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A review of our studies of the inverse electron demand Diels-Alder reactions of heteroaromatic and acyclic azadienes is presented and the application of a *N*-sulfonyl-1-aza-1,3-butadiene [4 + 2] cycloaddition reaction in the total synthesis of natural and *ent*-fredericamycin A is described in detail.

J. Heterocyclic Chem., **33**, 1519 (1996).

Heteroaromatic Azadienes.

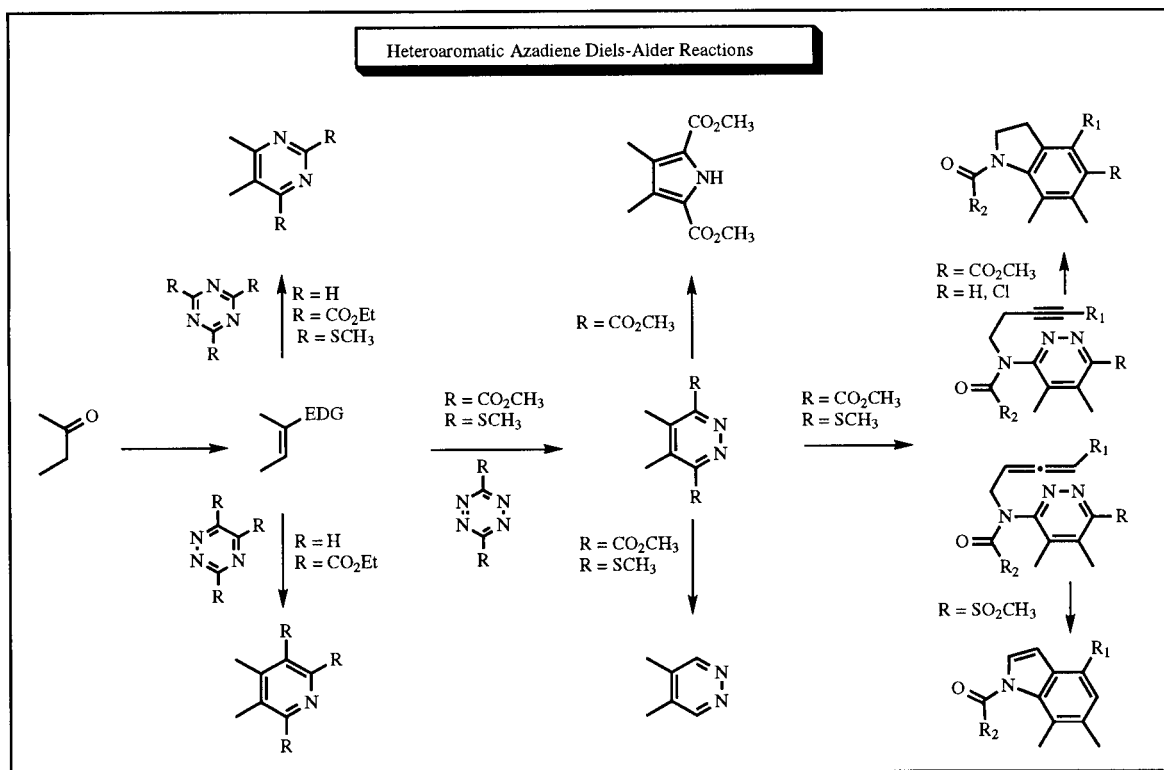
Heteroaromatic systems that possess an electron-deficient azadiene have proven well suited for use in LUMO_{diene}-controlled Diels-Alder reactions and it was the recognition of their inherent electron-deficient character that led to the proposed (1), demonstrated (2), and verified (3) rate acceleration that may accompany the reversal of the electronic properties of the Diels-Alder diene/dienophile partners. This ultimately led to the full investigation and development of the inverse electron demand Diels-Alder reaction.

Since the discovery (2), the participation of a range of electron-deficient heteroaromatic azadienes in inverse electron demand [4 + 2] cycloaddition reactions has been

disclosed and examined in detail (4-8). The early studies of Sauer and Neunhoeffer, and the more recent investigations of our group, Taylor, Warrenner, Seitz, Snyder, and others have served to expand on these early observations. Although our own efforts have arisen as a consequence of the opportunities the reactions provide for the introduction of highly functionalized or highly substituted heteroaromatic systems not easily accessed by more conventional methodology, the work has helped define the full scope of the heteroaromatic azadiene inverse electron demand Diels-Alder reaction (Scheme 1).

