

Use of sulfur fragments for the synthesis of nitrogen heterocycles*

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Abstract: This contribution contains a representative sampling from the Padwa laboratory of the conjugate addition of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene followed by a subsequent dipolar cycloaddition cascade to produce a variety of alkaloids. The resulting cycloadducts are cleaved reductively to provide azapolycyclic scaffolds with strategically placed functionality for further manipulation of the target compounds.

Keywords: heterocyclic chemistry; nitrogen; organic synthesis; rearrangements; sulfur; tandem reactions.

INTRODUCTION

Before chemistry was a science, there was alchemy. One of the supreme quests of alchemy was to transmute lead into gold. Indeed, this transmutation was believed to be not only possible but also actively practiced during the Middle Ages. The desired conversion was such a popular fad that mobs of people gathered to obtain the secret from a suspected alchemist who could have been beaten to death for not complying. It should be noted that the actual transmutation of lead into gold has indeed been achieved in recent years, since today's particle accelerators routinely transmute elements. While it may never be easy to transmute one element into another, in the hands of a modern-day synthetic organic chemist, it is desirable to take advantage of the unique chemistry of sulfur to synthesize nitrogen heterocycles. The result is bordering on alchemy, almost. For some time now, the Padwa research group has been taking advantage of the chemistry of various thio fragments to synthesize an assortment of alkaloids. In this short account, a North American perspective on an aspect of heteroatom chemistry, arising from the author's contributions to relevant chemical methodology and its applications in synthesis, is described.

Heteroatom-containing natural products are abundant in nature and exhibit diverse and important biological properties [1]. Accordingly, novel strategies for the stereoselective synthesis of hetero-polycyclic systems found in the alkaloid kingdom continue to receive considerable attention in the field of synthetic organic chemistry [2]. Although methods of preparing such complex architectures such as those shown in Fig. 1 vary widely, approaches that employ cycloaddition chemistry are particularly attractive given the rapid introduction of molecular complexity within a single chemical operation [3]. A significant improvement of the synthetic efficiency to a multitude of diverse heterocycles has been obtained in recent years through the development of domino reactions that allow the formation of complex compounds, starting from simple substrates, in a single transformation consisting of several steps [4]. Domino reactions, multicomponent reactions, and the so-called "telescoping" of reactions (the sequencing of multiple transformations in a single reaction vessel through the changing of conditions

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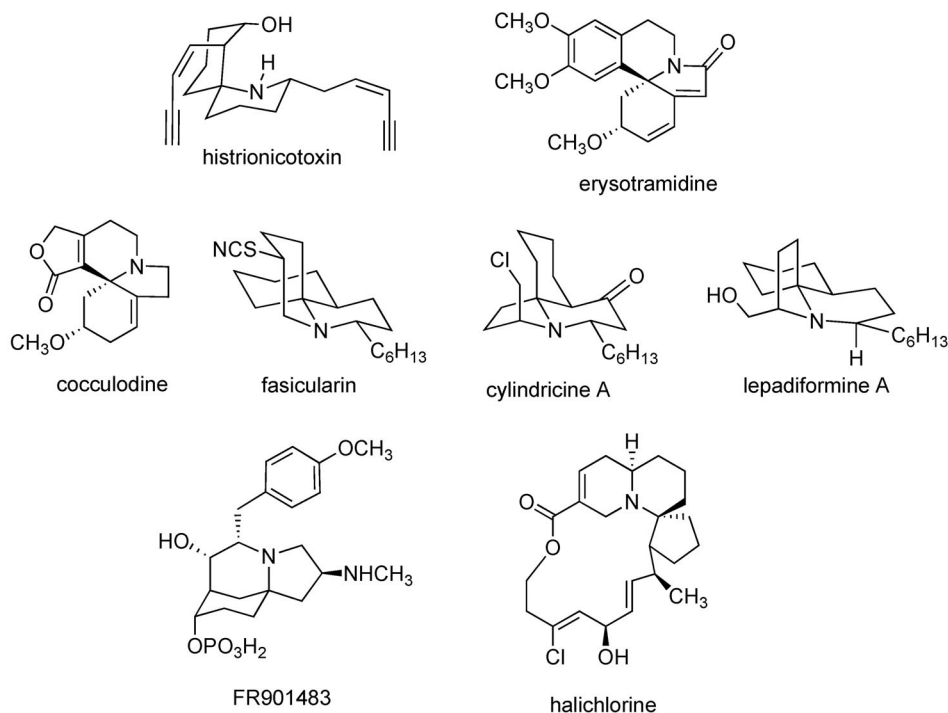


Fig. 1 Representative alkaloid natural products.

and/or adding of reagents at appropriate times) allow for the rapid increase in molecular complexity in a single chemical operation. Because of the rate at which they increase molecular complexity, the use of domino chemistry for the synthesis of alkaloids is receiving considerable attention from the synthetic organic community [5,6]. The development of sequences that combine transformations of differing fundamental mechanisms broadens the scope of such procedures in synthetic chemistry. Against this backdrop, the utilization of a cascade sequence which includes a 1,3-dipolar cycloaddition reaction represents a highly useful and efficient approach toward a wide variety of hetero-polycyclic natural products [7–9].

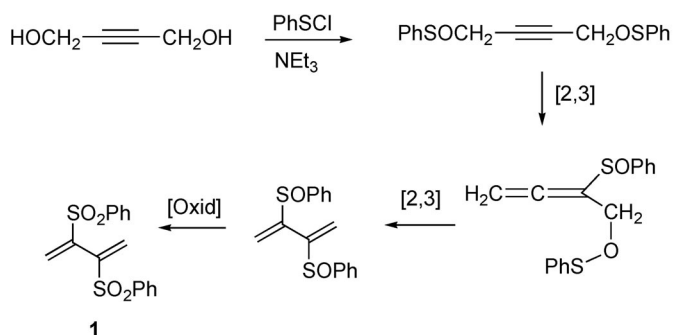
This review comprises a representative sampling from our laboratory over the past several years of the conjugate addition of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**) followed by a subsequent dipolar cycloaddition cascade to produce a variety of alkaloids.

