Heterocyclic and Acyclic Azadiene Diels-Alder Reactions: Total Synthesis of Nothapodytine B

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A summary of the applications of the inverse electron demand Diels-Alder reactions of heterocyclic and acyclic azadienes in the total synthesis of natural products is provided and a recent application in the total synthesis of nothapodytine B (mappicine ketone) is presented in detail.

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As the exploration of the properties of complex natural products becomes increasingly more powerful with advances in their screening and evaluation and as structural details of their interaction with biological targets become more accessible, the opportunities for providing unique solutions to complex biological problems have grown. A powerful complement to the examination of the naturally-derived agents themselves is the preparation and examination of key partial structures, agents containing deep-seated structural modifications, and their corresponding unnatural enantiomers. Well conceived deep-seated structural modifications may be used to address the structural basis of their interactions with biological targets and to define fundamental relationships between their structure and properties.

This is especially important in the case of natural products that are identified in directed screening efforts. In contrast to the study of the role of primary metabolites, the presence of secondary metabolites and the perceived value of an identified lead can be misinterpreted. Nature, with its vast array of secondary metabolites, provides a diverse library of small organic molecules for screening. Not always, and perhaps only rarely, is the role of the identified natural product related to the biological basis of the screening responsible for its identification. Consequently, it may be inaccurate to assume that nature has optimized or even devised the agent for the purposes for which the screening assay was set up. Rather, it may be more accurate to recognize that nature has only provided a novel lead that has not yet been optimized. The challenging problem remains to understand the beautiful solution and subtle design elements that nature has provided in the form of a natural product and to extend the solution through rational design elements to provide more selective or more potent agents designed specifically for the target under investigation.

Central to such studies is the development of dependable synthetic strategies and the advent of new synthetic methodology to permit the preparation of the natural products, key partial structures, and their analogs incorporating deep-seated structural changes. For nearly 20 years now we have been engaged in studies on the development and applications of inverse electron demand Diels-Alder reactions that continue to provide solutions to a range of complex synthetic problems [1-8]. The efforts have reduced many difficult or intractable synthetic challenges to manageable problems providing an approach not only to the natural product but one capable of simple extrapolation to a series of structural analogs as well. In our own efforts this has provided the opportunity to fully explore the structural origin of a number of natural product's properties and to devise agents with improved selectivity and efficacy.

The Diels-Alder reaction may be classified into one of three types of $\pi 2s + \pi 4s$ cycloaddition reactions: the normal $HOMO_{diene}$-controlled Diels-Alder reaction, the neutral Diels-Alder reaction, and the inverse electron demand or $LUMO_{diene}$-controlled Diels-Alder reaction [9]. Typically, it has been the normal Diels-Alder reaction employing an electron-rich diene and electron-deficient dienophile that has serviced the preparative needs of organic chemistry. By contrast, the inverse electron demand Diels-Alder reaction employing an electron-deficient diene and an electron-rich dienophile has not found as widespread application despite the fundamental rate acceleration, regiocontrol, and diastereocontrol available through its use.

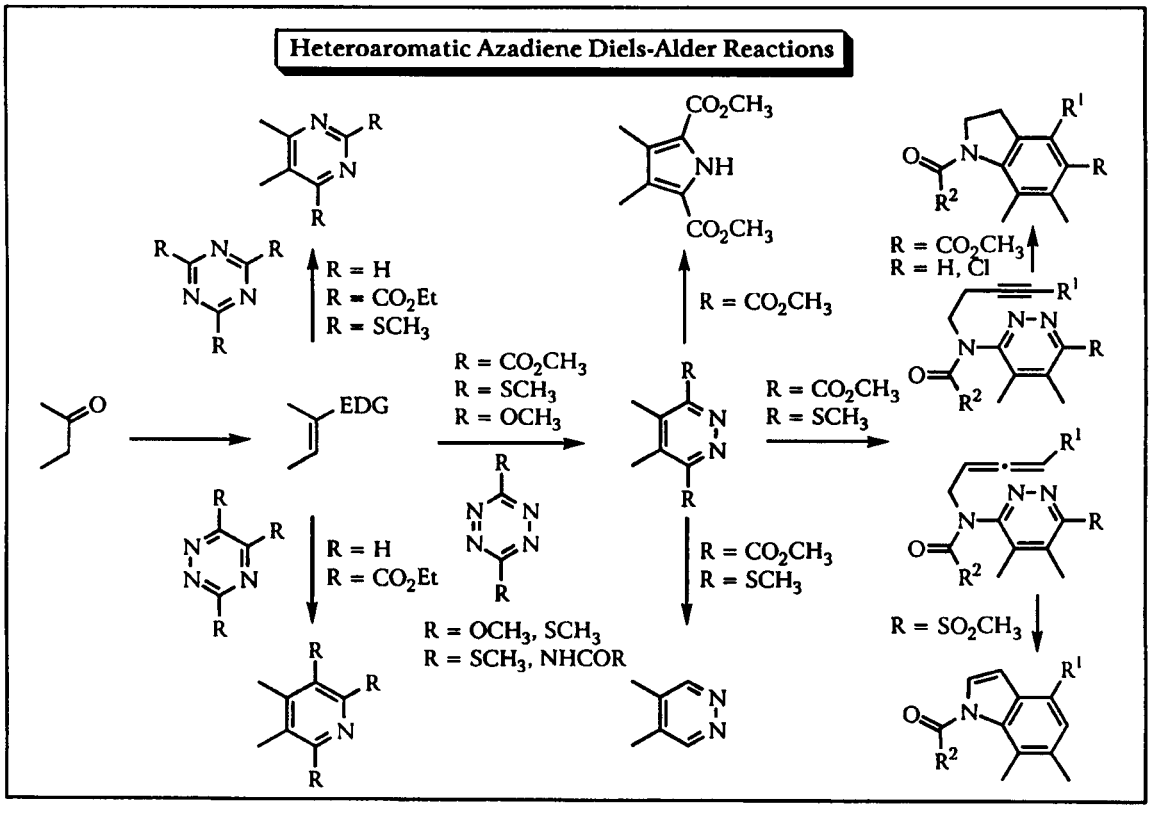
Heteroaromatic Azadienes.

