (d) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70.
(35) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.
(36) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.
(37) Urrutia, A.; Rodríguez, J. G. *Tetrahedron* **1999**, *55*, 11095.
(38) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546.
(39) For DMTSF-promoted Pummerer reactions in the context of the strychnos alkaloids, see: (a) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299. (b) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792.
(40) Catena, J.; Valls, N.; Bosch, J.; Bonjoch, J. *Tetrahedron Lett.* **1994**, *35*, 4433.
(41) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T.; McClure, M. S. *J. Org. Chem.* **1998**, *63*, 6778.
(42) (a) Padwa, A.; Danca, D. M. *Org. Lett.* **2002**, *4*, 715. (b) Padwa, A.; Danca, D. M.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2002**, *68*, 929.
(43) Ishibashi, H.; Sato, K.; Maruyama, K.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4593.
(44) Ishibashi, H.; Ozeki, H.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 654.
(45) For a recent review of mesoionic ring systems, see: Gribble, G. W. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley: Hoboken, NJ, 2003; pp 681−753.
(46) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **1999**, *64*, 2038.
(47) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368.
(48) Kim, T.; Kim, K.; Park, Y. J. *Eur. J. Org. Chem.* **2002**, 493.
(49) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1992**, *48*, 7803.
(50) Shinohara, T.; Takeda, A.; Toda, J.; Terasawa, N.; Sano, T. *Heterocycles* **1997**, *46*, 555.
(51) (a) Shinohara, T.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **1997**, *45*, 813. (b) Shinohara, T.; Takeda, A.; Toda, J.; Kohno, M.; Sano, T. *Heterocycles* **1999**, *51*, 119.
(52) For some related cyclizations, see: (a) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932. (b) Takano, S.; Iida, H.; Inomata, K.; Ogasawara, K. *Heterocycles* **1993**, *35*, 47.
(53) Toda, J.; Niimura, Y.; Takeda, K.; Sano, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 906.
(54) Jousse, C.; Desmaële, D. *Eur. J. Org. Chem.* **1999**, *909*, 9.
(55) Hucher, N.; Daich, A.; Decroix, B. *Org. Lett.* **2000**, *2*, 1201.
(56) (a) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1239. (b) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158. (c) Bennasar, M.-L.; Zulaica, E.; Sufi, B. A.; Bosch, J. *Tetrahedron* **1996**, *52*, 8601.
(57) For some related Pummerer cyclizations used for the synthesis of the strychnos and ibophyllidine alkaloids, see: (a) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939. (b) Bonjoch, J.; Catena, J.; Valls, N. *J. Org. Chem.* **1996**, *61*, 7106.
(58) Bennasar, M.-L.; Vidal, B.; Sufi, B. A.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1998**, 2639.
(59) Bennasar, M.-L.; Jiménez, J.-M.; Vidal, B.; Sufi, B. A.; Bosch, J. *J. Org. Chem.* **1999**, *64*, 9605.
(60) Amat, M.; Bennasar, M.-L.; Hadida, S.; Sufi, B. A.; Zulaica, E.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5217.
(61) Bernard, A. M.; Cadoni, E.; Frongia, A.; Piras, P. P.; Secci, F. *Org. Lett.* **2002**, *4*, 2565.
(62) (a) Abe, H.; Shibaike, K.; Fujii, H.; Tsuchida, D.; Akiyama, T.; Harayama, T. *Heterocycles* **1999**, *50*, 291. (B) Abe, H.; Itani, J.; Masunari, C.; Kashino, S.; Harayama, T. *J. Chem. Soc., Chem. Commun.* **1995**, 1197. (c) Abe, H.; Fujii, H.; Masunari, C.; Itani, J.; Kashino, S.; Shibaike, K.; Harayama, T. *Chem. Pharm. Bull.* **1997**, *45*, 778.
(63) Abe, H.; Fujii, H.; Koshiba, N.; Takeuch, Y.; Harayama, T. *Heterocycles* **2000**, *52*, 465.
(64) Aitken, R. A.; Hill, L.; Lightfoot, P.; Wilson, N. J. *J. Chem. Soc., Chem. Commun.* **1999**, 1673.
(65) For ring contaction reactions of dihydro- and tetrahydrothiazepines to isothiazolone derivatives under Pummerer conditions, see: Yamamoto, K.; Yamazaki, S.; Murata, I.; Fukazawa, Y. *J. Org. Chem.* **1987**, *52*, 5239.
(66) (a) Kita, Y.; Tamura, O.; Miki, T.; Tono, H.; Shibata, N.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 729. (b) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimor, C.; Ohishi, H. *J. Am. Chem. Soc.* **1994**, *116*, 5116.
(67) Kaneko, T. *J. Am. Chem. Soc.* **1985**, *107*, 5490
(68) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.
(69) Kita, Y.; Shibata, N.; Yoshida, N.; Fijita, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3335.
(70) Kita, Y.; Shibata, N. *Synlett* **1996**, 289.
(71) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimor, C.; Matsumoto, K.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2405.
(72) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimor, C.; Matsumoto, K. *Tetrahedron Lett.* **1995**, *36*, 115.
(73) Ishibashi, H.; Harada, S.; Okada, M.; Somekawa, M.; Kido, M.; Ikeda, M. *Chem. Pharm. Bull.* **1989**, *37*, 939.