SYNTHETIC METHODS

Origin of the 2,3-bis(phenylsulfonyl)-1,3-butadiene mediated synthesis of piperidone derivatives

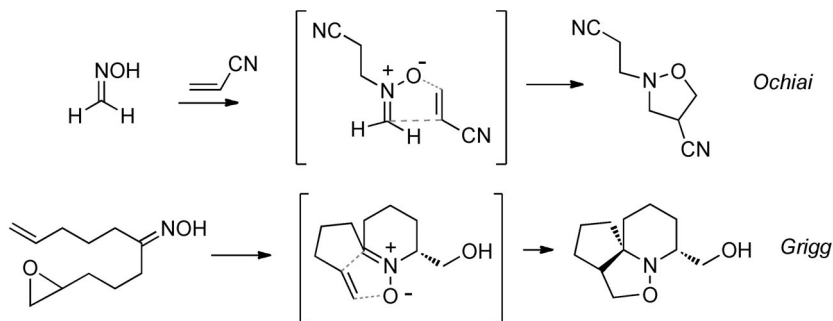
Conjugated dienes with electron-donating or -withdrawing substituents within the diene unit have attracted considerable attention during recent years [10–13]. Sulfur-substituted dienes, in particular, have been widely used in the Diels–Alder reaction [14]. The sulfur atom not only increases the reactivity of the diene but also adds control to the regioselectivity of the cycloaddition. Furthermore, the richness of synthetic transformations involving sulfur functionality make the [4 + 2]-adducts very useful in organic synthesis. 2,3-Bis(phenyl-sulfonyl)diene (**1**) is a crystalline compound, is easily prepared, and possesses indefinite shelf life, adding to its attractiveness as a synthetic reagent [15]. In spite of its simplicity and its obvious potential as an activated diene, this compound had not been extensively uti-

lized for organic synthesis prior to 1990 [16]. The phenylsulfonyl group is an extremely useful functionality in organic synthesis since it can enhance chemical reactivity and then be easily removed to provide sulfur-free compounds. Diene **1** can be easily prepared in multigram quantities by a modification of the procedure of Okamura and Jeganathan [17]. Thus, treatment of 2-butyne-1,4-diol with benzene-sulfonyl chloride produced the disulfenate ester as a transient species, which rapidly undergoes a series of 2,3-sigmatropic rearrangements to give the corresponding divinyl sulfoxide. This material could be readily oxidized to the corresponding phenylsulfonyldiene **1** with *m*-chloroperoxybenzoic acid (MCPBA) in excellent yield (Scheme 1) [15].

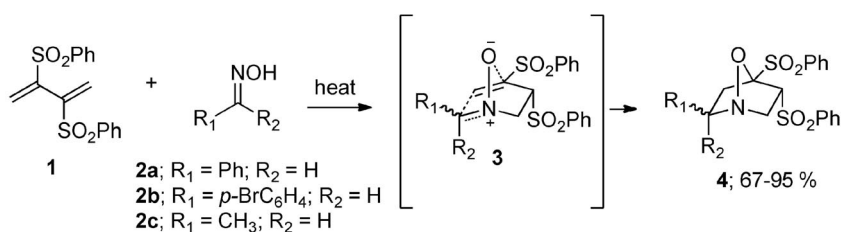


Scheme 1 Preparation of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**).

In the late 1960s, Ochiai and co-workers reported the first example of an oxime reacting with an electron-deficient alkene to furnish a substituted nitrone [18]. Once formed, the nitrone was observed to undergo both inter- and intramolecular 1,3-dipolar cycloaddition (Scheme 2). Shortly thereafter, the Grigg group exploited this methodology for the synthesis of various nitrogen-containing heterocycles, further establishing the concept that nitrones could be readily formed by treating oximes with various electrophilic reagents [19]. Inspired by the facility with which oximes react with various electrophiles to afford nitrones as reported by Ochiai [18] and Grigg [19], an extension of this methodology to 2,3-bis(phenylsulfonyl)butadiene (**1**) seemed both logical and intriguing (Scheme 3). We soon discovered that treating various aldehyde and keto oximes (**2**) with phenylsulfonyldiene **1** resulted in the formation of cycloadducts of type **4** in high yield [20].

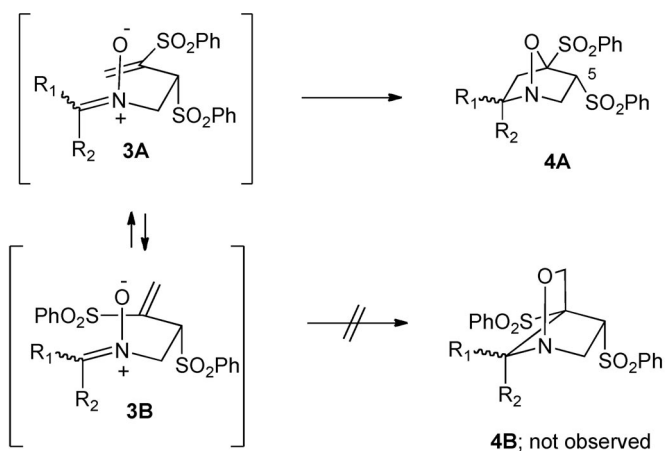


Scheme 2 Oxime-derived nitrone dipolar cycloadditions.



Scheme 3 Michael addition/dipolar cycloaddition cascade of bis(phenylsulfonyl)diene (**1**).

We believe that the mechanism by which cycloadduct **4** is formed involves an initial conjugate addition of the oxime to one of the terminal π -bonds of the phenylsulfonyl substituted diene followed by a proton transfer to generate a transient nitron (i.e., **3**) which immediately undergoes a highly regioselective dipolar cycloaddition reaction. In principle, the intramolecular cycloaddition reaction can proceed from two possible transition states (i.e., **3A** and **3B**) which could result in the formation of two possible regioisomeric cycloadducts **4A** and **4B** (Scheme 4). Molecular modeling calculations (MM2) were performed to determine the relative energies of the regioisomeric cycloadducts [20]. These studies revealed that the preferential formation of the lower-energy product **4A** (relative to that of **4B**) mimicked the energetic values of the transition states derived from nitrones **3A** and **3B**, respectively. A cycloaddition product derived from the higher energy nitron conformer **3B** would have resulted in the formation of cycloadduct **4B**. However, this particular regioisomer has not been observed in any of the cases studied.

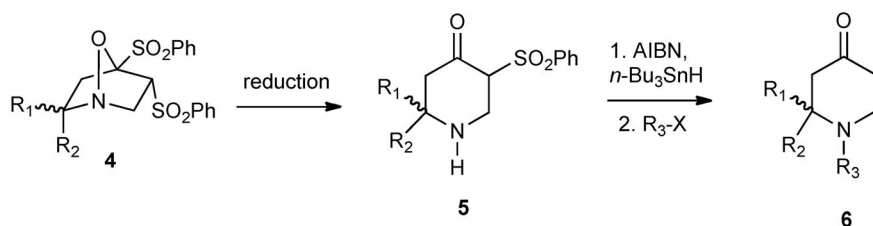


Scheme 4 Possible dipolar cycloaddition regiochemical outcomes.