Heteroaromatic systems that possess an electron-deficient azadiene have proven well suited for use in $LUMO_{diene}$-controlled Diels-Alder reactions and it was the recognition of their inherent electron-deficient character that led to the proposed [10], demonstrated [11], and verified [12] rate acceleration that accompanies the reversal of the electronic properties of the Diels-Alder diene/-dienophile partners. This ultimately led to the investigation and development of the inverse electron demand Diels-Alder reaction.

Since this initial work, the participation of a range of electron-deficient heteroaromatic azadienes in inverse electron demand [4 + 2] cycloaddition reactions has been examined in detail [1-8]. The early studies of Sauer and Neunhoeffer with tetrazines and triazines, and the more

recent investigations of our group, Taylor, Warrener, Seitz, Snyder, and others have served to expand on the initial observations of Carboni and Lindsey [11]. Although our own efforts have arisen as a consequence of the opportunities the reactions provide for the introduction of highly functionalized heteroaromatic systems not easily accessed by more conventional methodology, the work has helped define the scope of the heteroaromatic azadiene inverse electron demand Diels-Alder reaction (Scheme 1).

Scheme 1



Our investigations on the scope of the 1,2,4,5-tetrazine [13-19], 1,2,4-triazine [20-24], 1,3,5-triazine [25-28], and intramolecular 1,2-diazine Diels-Alder reactions [17,29] and their applications in the total synthesis of streptonigrin [30], lavendamycin [31], OMP [14], prodigiosin [32], isochrysohermidin [33], *cis*- and *trans*-trikentrin A [34], (+)- and *ent*-(-)-CC-1065 [35], P-3A [36], and bleomycin A_2 [37] have been described and reviewed in detail [1-8] (Figures 1 and 2). A number of additional applications including polycitone A and phomazarin are presently in progress.

In three instances, the efforts have been extended to the preparation of an extensive series of analogs of the natural products in studies to define the nature and origin of their interactions with duplex DNA. Isochrysohermidin was shown to be only the fourth natural product, or class of natural products, capable of interstrand DNA cross-linking [33]. It is the oxidative degradation product of a purple pigment that contributes to the intense color of chrysanthemums. It is unlikely that its potentially productive DNA cross-linking properties are related to its selective generation in Nature.

An extensive series of CC-1065 and duocarmycin analogs have been prepared and examined in efforts to define the structural origin of the sequence selectivity of their characteristic DNA alkylation reaction (Figure 3) and, more recently, the source of catalysis for the reaction with duplex DNA [38-45]. Our efforts have suggested that the activation for DNA alkylation, which proved independent of *p*H, arises from a DNA binding-induced conformational change in the agents which twists the linking amide disrupting the alkylation subunit vinylogous amide stabilization [46-48]. This leads to preferential activation within the narrower, deeper AT-rich minor groove sites where the inherent twist in the linking amide and helical rise of the bound agent is greatest. Thus, shape-selective recognition entailing preferential AT-rich noncovalent binding in conjunction with shape-dependent catalysis derived from the induced twist in the linking amide combine to restrict S_N2 alkylation to accessible adenine N3 sites within the preferred binding sites (Figure 4).