(74) Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett.* **1995**, *36*, 6733.
(75) Ishibashi, H.; Takagaki, K.; Imada, N.; Ikeda, M. *Tetrahedron* **1994**, *50*, 10215.

(76) Ishibashi, H.; Takagaki, K.; Imada, N.; Ikeda, M. *Synlett* **1994**, 49.
(77) Ishibashi, H.; Okada, M.; Akiyama, A.; Nomura, K.; Ikeda, M. *J. Heterocycl. Chem.* **1986**, *23*, 1163.
(78) Toda, J.; Ichikawa, T.; Saitoh, T.; Horiguchi, Y.; Sano, T. *Heterocycles* **2000**, *53*, 2009.
(79) Horiguchi, Y.; Saitoh, T.; Terakado, S.; Honda, K.; Kimura, T.; Toda, J.; Sano, T. *Heterocycles* **2001**, *54*, 967.
(80) Toda, J.; Niimura, Y.; Sano, T.; Tsuda, Y. *Heterocycles* **1998**, *48*, 1599.
(81) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 6611.
(82) Bennasar, M.-L.; Zulaica, E.; Ramírez, A.; Bosch, J. *Tetrahedron* **1999**, *55*, 3117.
(83) Kita, Y.; Tamura, O.; Miki, T.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 6479.
(84) (a) Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159. (b) Padwa, A.; Waterson, A. G. *Tetrahedron Lett.* **1998**, *39*, 8585.
(85) Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235.
(86) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256.
(87) (a) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517. (b) Sidall, T. H.; Garner, R. *Can. J. Chem.* **1966**, *44*, 2389. (c) Oki, M. *Top. Stereochem.* **1983**, *14*, 1.
(88) Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J.-I. *Chem. Pharm. Bull.* **1986**, *34*, 1061.
(89) Bates, D. K.; Tafel, K. A. *J. Org. Chem.* **1994**, *59*, 8076.
(90) Picard, J. A.; Chen, S.; Bates, D. K. *Heterocycles* **1994**, *38*, 1775.
(91) Bates, D. K.; Habib, Q. A. *J. Hetercycl. Chem.* **1995**, *32*, 1477.
(92) Tafel, K. A.; Bates, D. K. *J. Org. Chem.* **1992**, *57*, 3676.
(93) Wang, H.-M.; Lin, M.-C.; Chen, L.-C. *J. Chin. Chem. Soc.* **1994**, *41*, 217.
(94) Wang, H.-M.; Lin, M.-C.; Chen, L.-C. *Heterocycles* **1994**, *38*, 1519.
(95) Greaney, M. F.; Motherwell, W. B. *Tetrahedron Lett.* **2000**, *41*, 4467.
(96) (a) Wang, H.-M.; Huang, H.-Y.; Kang, I.-J.; Chen, L.-C. *Heterocycles* **2001**, *55*, 1231. (b) Volonterio, A.; Bravo, P.; Zanda, M. *Tetrahedron Lett.* **2002**, *43*, 6537.
(97) (a) Bates, D. K.; Winters, R. T.; Picard, J. A. *J. Org. Chem.* **1992**, *57*, 3094. (b) Bates, D. K.; Tafel, K. A. *J. Org. Chem.* **1994**, *59*, 8076.
(98) Bates, D. K.; Xia, M. *J. Org. Chem.* **1998**, *63*, 9190.
(99) For an example of an interupted Pummerer reaction leading to an unusual rearrangement product, see: Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1994**, *50*, 13501.
(100) (a) Arnone, A.; Bravo, P.; Bruché, L.; Crucianelli, M.; Vichi, L.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 7301. (b) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **1996**, *61*, 3375.
(101) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965.
(102) For some leading references to σ-sulfuranes, see: (a) Hornbuckle, S. F.; Livant, P.; Webb, T. R. *J. Org. Chem.* **1995**, *60*, 4153. (b) Szabó, D.; Szendeffy, S.; Kapovits, I.; Kucsman, Á.; Czugler, M.; Kálmán, A.; Nagy, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2411. (c) Zhang, J.; Saito, S.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 1631.
(103) (a) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 1896. (b) Morin, R. B.; Jackson, B. G.; Mueller, R. A.; Lavagnino, E. R.; Scanlon, W. B.; Andrews, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 1401.
(104) (a) Hart, D. J.; Magomedov, N. A. *J. Org. Chem.* **1999**, *64*, 2990. (b) Freed, J. D.; Hart, D. J.; Magomedov, N. A. *J. Org. Chem.* **2001**, *66*, 839.
(105) (a) Harmata, M.; Gamlath, C. B. *J. Org. Chem.* **1988**, *53*, 6154. (b) Harmata, M.; Gamlath, C. B.; Barnes, C. L. *Tetrahedron Lett.* **1990**, *31*, 5981.
(106) Harmata, M.; Fletcher, V. R.; Claassen, R. J., II *J. Am. Chem. Soc.* **1991**, *113*, 9861.
(107) (a) Hu, Y.; Ou, L.; Bai, D. *Tetrahedron Lett.* **1999**, *40*, 545. (b) Ou, L.; Hu, Y.; Song, G.; Bai, D. *Tetrahedron* **1999**, *55*, 13999.

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