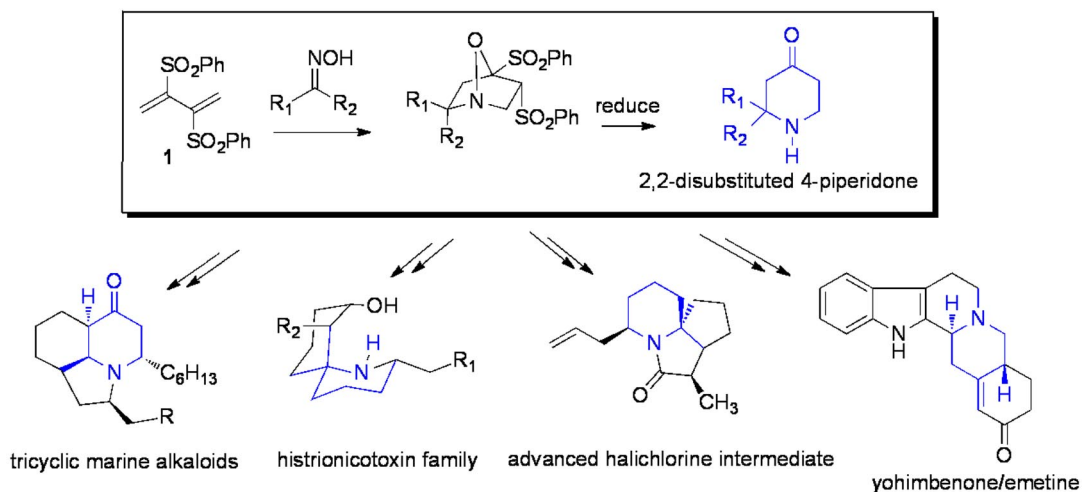
Another interesting issue regarding the cycloaddition is that steric repulsion between the vicinal phenylsulfonyl groups is clearly responsible for the orientation of the sulfonyl group at the C-5 position of the resulting ring system. This large group resides exclusively in a pseudoaxial orientation about the ring system, and this can be rationalized by assuming that the two bulky phenylsulfonyl groups tend to avoid any eclipsing interactions in the transition state for the cycloaddition. Steric repulsion forces the phenylsulfonyl group at C-5 to adopt a pseudoaxial orientation relative to the bicyclic system, thereby accounting for the stereospecificity of the reaction.

Subsequent work from our group showed that the resulting oxa-azabicyclic adducts **4** underwent smooth Raney nickel reduction of the *N*-O bond to provide 2,2-disubstituted piperidones of type **5**

(Scheme 5) [20]. The remaining phenylsulfonyl group present in the initially formed piperidone **5** could be easily removed by treatment with an excess of tributyltin hydride [21] and azobisisobutyronitrile (AIBN). The ensuing secondary amine was further derivatized using a wide assortment of different electrophiles (R_3-X). The overall cascade sequence represents a high-yielding method for the preparation of a variety of 2,2-disubstituted piperidones. The easy accessibility of dienylyl sulfone **1** led us to use this method for the synthesis of a number of alkaloid targets that are depicted in Scheme 6. Our efforts toward their construction are summarized in the following sections.



Scheme 5 Reduction of *N*-*O* cycloadducts.

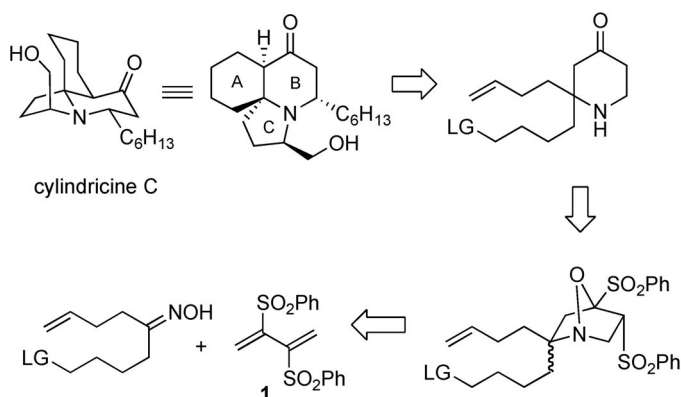


Scheme 6 Piperidine-containing alkaloid targets arising from Michael addition/dipolar cycloaddition strategy.

ALKALOID TARGET SYNTHESIS

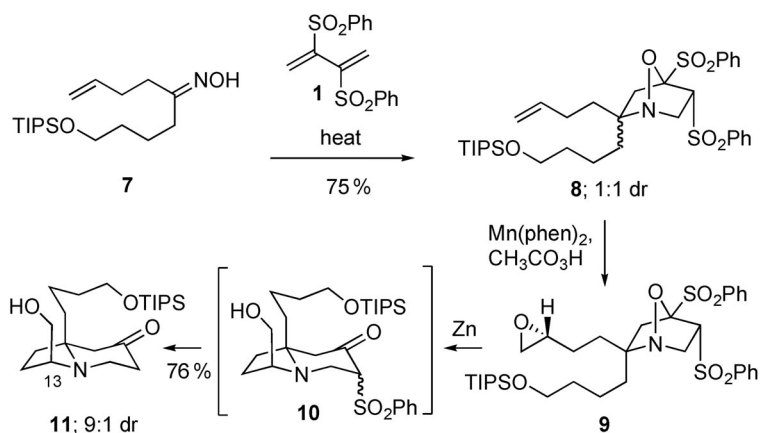
(±)-Cylindricine C

The synthesis of the marine alkaloid (±)-cylindricine C [22] by this strategy required the preparation of oxime-bearing side-chains, which would react in a differentiable manner (Scheme 7) [23]. Construction of the A- and C-rings of the cylindricine framework after the piperidonyl B-ring can be realized by making use of the *Michael addition/dipolar cycloaddition/reduction* protocol. In practice, the requisite oxime **7** needed for the synthesis of cylindricine C was prepared in gram scale in 77 % yield in four steps starting from δ -valerolactone. Heating a sample of this oxime in the presence of phenylsulfonyl-diene **1** afforded azaoxabicyclic **8** as a 1:1 mixture of diastereomers in 75 % yield. A modified Stack [24] epoxidation protocol was then used to convert the terminal π -bond **8** into the corresponding epoxide **9**. The stereoconfiguration of epoxide **9** most likely arises from a preferential approach of electrophilic oxygen onto the *exo*-position of alkene **8**. The epoxidation presumably involves complexation of