Our investigations on the scope of the 1,2,4,5-tetrazine (9-14), 1,2,4-triazine (15-20), 1,3,5-triazine (21-24), and intramolecular 1,2-diazine Diels-Alder reactions (13, 25-26)

Scheme 1



and their applications in the total synthesis of streptogrin (1) (27), lavendamycin (2) (28), OMP (3) (10), prodigiosin (4) (29), isochrysohermidin (5) (30), *cis*- and

trans-trikentrin A (6) (31), (+)- and *ent*(-)-CC-1065 (7) (32), P-3A (8) (33), and bleomycin A₂ (9) (34) have been described in detail (Figures 1 and 2).

Figure 1

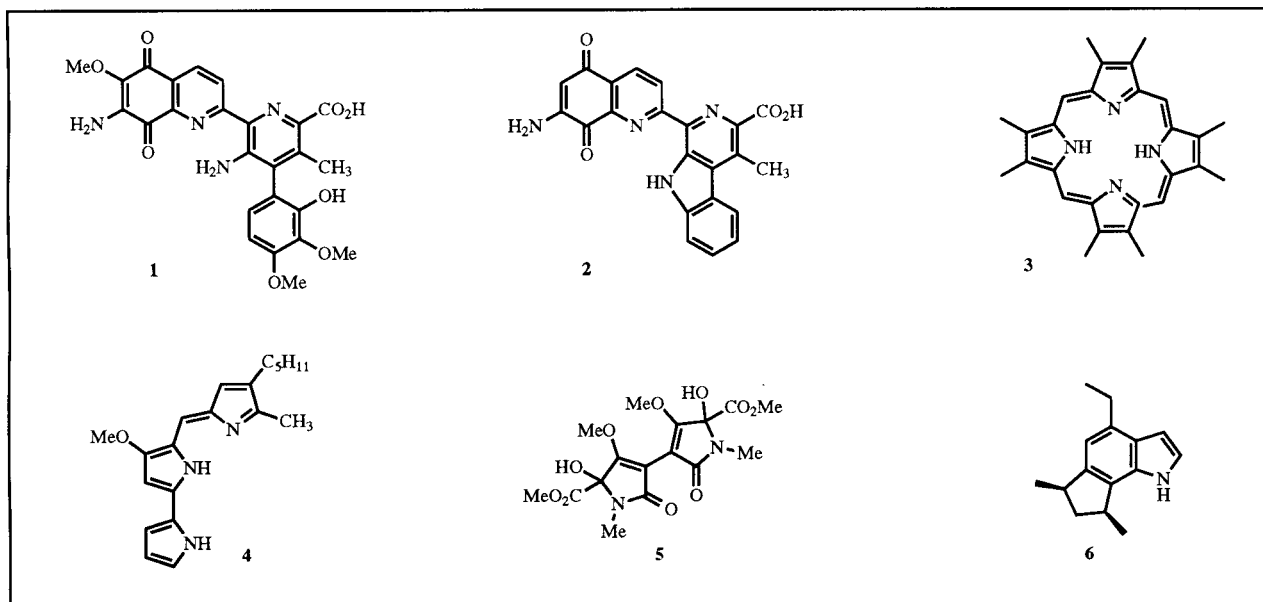
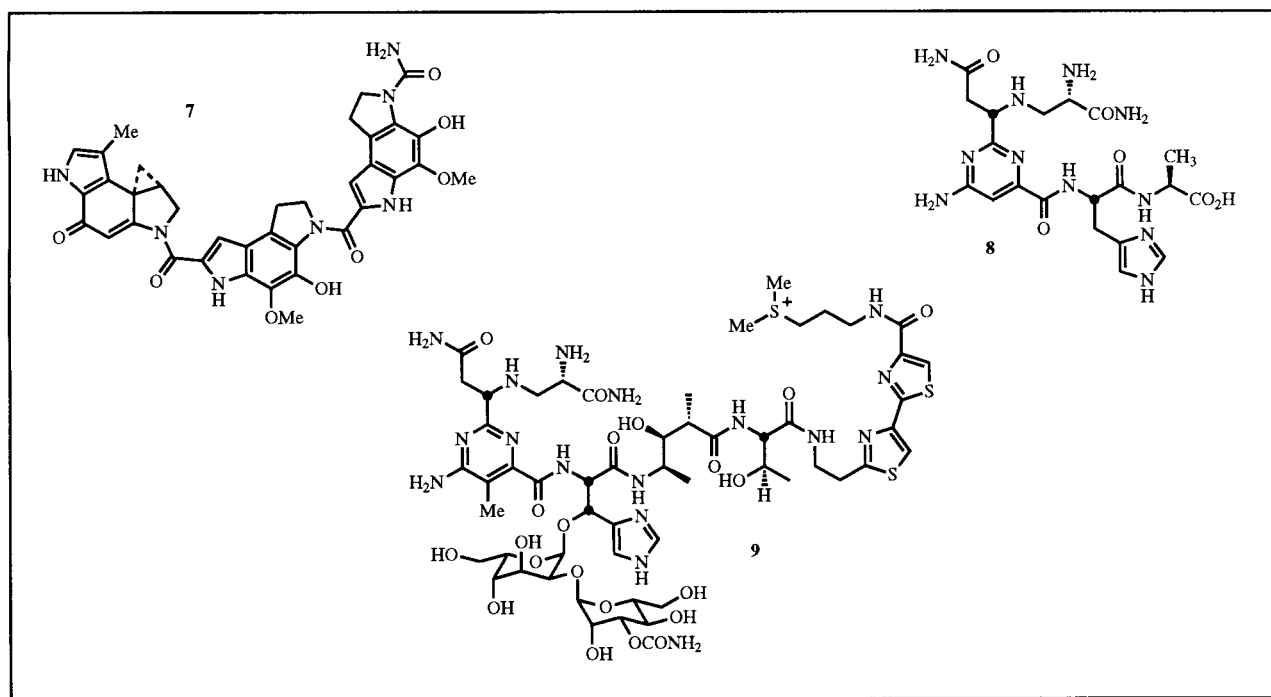