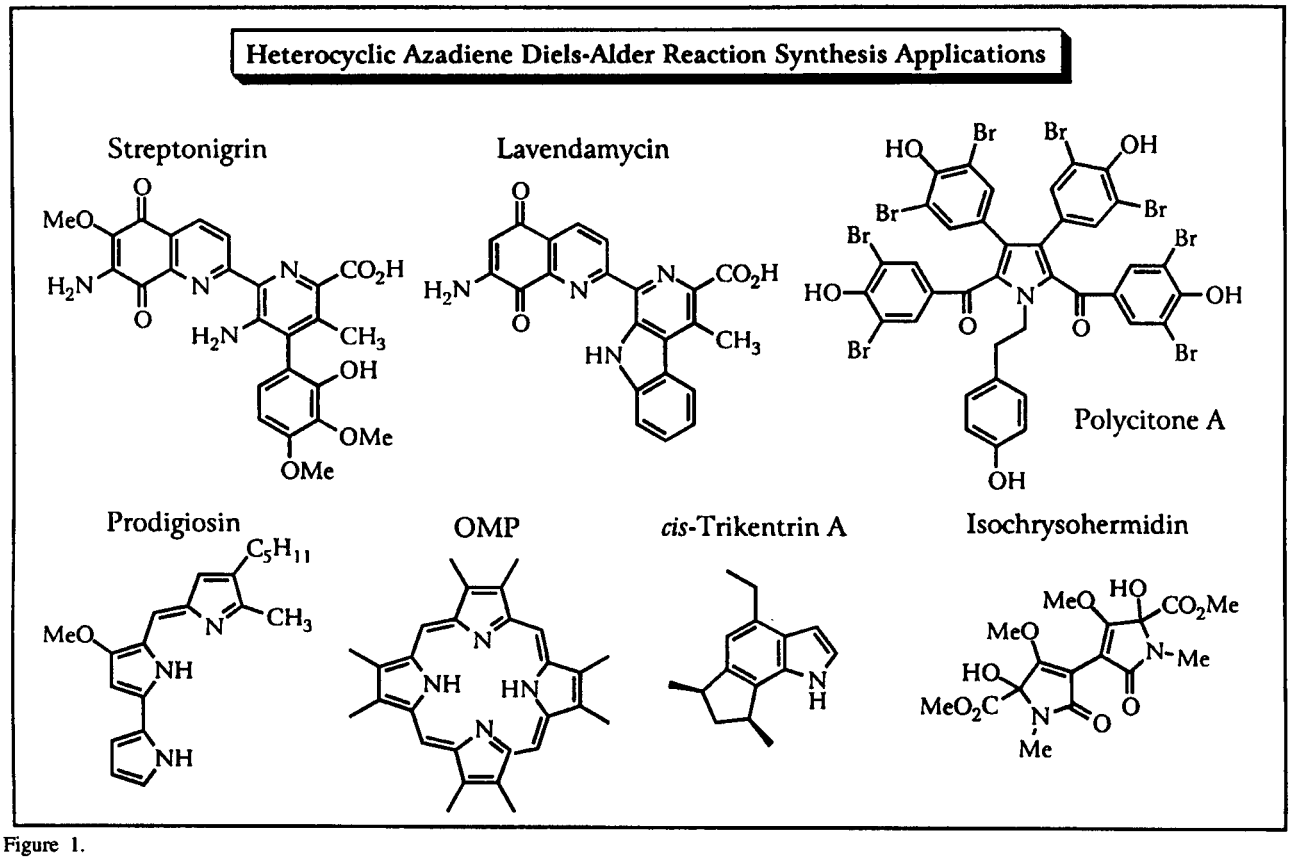


Figure 1.

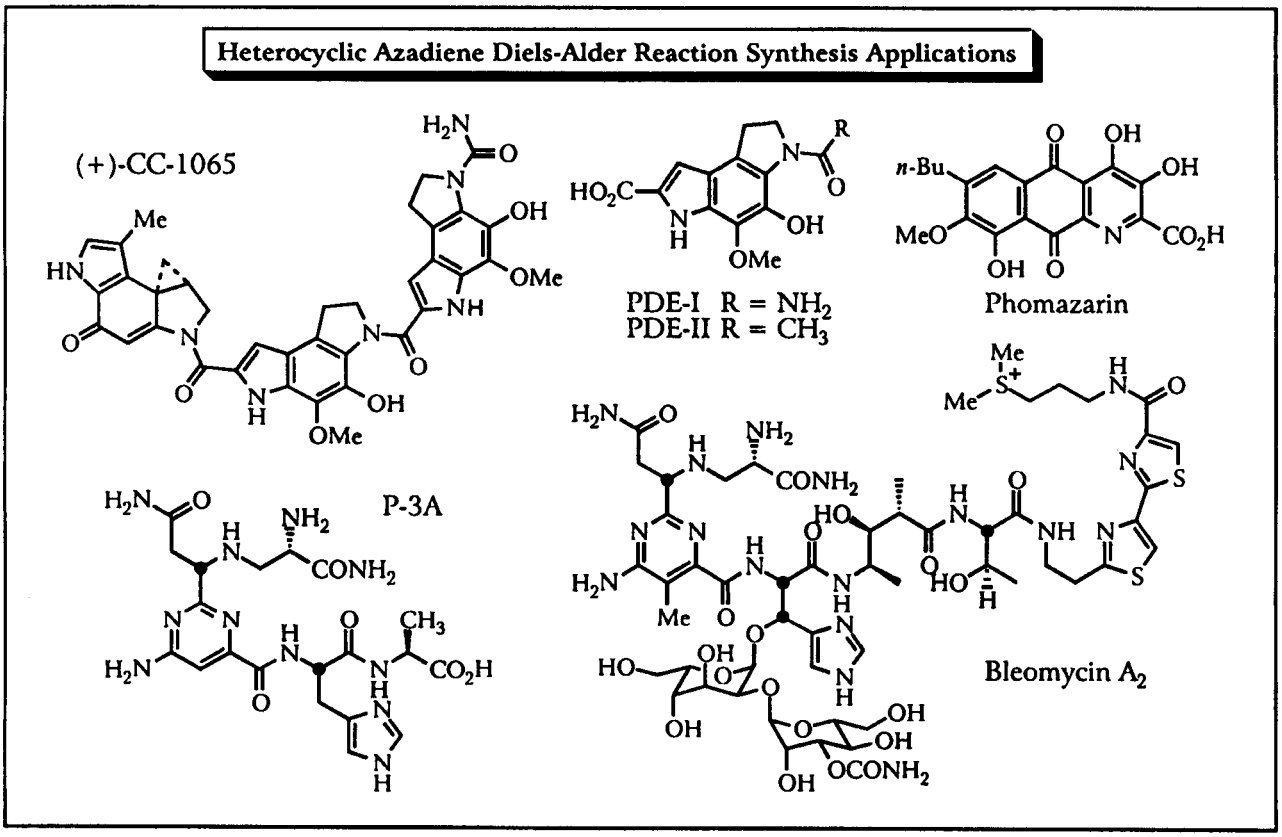


Figure 2.