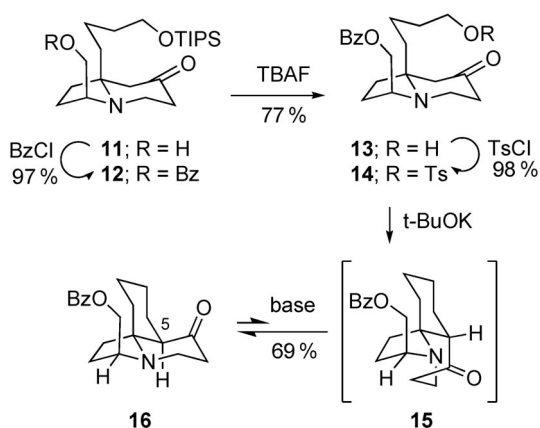
Scheme 7 Michael addition/dipolar cycloaddition approach to (±)-cylindricine C.

the manganese catalyst with the *N*-*O* cycloadduct to direct the facial selectivity. Treatment of epoxide **9** with excess zinc dust [25] triggered a *reductive/cyclization* cascade whereby *N*-*O* bond scission was followed by spontaneous ejection of phenylsulfonic acid. Attack of the resulting secondary amine onto the pendant epoxide ring produces the 7-indolizidone ring system. Further reduction of the α -keto phenylsulfonyl group occurred in situ and ultimately led to the formation of indolizidinone **11**. This key azabicyclic alcohol was obtained in 76 % yield as a 9:1 diastereomeric mixture from epoxide **9**, and the major diastereomer possessed the required cylindricine C geometry at C-13. The remaining 24 % of recovered material corresponded to ketone **10**. Further reduction of **10** with tributyltin hydride and AIBN provided an additional 20 % of the diastereomerically pure alcohol **11** (Scheme 8).



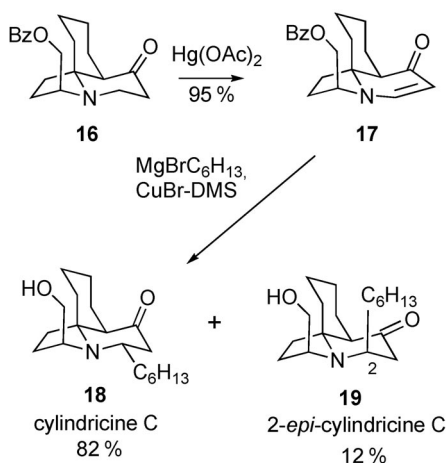
Scheme 8 Assembly of the BC-ring skeleton of cylindricine C.

The stereo-enriched alcohol **11** was converted to the corresponding benzoyl ester at which point the minor diastereomer could be chromatographically removed. Desilylation of ester **12** produced alcohol **13** which was readily transformed into tosylate **14**. Subjection of **14** to an intramolecular enolate alkylation reaction [26] furnished the core azadecalin ring system **16**. This reaction presumably proceeds through the intermediacy of the *trans*-azadecalin **15**, which is readily epimerized to the thermodynamically more stable *cis*-conformation under the basic reaction conditions [27], thereby producing the required cylindricine configuration at C-5 (Scheme 9).



Scheme 9 Formation of ring-A for cylindricine C synthesis.

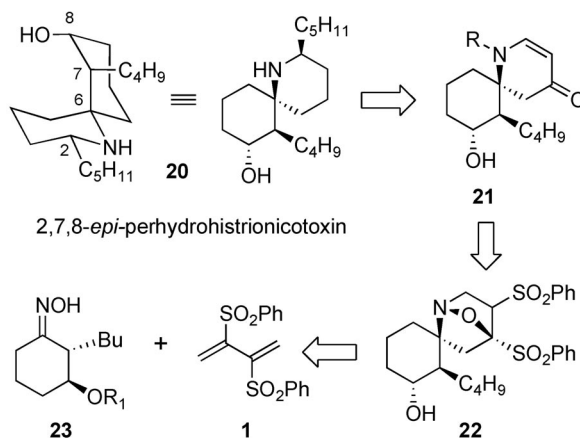
Completion of the synthesis of (\pm)-cylindricine C required an oxidation of **16** to the corresponding *2H*-piperidonyl enone **17** in order to incorporate the *n*-hexyl side-chain at C-2 by an eventual cuprate conjugate addition. A variety of standard oxidative methods such as IBX [28], PhSeCl/oxidation [29], Saegusa [30], and α -halo elimination failed to produce any synthetically useful quantity of enone **17**. However, mercuric acetate eventually emerged as a superior reagent for introducing unsaturation into the 4-piperidone ring [31]. The use of this oxidant resulted in a near-quantitative conversion of tricycle **16** to 2,3-dihydropyridinone **17** (Scheme 10). The tricyclic topography of **17** influenced attack of the cuprate reagent that occurred from the pseudo-equatorial face of the conjugated π -array [32], thereby installing the *n*-hexyl side-chain into the desired stereochemical position at C-2 [27,33]. In order to complete the synthesis, saponification of the benzoyl ester furnished a chromatographically separable mixture of (\pm)-cylindricine C (**18**) and 2-*epi*-cylindricine C (**19**) in 90 % overall conversion from 2,3-dihydropyridinone **17**.



Scheme 10 Final approach to (\pm)-cylindricine C.