Figure 2

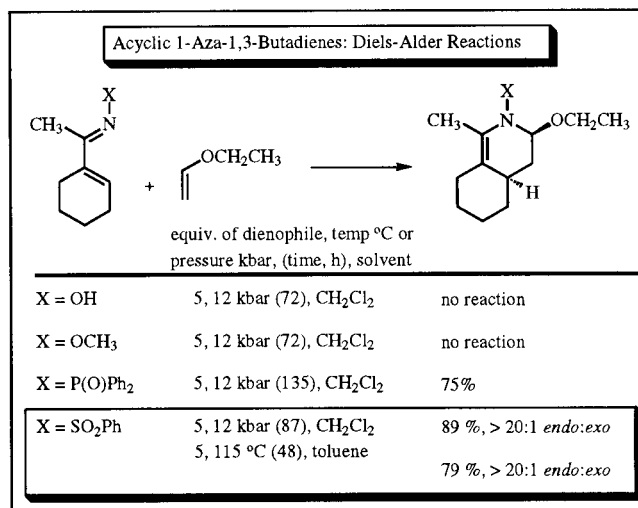


Acyclic Azadiene Diels-Alder Reactions.

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 magnitude of the appropriate HOMO-LUMO separation accelerate the rate of [4 + 2] cycloaddition and this recognition of the mechanistic origin of the complementary choice of diene/dienophile partners has played a major role in the development, predictive success, and application of the normal and inverse electron demand Diels-Alder reactions.

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 (4, 6). In the conduct of our studies, we have examined approaches to the predictable control of the intermolecular 4π participation of 1-aza-1,3-butadienes in Diels-Alder reactions. The complementary N1 or C3 substitution of an α,β -unsaturated imine with an electron-withdrawing substituent would be expected to accentuate their inherent electron-deficient character and accelerate their 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. Initial studies with stable imine derivatives of 1-acetylcyclohexene

Scheme 2



demonstrated that N1 substitution of a 1-aza-1,3-butadiene with bulky electron-withdrawing groups accelerates the rate of Diels-Alder reaction and provided a well-behaved [4 + 2] cycloaddition reaction (Scheme 2) (35).

The investigation of the full scope of the [4 + 2] cycloaddition reactions of *N*-sulfonyl-1-aza-1,3-butadienes has revealed the general nature of the reaction (Figure 3) (35-39).