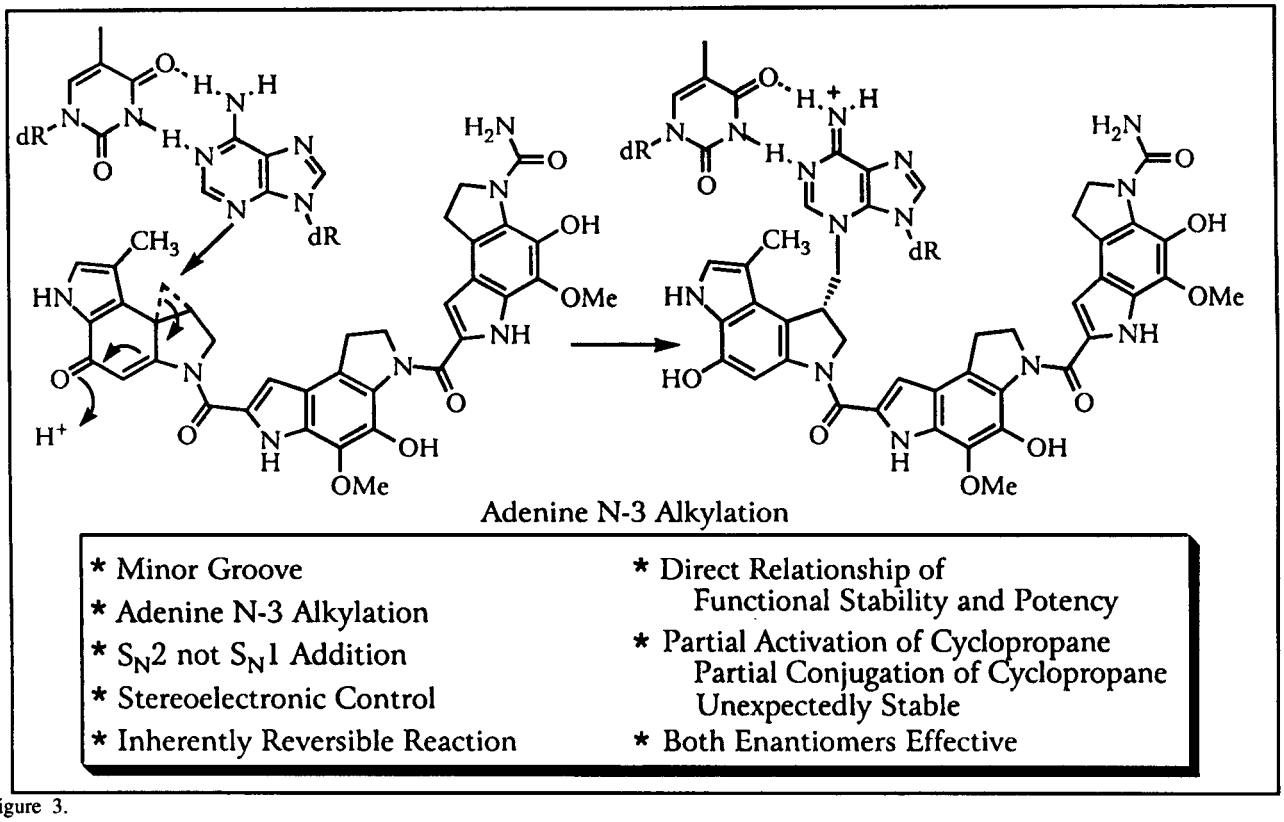


Figure 3.

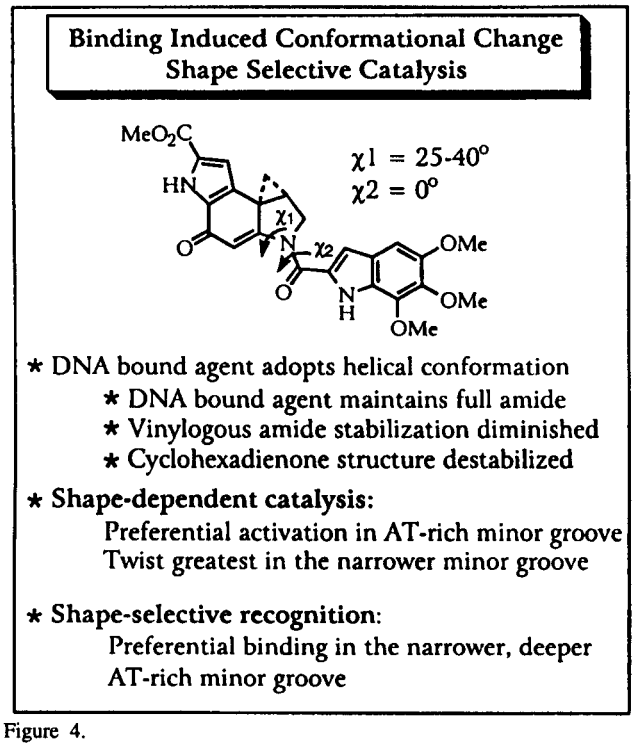


Figure 4.

Similarly, an extensive series of bleomycin A_2 analogs have been prepared and examined. Most notable were the analogs in which the C4 amino group of the pyrimidoblamic acid subunit had been removed or replaced with a dimethylamino group [49]. The results of their examination seem to confirm that the basis of the metal ion and oxygen dependent DNA cleavage selectivity resides in a minor groove triplex-like hydrogen bonding recognition between the bleomycin metal binding domain and guanine at the 5'-GPu cleavage sites first implicated in the Stubbe structural studies [50] (Figure 5).

Acyclic Azadiene Diels-Alder Reactions.

The rate of the Diels-Alder reaction has been correlated with the lowest HOMO-LUMO separation attainable by the diene/dienophile reaction partners. Consequently, structural and electronic factors which lower the appropriate HOMO-LUMO separation accelerate the rate of [4 + 2] cycloaddition. This recognition of the importance of the complementary choice of diene/dienophile partners and its mechanistic origin has played a major role in the development, predictive success, and application of the Diels-Alder reaction.