Approach to the perhydrohistrionicotoxin (PHTx) core

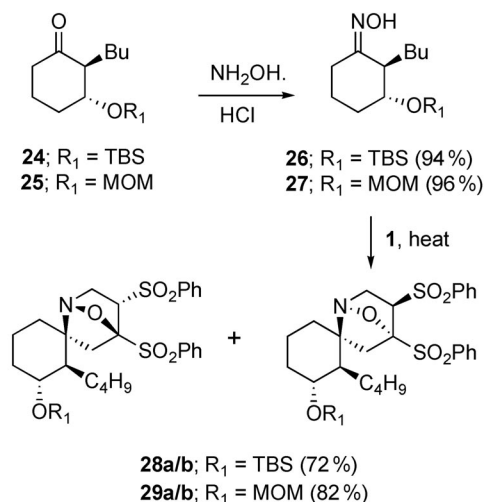
Azaspirocyclic alkaloids isolated from the skin extracts of the neotropical frog *Dendrobates histrionicus* have emerged as important neurophysiological probes owing to their unusual effects as selective inhibitors of the neuromuscular, ganglionic, and nACh receptors [34,35]. The unique neurophysiological properties associated with the skeleton of this class of alkaloids have prompted numerous synthetic approaches toward the azaspiro[5.5]undecane core of perhydrohistrionicotoxin (PHTx) [36,37]. Studies in our laboratory demonstrated that the tandem *Michael addition/dipolar cycloaddition* cascade utilizing 2,3-bis(phenylsulfonyl)butadiene (**1**) represents a very efficient strategy for producing a functionalized azaspiro[5.5]undecane scaffold capable of being transformed into 2,7,8-*epi*-PHTx (**20**). The synthesis of this alkaloid was envisaged to arise from cuprate addition onto 2,3-dihydropyridinone **21**. The latter compound could be formed from the spirocyclic adduct **22** derived from the *Michael addition/dipolar cycloaddition* cascade. Guided by this synthetic approach, the assembly of an oxime related to **23** was undertaken (Scheme 11) [38].



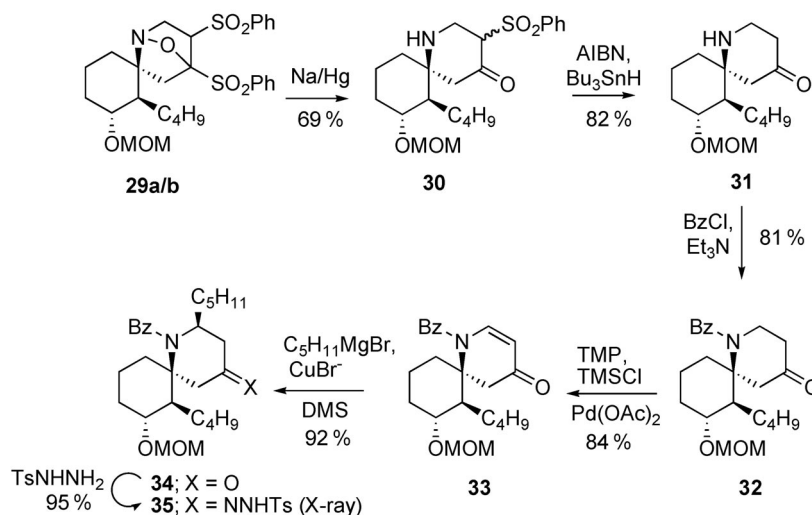
Scheme 11 Michael addition/dipolar cycloaddition approach to (±)-2,7,8-*epi*-PHTx.

By following a protocol originally developed by Wender [39], ketones **24** and **25** were used to set the C-7 and C-8 stereochemistry of the final target. These ketones were prepared using the silyl (**24**) and methoxymethyl (MOM) (**25**) ether-protected alcohols. Thus, reaction of these two compounds with hydroxylamine hydrochloride furnished the desired oximes **26** and **27** in excellent yields. When these oximes were allowed to react with phenylsulfonyldiene **1**, the expected silylated cycloadducts **28a** and **28b** were formed as a 3:2-mixture of diastereomers in 72 % overall yield (Scheme 12).

X-ray analysis of cycloadducts **28a** and **28b** indicated that the 1,3-dipolar cycloaddition had proceeded with complete stereocontrol, but gave the undesired stereochemistry at the C-7 and C-8 stereocenters of histrionicotoxin. However, by adopting an epimerization protocol previously reported by Godleski [40], we were able to adjust these stereocenters at a later stage of the synthesis. Since the diastereomeric mixture of cycloadducts **28a/b** differed only in terms of the orientation of the oxido bridge and C3 sulfonyl stereochemistry (both of which would be destroyed during the reductive cleavage step), separation of this mixture was deemed unnecessary. Unfortunately, all our attempts to carry out a reductive *N–O* cleavage of the mixture of cycloadducts **28a/b** were unsuccessful, leading only to recovered starting material or decomposition products. In contrast to the silylated cycloadducts **28a/b**, *N–O* bond reduction of the less-hindered MOM ether-protected cycloadducts **29a/b** did proceed smoothly when treated with sodium mercury amalgam, giving piperidone **30** in 69 % yield, accompa-

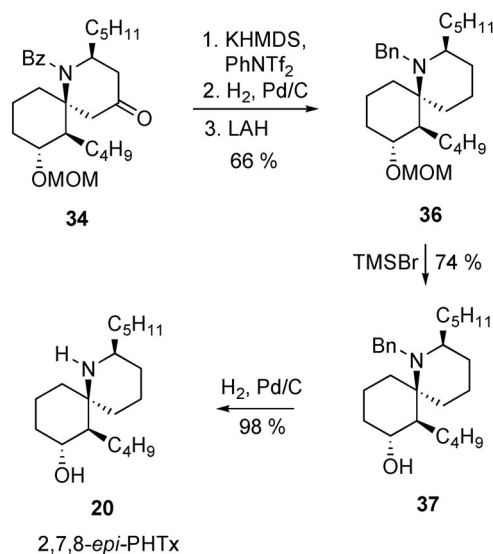


Scheme 12 Oxa-azacycle formation.

Scheme 13 Oxazacycle reductive *N*-*O* cleavage and *n*-pentyl installation.

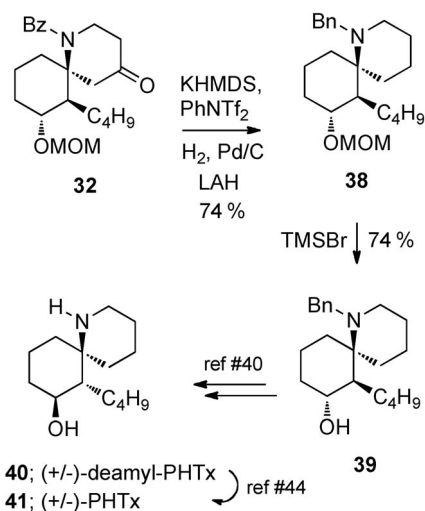
nied by a small amount of the over-reduced product **31** (Scheme 13). Further reductive desulfonylation of **30** provided more of the key aza-spiropiperidone **31** in excellent yield. Reaction of the secondary amine with benzoyl chloride gave amide **32** which was converted to 2,3-dihydropyridinone **33** by means of Saegusa oxidation [41]. Introduction of the final stereocenter was carried out by conjugate addition of copper-complexed pentylmagnesium bromide onto the π -system of the vinylogous amide **33**. This reaction provided piperidone **34** in excellent yield. The stereochemical configuration about the newly formed C-2 carbon center of **34** could not be easily determined through conventional NMR spectroscopic techniques, necessitating preparation of a crystalline derivative for X-ray analysis. Thus, condensation of **34** with tosyl hydrazine afforded the corresponding hydrazone **35** [38]. X-ray analysis of **35** confirmed that the 1,4-cuprate addition to **33** had given rise to the correct axial side-chain stereochemistry at C-2. This result can be attributed to the steric constraints imposed by the dihydropyridi-