The complementary addition of an electron-withdrawing group to C3 further lowers the diene LUMO, substantially accelerates the 1-azadiene Diels-Alder reaction (≤ 25 °C), further enhances the expected regioselectivity, and main-

Figure 3

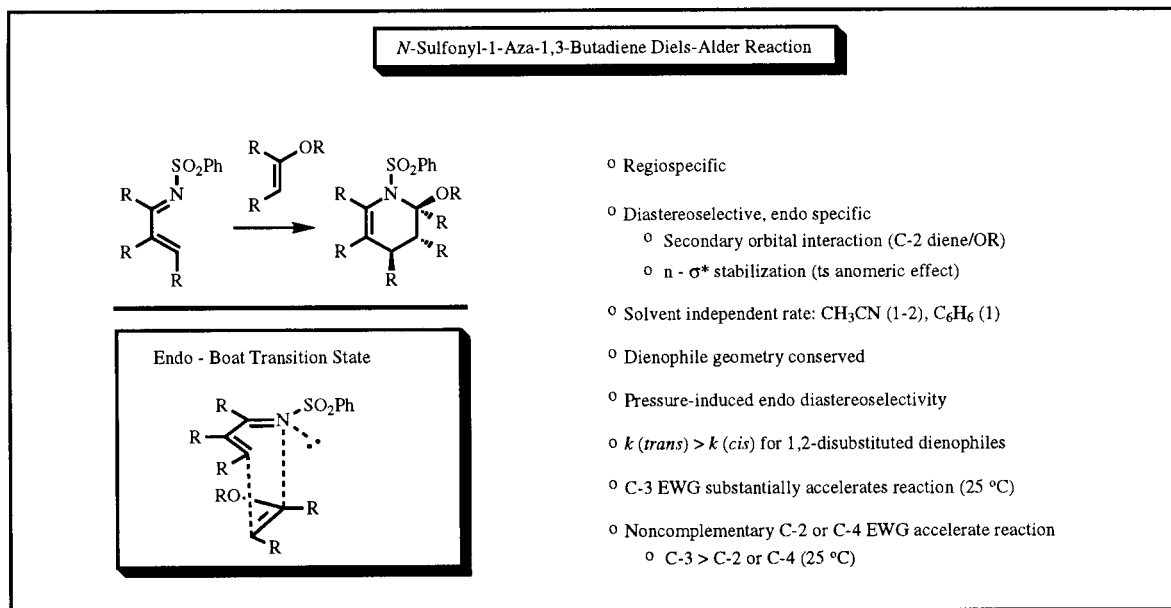
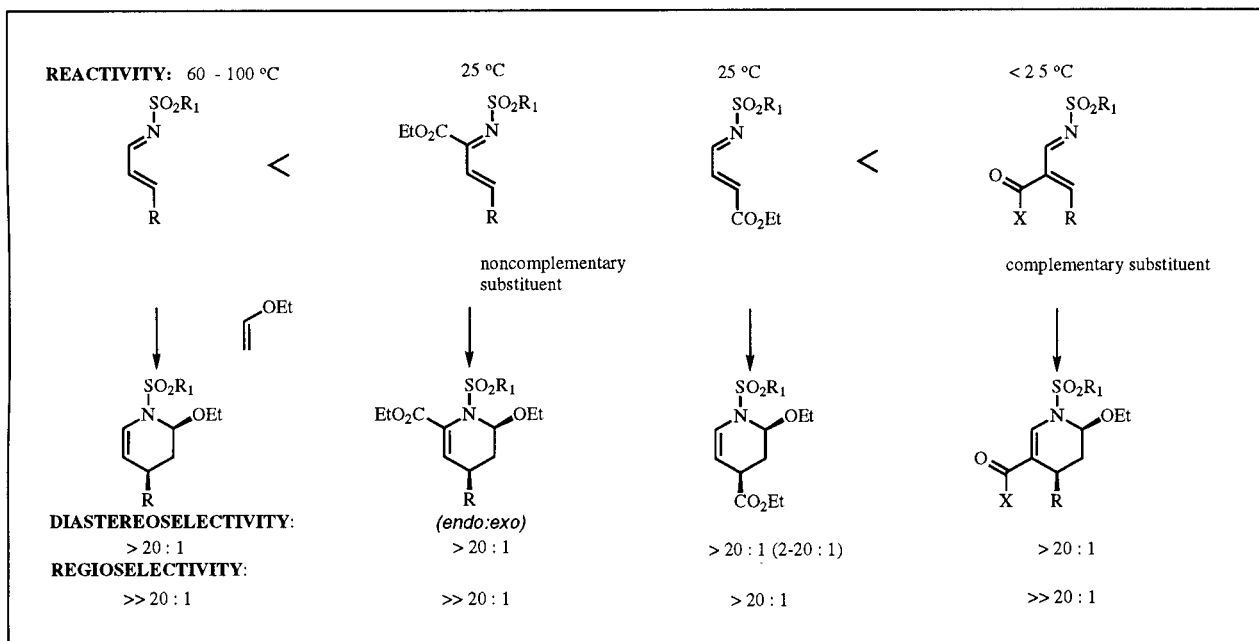