In general, the 4π participation of simple α,β-unsaturated imines, electron-deficient 1-aza-1,3-butadienes, is rarely observed and typically suffers low conversions, competitive imine addition, or imine tautomerization precluding [4 + 2] cycloaddition [6-8]. In the conduct of our studies, we have examined approaches to the predictable control of the 4π participation of 1-aza-1,3-butadienes in Diels-Alder reactions [51-55]. The complementary N1 or C3 substitution of an α,β-unsaturated imine with an elec-

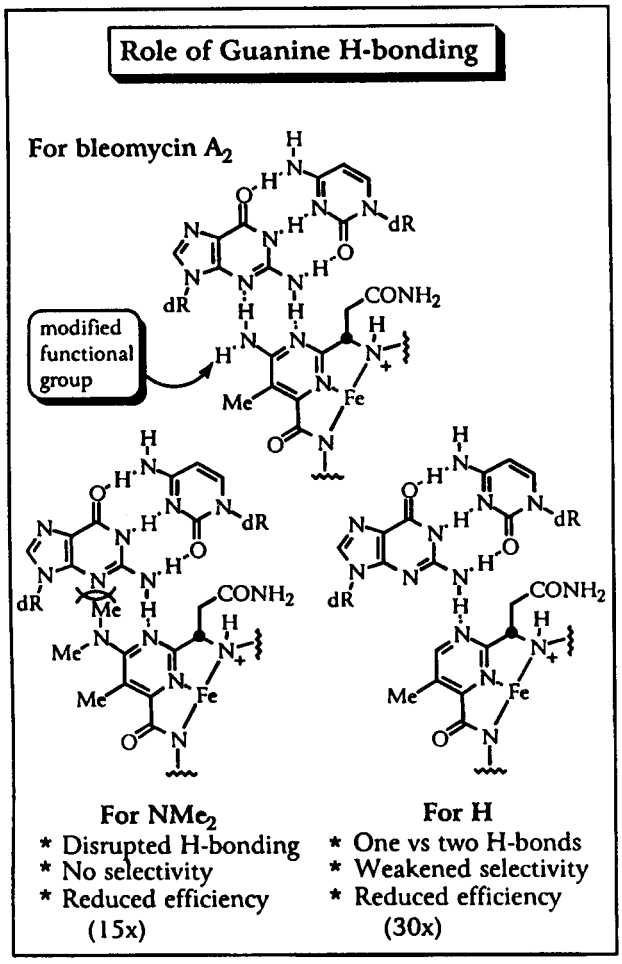


Figure 5.

tron-withdrawing substituent would be expected to accentuate its inherent electron-deficient character and accelerate its participation in $LUMO_{diene}$-controlled Diels-Alder reactions with electron-rich dienophiles. In addition, a bulky electron-withdrawing N1 substituent would be expected to preferentially decelerate 1,2-imine addition and convey stability to the enamine product under the reaction conditions while enhancing the electron-deficient character of the diene. The investigation of the [4 + 2] cycloaddition reactions of *N*-sulfonyl-1-aza-1,3-butadienes revealed the general nature of their dependable participation in such Diels-Alder reactions (Figure 6). In addition to exhibiting a behavior characteristic of concerted cycloaddition reactions, it was unusually diastereoselective for formation of the *endo* adduct. This may be attributed to both stabilizing secondary orbital interactions as well as a transition state anomeric effect accessible only in the *endo* boat transition state.

The complementary addition of an electron-withdrawing group to C3 further lowers the diene LUMO, accelerates the 1-azadiene Diels-Alder reaction (≤25°), further enhances the expected regioselectivity, and maintains the superb *endo* diastereoselectivity (≥20:1). Similarly, the *noncomplementary* C2 or C4 addition of an electron-withdrawing group also lowers the 1-azadiene LUMO, accelerates the 1-azadiene Diels-Alder reaction (25°), and maintains the superb *endo* diastereoselectivity (≥20:1) without affecting the inherent regioselectivity of the [4 + 2] cycloaddition reaction.