none ring **33**, which results in an axial trajectory for *n*-pentyl addition to π -array [42]. Control of the configuration at C-2 of ketone **34** represented an opportunity to specifically prepare the PHTx derivative 2,7,8-*epi*-PHTx. Toward this end, trapping the enolate anion derived from ketone **34** with *N*-phenyltriflamide [43] followed by subsequent catalytic hydrogenation resulted in the facile removal of the carbonyl functionality at C-4. This was followed by LAH reduction which provided benzylamine **36**. The MOM ether group was removed to give alcohol **37** in good yield, which upon hydrogenolysis of the benzyl group completed the total synthesis of (\pm)-2,7,8-*epi*-PHTx (**20**) (Scheme 14).



Scheme 14 Final approach to (\pm)-2,7,8-*epi*-PHTx.

This particular route to 2,7,8-*epi*-PHTx also represents an excellent opportunity to intercept several intermediates previously reported by the Godleski [40] and Corey [44] groups en route to (\pm)-deamyl-PHTx and (\pm)-PHTx. In this regard, ketone **32** was first converted to the corresponding enol triflate prior to catalytic hydrogenation and was then subjected to LAH reduction to furnish benzylamine **38** (Scheme 15). Trimethylsilylbromide-mediated MOM deprotection provided Godleski alcohol **39**, thereby formally intercepting this investigator's route to (\pm)-deamyl-PHTx (**40**) [40]. The isolation of intermediate **39** also represents an indirect formal synthesis of (\pm)-PHTx since this same compound had been previously synthesized from (\pm)-deamyl-PHTx (**40**) by Corey and co-workers in the mid-1970s [44].



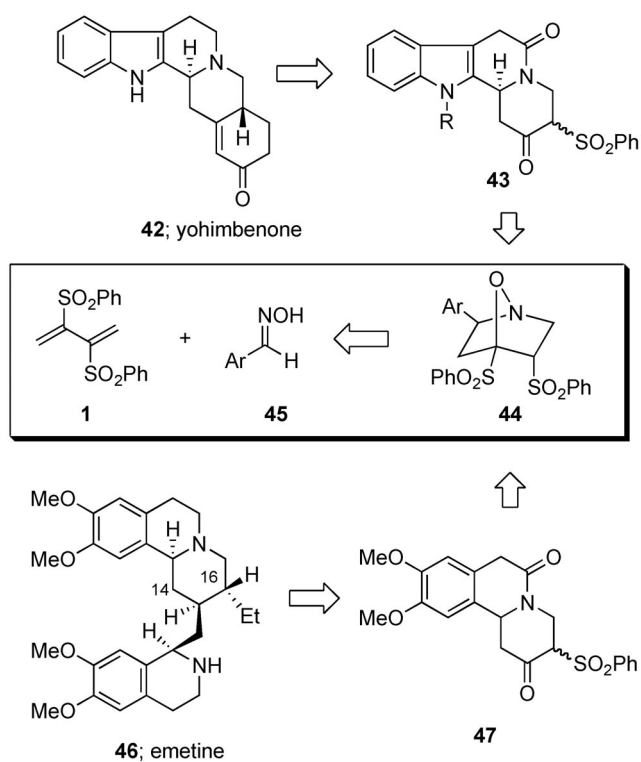
Scheme 15 Formal synthesis of (±)-deamyl-PHTx and (±)-PHTx.

Synthesis of benzo[a]quinolizine and indolo[a]quinolizine scaffolds

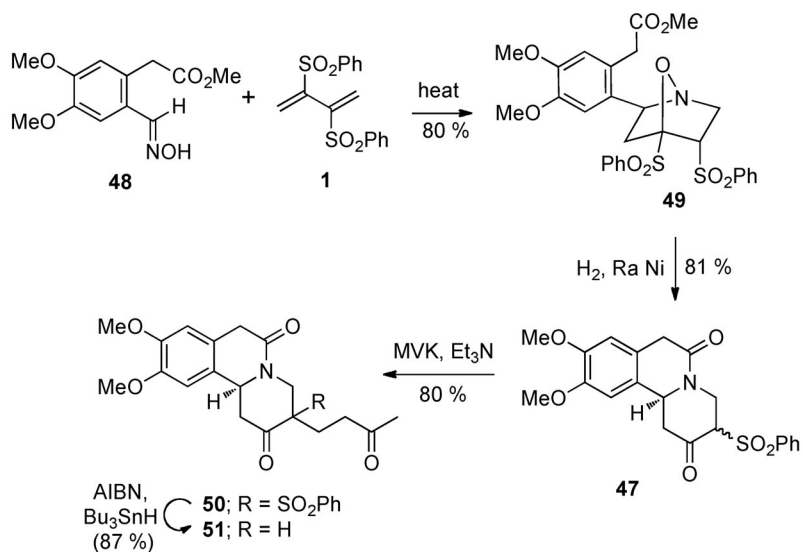
Because of their clinical importance as anti-hypertensive agents, alkaloids isolated from the West African evergreen *Pausinystalia yohimbe* have emerged as important pharmacological agents, particularly the pentacyclic alkaloid (±)-yohimbenone (**42**) [45]. The roots derived from *C. ipecacuanha* have been used for centuries as an emetic, and have also been found to show antiemetic activity [46]. As part of our research employing cascade strategies for alkaloid synthesis, we felt that the *tandem Michael addition/dipolar cycloaddition cascade* had high potential of being utilized as an entry to this class of alkaloids. The advantage of this reaction platform is that it generates a vestigial phenylsulfonyl group (i.e., **43** and **47**) that allows for further synthetic elaboration through site-specific enolate chemistry. As an initial model for an eventual yohimbenone synthesis, we first undertook a formal synthesis of (±)-emetine (Scheme 16) [47].