Figure 4



tains the superb *endo* diastereoselectivity ($\leq 20:1$, Figure 4). 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 °C), and maintains the superb *endo* diastereoselectivity ($\leq 20:1$) without effecting the inherent regioselectivity of the [4 + 2] cycloaddition reaction (Figure 4).

In the course of these studies, a number of general approaches to the preparation of the unusually stable *N*-sulfonyl-1-aza-1,3-butadienes have been developed and are summarized in Figure 5 (35, 40).

The application of the methodology in the synthesis of complex natural products has proven unusually successful. The first total synthesis of streptonigrone (41) was

Figure 5

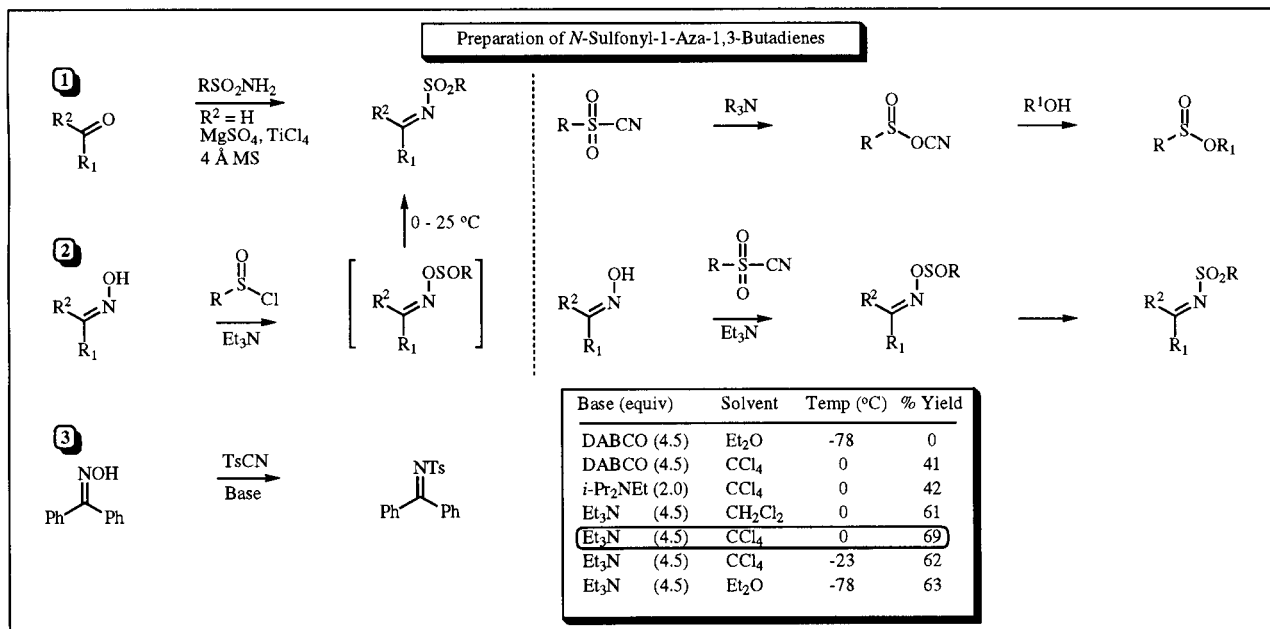
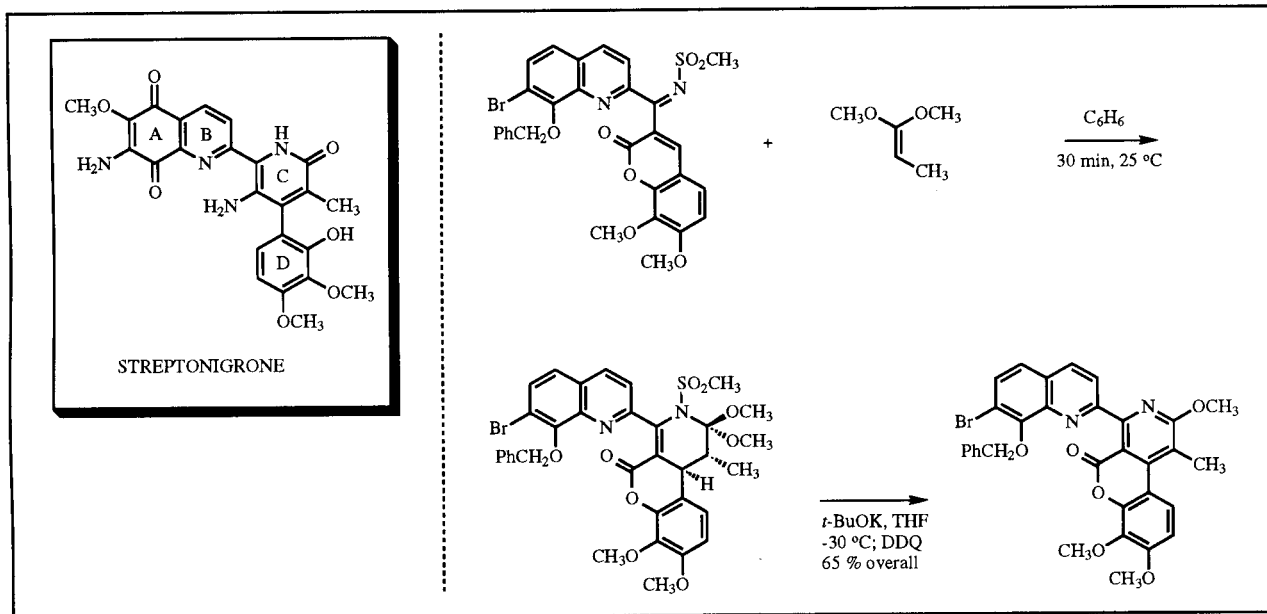