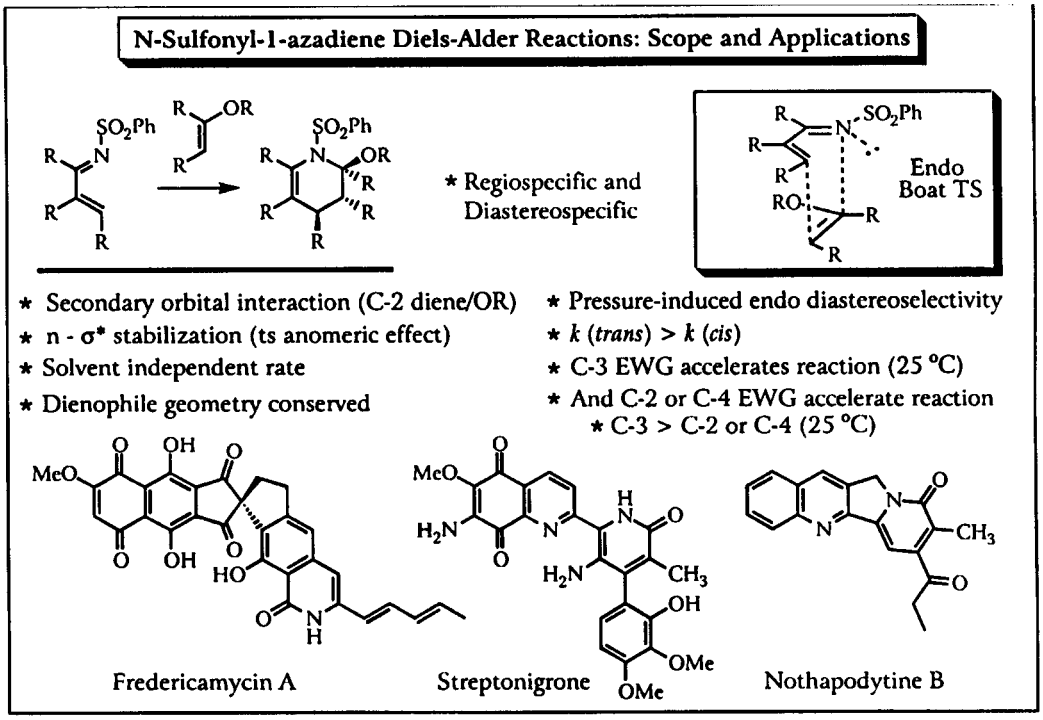


Figure 6.

The application of the methodology in the synthesis of complex natural products has proven unusually successful. In addition, the completed total syntheses of streptonigrone [56], fredericamycin A [57], and nothapodytine B [58] highlight nicely the impact of an azadiene C2, C3, and C4 electron-withdrawing group in providing a room-temperature, [4 + 2] cycloaddition reaction. Our total synthesis of streptonigrone [56], which complements our earlier efforts on streptonigrin, was based on a room-temperature inverse electron demand Diels-Alder reaction of a *N*-sulfonyl-1-azadiene in a reaction that by design was accelerated through the complementary substitution of the diene with a C3 electron-withdrawing group. Thus, the diene C3 carboxylate served to accelerate the rate of the [4 + 2] cycloaddition reaction, offered a convenient manner to protect the D-ring phenol, and served as the necessary functionality to permit introduction of the pyridone C-ring amine (Figure 7).

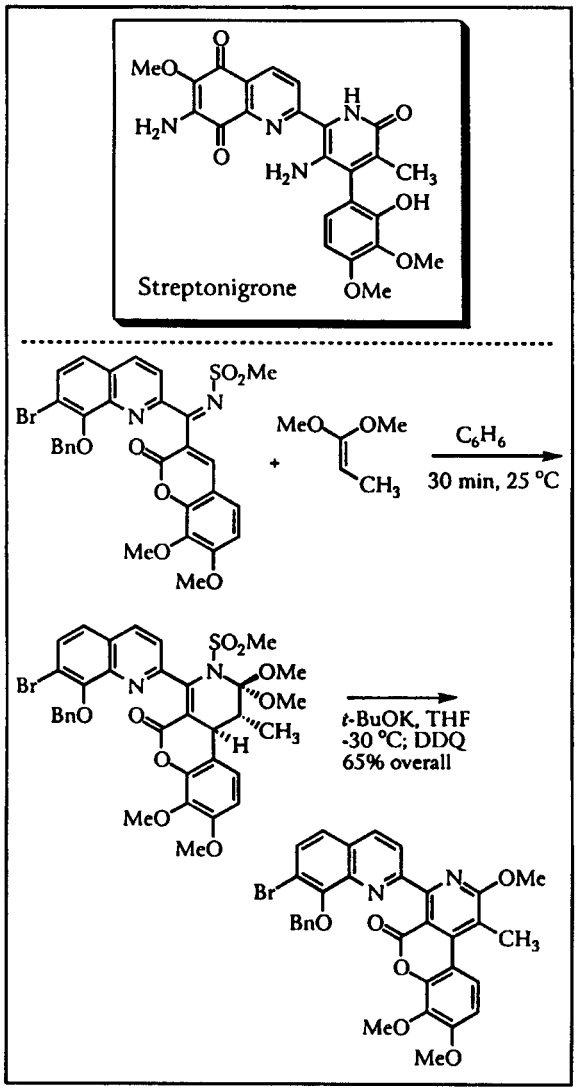


Figure 7.

Fredericamycin A, a structurally unique and potent antitumor antibiotic isolated from *Streptomyces griseus*, has been the subject of extensive investigation since its structure determination by single-crystal X-ray analysis after extensive spectroscopic studies failed to resolve tautomeric structures. Fredericamycin A exhibits potent cytotoxic activity, efficacious antitumor activity, and inhibits procaryotic RNA and protein synthesis earlier and to a greater extent than DNA synthesis. Recent studies have demonstrated that fredericamycin A inhibits both topoisomerase I and II at biologically relevant concentrations and additional DNA processing enzymes at higher concentrations. This latter observation contrasts the report that the agent may not interact with DNA suggesting direct enzyme inhibition or selective stabilization of a tertiary complex of DNA, topoisomerase, and fredericamycin A. We have detailed a convergent total synthesis of fredericamycin A in efforts to provide the natural product and key agents necessary to address the origin of its biological properties [57]. Our efforts provided natural and *ent*-fredericamycin A as well as a set of important partial structures of the natural product. The key steps of the convergent approach were the implementation of a regiospecific intermolecular chromium carbene benzannulation reaction for AB ring construction, a simple aldol closure for introduction of the spiro[4.4]nonene CD ring system, a room temperature inverse electron demand Diels-Alder reaction of a *N*-sulfonyl-1-aza-1,3-butadiene for assemblage of a pyridone F ring precursor, and a single-step Michael addition-Claisen condensation for annulation of the DE ring system on this pyridone F ring precursor. The deliberate early stage introduction of the pentadienyl side chain increased the convergency of the total synthesis and provided the opportunity to prepare and examine the fully functionalized DEF ring system.