Oxime **48** was readily available from commercial 2-(3,4-dimethoxyphenyl)acetic acid and was treated with phenylsulfonyldiene **1** so as to generate cycloadduct **49** (80 % yield). By analogy to previous results encountered with several aldehyde oximes, the aryl group prefers to exist in an *endo*-orientation in the newly formed cycloadduct **49** (Scheme 17).

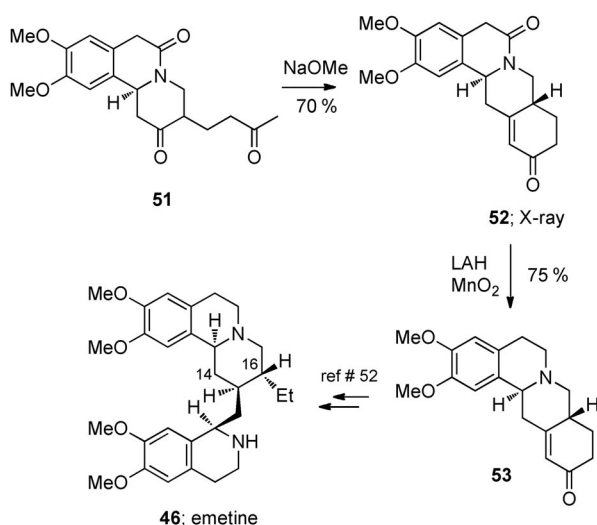
Subjection of cycloadduct **49** to reduction using Raney nickel under an atmosphere of hydrogen triggered a cyclization cascade sequence whereby cleavage of the *N*-*O* bond was followed by spontaneous intramolecular acylation of the nitrogen atom with the proximal ester group to furnish **47** in excellent yield as a 1:1-mixture of diastereomers. In order to obtain synthetically useful quantities of the required late-stage intermediates, the key Robinson annulation reaction relied upon a specific order of operations [48]. Thus, conjugate addition of methyl vinyl ketone (MVK) in the presence of catalytic triethylamine to **47** afforded a 1:1-mixture of the diastereomeric ketones **50** in 80 % yield [49]. A tin-mediated phenylsulfonyl reduction of **50** furnished **51** as a 1:1-mixture of diastereomeric amides. Finally, subjecting **51** to an intramolecular aldol condensation-dehydration sequence using sodium methoxide gave rise to a 5:1-mixture of diastereomeric tetracycles **52**. The major diastereomer corresponded to that of the natural configuration of the alkaloid emetine, and this was confirmed by X-ray crystallographic analysis (Scheme 18).



Scheme 16 Approaches to (±)-yohimbenone and (±)-emetine.

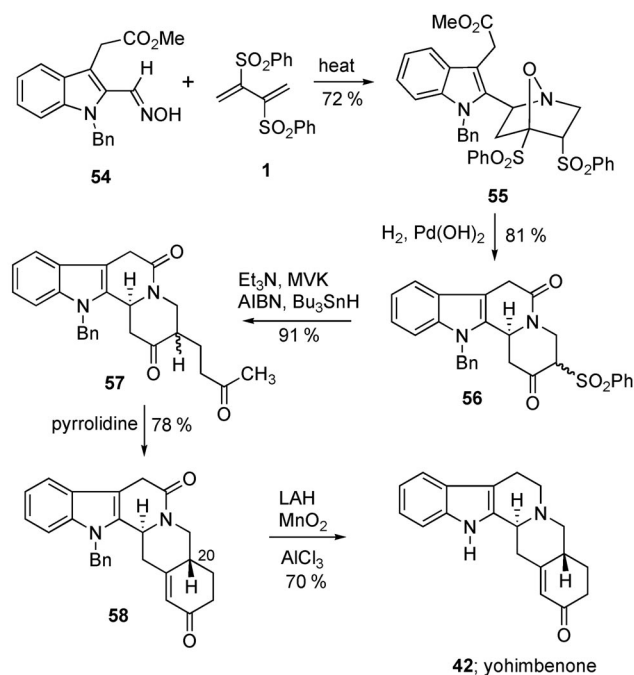


Scheme 17 Michael addition/dipolar cycloaddition approach to (±)-emetine.



Scheme 18 Robinson annulation and formal synthesis of (\pm)-emetine.

The 5:1-mixture of diastereomers was easily separated chromatographically, and the major isomer **52** was subjected to LAH reduction which not only reduced the amide carbonyl group, but also delivered an over-reduced allylic alcohol as an undesired side product [50]. However, a subsequent manganese oxidation of the crude reduction mixture cleanly converted the mixture to the known Takano enone **53** [51,52], thereby resulting in a formal synthesis of (\pm)-emetine. The related alkaloid (\pm)-yohimbenone was also synthesized using a similar approach. Thus, treatment of oxime **54** with phenylsulfonyl diene **1** resulted in a smooth *conjugate addition/dipolar cycloaddition cascade* to produce cycloadduct **55** in 72 % yield. Reductive *N–O* cleavage of **55** using Pearlman's catalyst with acetic acid in ethyl acetate under an atmosphere of hydrogen gas afforded the key ABCD yohimbenone construct **56** in 81 % yield as a 2:1-mixture of diastereomers. As was the case in the emetine synthesis, MVK was added to compound **56** and this was followed by reductive removal of the phenylsulfonyl group to furnish **57** in excellent yield for the overall sequence of reactions. Unlike the emetine approach, we found that pyrrolidine was much more efficient than sodium methoxide for converting **57** into the desired Robinson product **58**. With formation of the E-ring secured, amide reduction of **58** followed by an oxidation of the allylic alcohol and a subsequent debenzoylation using AlCl_3 gave (\pm)-yohimbenone (**42**) in 72 % yield for the three-step sequence (Scheme 19).



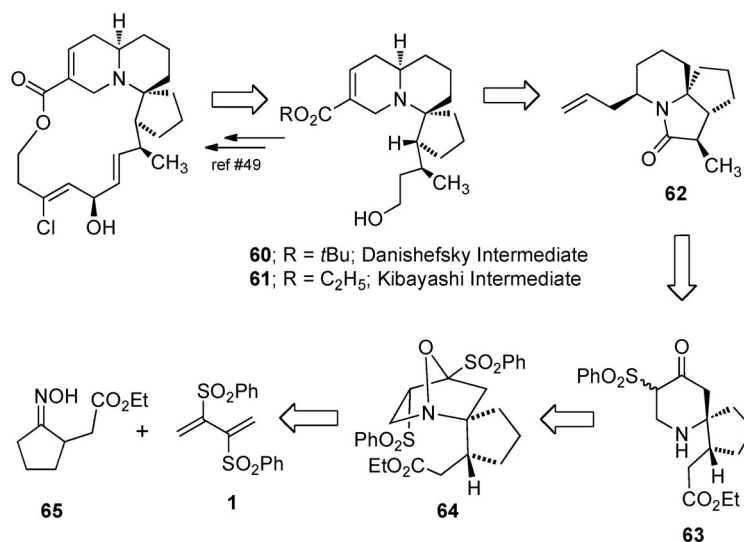
Scheme 19 Total synthesis of (±)-yohimbenone.