Central to our approach was a concise, four-step synthesis of the DEF ring system employing a Diels-Alder reaction of a *N*-sulfonyl-1-aza-1,3-butadiene followed by a single-step Michael addition-Claisen condensation. The *noncomplementary* addition of the strong electron-withdrawing C2-ethoxycarbonyl group further lowered the inherent low lying LUMO of the *N*-sulfonyl-1-aza-1,3-butadiene to the extent that even a modestly reactive dienophile participated in a room temperature [4 + 2] cycloaddition reaction. This unusually facile reaction at 25° precluded the need for conventional thermal reaction conditions and the competitive diene tautomerization that occured at elevated temperatures.

The most recent application constitutes a total synthesis of nothapodytine B [58]. Nothapodytine B was recently isolated from *Nothapodytes foetida* of which the ethanol extract exhibits significant cytotoxity in the human KB cell line [59]. Nothapodytine B is an oxidized derivative

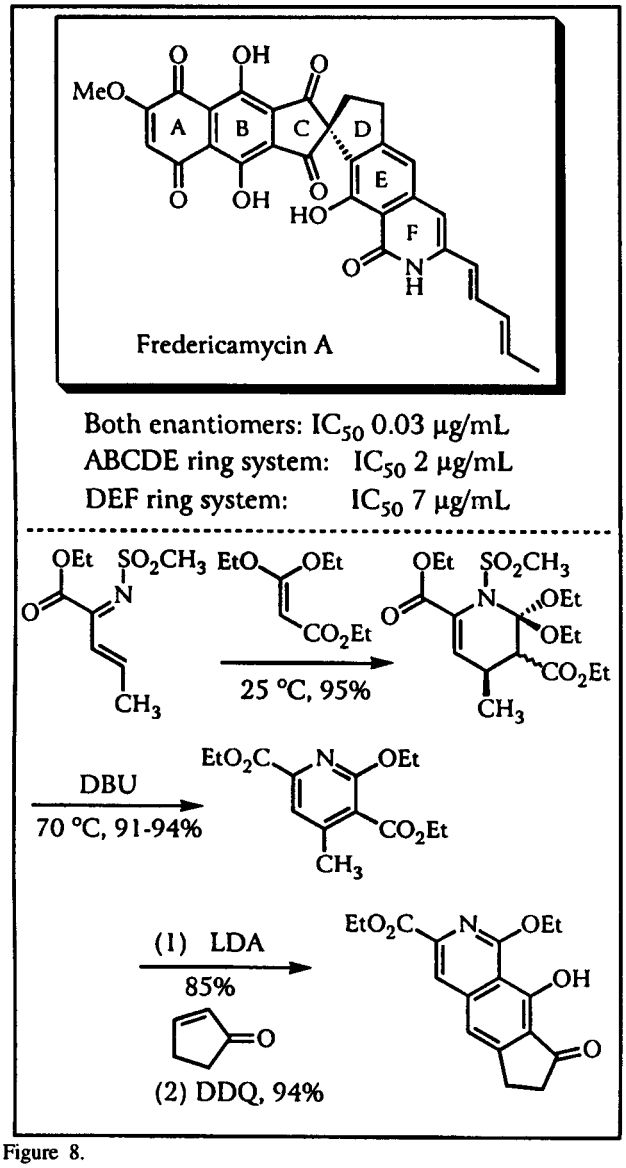


Figure 8.

of mappicine [60] and an E ring decarboxylated analog of camptothecin which is the parent member of a clinically useful class of DNA topoisomerase I inhibitors that exhibit efficacious antitumor activity (Figure 9). Recently, nothapodytine B (mappicine ketone) has been identified as an exciting antiviral lead with selective activities against HSV-1, HSV-2, and human cytomegalovirus (HCMV) with PR_{50}'s of 2.9, 0.5, and 13.2 μ*M*, respectively. Because the antiviral mechanism of nothapodytine B is distinct from that of Acyclovir (ACV) as demonstrated by the observations that ACV-resistant HSV-1 and HSV-2 are inhibited by nothapodytine B (1) and that nothapodytine B-resistant mutants remain sensitive to ACV, it can be used with ACV cooperatively.

In conjunction with synthetic efforts on this important class of naturally occurring alkaloids, we recently detailed concise total syntheses of nothapodytine B and mappicine. Central to our approach was the implementation of a room-temperature, inverse electron demand Diels-Alder reaction of a *N*-sulfonyl-1-aza-1,3-butadiene for the introduction of the pyridone D ring with assemblage of the full carbon skeleton (Figure 10). The nonobvious and noncomplementary incorporation of a C4 electron-withdrawing substituent into the electron-deficient azadiene accelerates its rate of participation in the $LUMO_{diene}$-controlled Diels-Alder reaction to the extent that cycloaddition could be confidently expected to occur at 25° without altering the inherent cycloaddition regioselectivity.

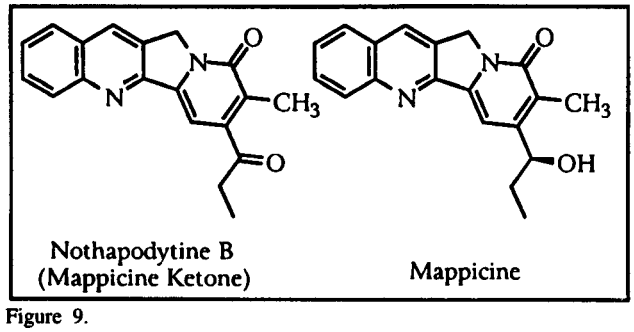


Figure 9.