Preparation of the azatricyclic core of (±)-halichlorine

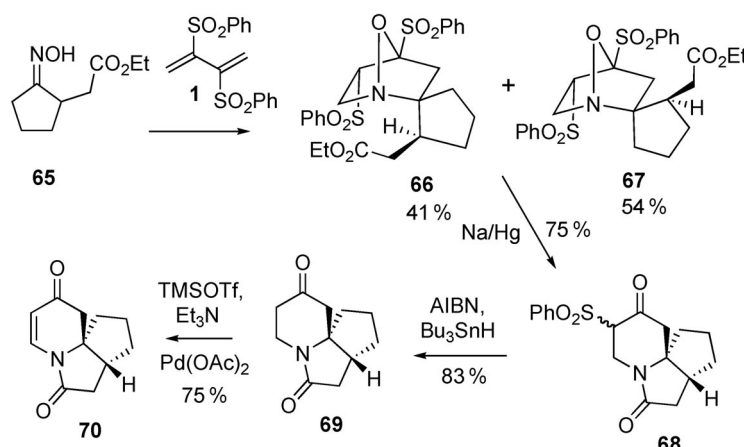
Since Danishefsky first reported the total synthesis of halichlorine (**59**) in 1999 [53,54], a flurry of synthetic efforts devoted to accessing this naturally occurring marine alkaloid have been reported [55]. While the primary alkaloid isolated from the marine sponge *Halichondria okadai* Kadota exhibits remarkable vascular cell inhibition [56,57], substructures of this complex natural product, particularly in the azacyclic-containing region of the molecule, have garnered the attention of several research groups. As a consequence of our interests in using cascade chemistry for alkaloid synthesis, a *Michael addition/dipolar cycloaddition cascade* was envisioned as a method to access an advanced intermediate reported by Feldman (**62**) [58], which would constitute a formal synthesis of (±)-halichlorine (**59**) (Scheme 20).

In order to establish the feasibility of this approach toward halichlorine, oxime **65** was prepared and treated with phenylsulfonyldiene **1** which afforded a 1.3:1-mixture of the diastereomers of the expected cycloadducts (i.e., **66** and **67**) in 95% yield (Scheme 21) [59].

The mixture was reduced with sodium mercury amalgam in order to cleave the *N*-*O* bridge. After the reduction occurred, the resulting secondary amine underwent spontaneous intramolecular acylation to furnish azatricyclic **68** as a mixture of diastereomers. Desulfonylation using tributyltin hydride and AIBN followed by a Saegusa oxidation gave the vinylogous amide **70**. This 2,3-dihydropyridinone proved to be somewhat resistant to conventional 1,4-addition using a variety of organometallic reagents, preferring to give the alternative 1,2-addition product instead. However, conjugate addition to the β -carbon of **70** was eventually achieved via the addition of allyl stannane in the presence of TMSOTf which furnished **71** in 78% yield as a 15:1-mixture of diastereomers. The preferred configuration at the C-5 position arises by approach of the nucleophilic reagent from the convex face of **70**, setting the requisite geometry at this carbon center. The keto group in **71** was protected as the 1,3-dithiane in order to allow for exclusive methylation at the γ -lactam position. Thus, reaction of the enolate anion derived from amide **72** with methyl iodide gave rise to the methylated amide **73** derived by attack from the least hin-

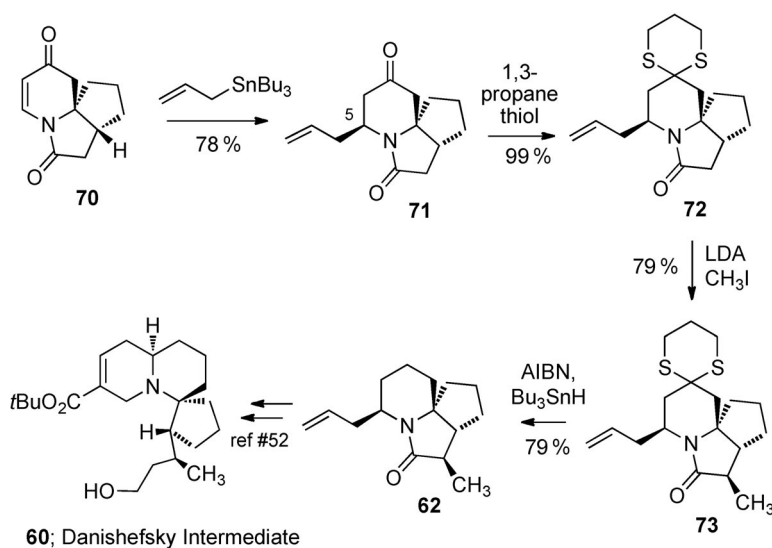


Scheme 20 Michael addition/dipolar cycloaddition entry to the (±)-halichlorine azacyclic core.



Scheme 21 Dienyl sulfone entry into (±)-halichlorine tricyclic enone core.

dered face of **72**. The resulting dithiane was reduced with tributyltin hydride and AIBN to furnish Feldman's intermediate **62** [58], which had previously been taken on to (±)-halichlorine (**59**) (Scheme 22).



Scheme 22 Final approach to azatricyclic skeleton of (±)-halichlorine.

CONCLUSION

In conclusion, tandem cycloaddition chemistry continues to be of great interest both mechanistically and synthetically. The many structurally diverse and highly successful examples of heterocyclic ring formation cited in this article clearly indicate that tandem cycloaddition cascades have evolved as an important strategy in heterocyclic synthesis. In particular, the alkaloid targets summarized in this article have been achieved through the use of a *Michael addition/dipolar cycloaddition cascade* using bis-2,3-diphenylsulfonyl butadiene, and this approach represents a versatile and easy entry to 2,2-disubstituted piperidone and piperidine-containing systems.

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