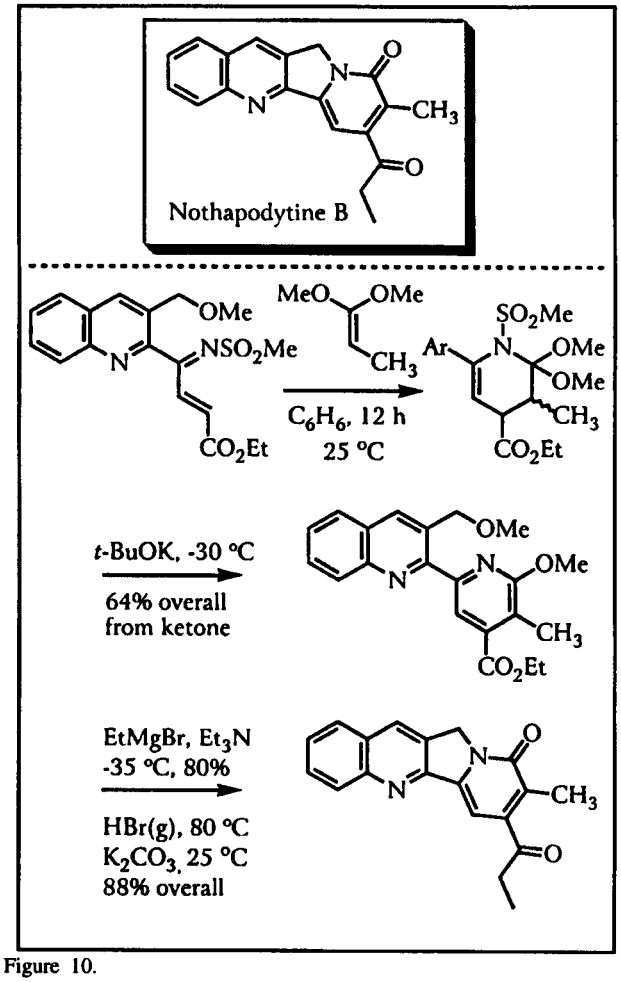


Figure 10.

Wadsworth-Horner-Emmons reaction of a β-keto phosphonate [61] was utilized to provide the α,β-unsaturated γ-keto ester precursor and was carried out with ethyl glyoxylate and *t*-BuOK in DME (-20 to 25°, 5 hours). Two approaches for its conversion to the key *N*-sulfonyl-1-aza-1,3-butadiene required for use in the Diels-Alder reaction were examined (Figure 10). The first two-step procedure requiring ketone conversion to the corresponding oxime (NH_2OH-HCl, EtOH, 25°, 24 hours, 84-92%) followed by oxime *O*-methanesulfinate formation (CH_3SOCl, Et_3N, CH_2Cl_2, 0°, 20 minutes) and *in situ* homolytic rearrangement, failed to provide the azadiene competitive with a direct $TiCl_4$-promoted (1.3 equivalents) condensation with methanesulfonamide (1.5 equivalents, 3 equivalents of Et_3N, CH_2Cl_2, -30 to 25°, 1 hour). This latter one-step procedure afforded the diene in high yield and of sufficient purity that it could be employed directly in the following Diels-Alder reaction. Treatment of the azadiene with 1,1-dimethoxy-1-propene at *room temperature* (C_6H_6, 12 hours) led to the formation of the sensitive [4 + 2] cycloadduct. The deliberate incorporation of the noncomplementary C4 electron-withdrawing substituent resulted in a Diels-Alder cycloaddition that proceeded at 25° presumably by lowering the diene LUMO without altering the inherent [4 + 2] cycloaddition regioselectivity. Due to the expected sensitivity of the Diels-Alder adduct to hydrolysis, subsequent aromatization of the crude adduct (*t*-BuOK, THF, -35°, 30 minutes) was conducted in yields as high as 65% overall from the starting ketone (3 steps) without attempts to isolate the intermediates. Presumably, aromatization proceeds by initial base-catalyzed elimination of methanesulfinic acid followed by elimination of methanol.

Addition of EtMgBr in the presence of a tertiary amine (EtMgBr, Et_3N, toluene, -10°, 4 hours, 79%) proceeded cleanly to give the corresponding ethyl ketone without competitive tertiary alcohol formation by virtue of tertiary amine-promoted ketone enolization. The final conversion to nothapodytine B required deprotection of both the benzylic and pyridone methyl ethers and subsequent cyclization to form the C ring. This was accomplished in one operation by treatment with HBr(g) saturated CF_3CH_2OH (110°, 24 hours) followed by the addition of K_2CO_3 (25°, 1 hour) to provide the natural product directly without isolation of the intermediate benzylic bromide. This approach worked beautifully to give nothapodytine B in 88% overall yield, and the final product proved identical in all respects with the properties reported for authentic material.

Finally, it remains for me to thank the award selection committee for the distinguished honor of being the first recipient of the Katritzky Award in Heterocyclic Chemistry. Many may recognize that for me this is a very special personal as well as professional honor. Our work, that the award recognizes, extends back to the very beginning of my academic career, which entails the efforts of many of the graduate students and postdoctoral fellows I have had the pleasure of working with, and conjure up a number of the most enjoyable memories of my career to date. What many will not recognize is that I have known Professor Katritzky for a number of years now and have had the pleasure of working with him through Pergamon Press and the Tetrahedron Publications. Not only is his name synonymous with heterocyclic chemistry, but those who know him recognize that he possesses a boundless energy and spirit that I am sure led him to spearhead the effort to introduce a junior award in heterocyclic chemistry which now appropriately bears his name.

Acknowledgements.

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