Figure 6



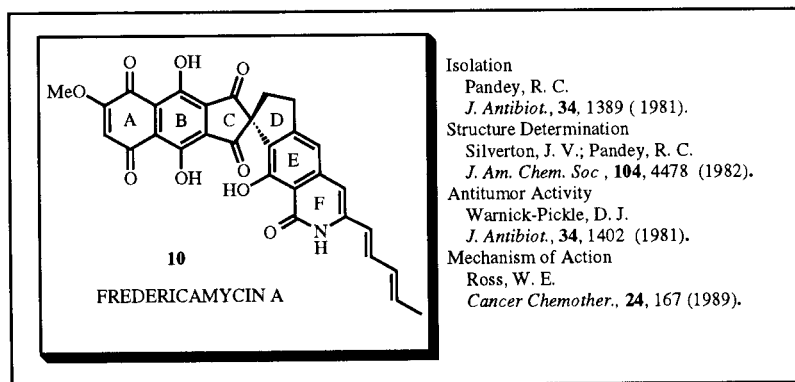
based on the use of a room-temperature inverse electron demand Diels-Alder reaction of a *N*-sulfonyl-1-azadiene in a reaction that by design was accelerated through the complementary substitution of the diene with a C3 electron-withdrawing group. Thus, the diene C3 carboxylate served to accelerate the 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 6).

Total Synthesis of Natural and *Ent*-Fredericamycin A (42, 43).

Fredericamycin A (**10**), a structurally unique and potent antitumor antibiotic isolated from *Streptomyces griseus* (44, 45), has been the subject of extensive investigation

since its unambiguous structure determination by single-crystal X-ray analysis (46) after extensive spectroscopic studies failed to resolve tautomeric structures (47) (Figure 7). Fredericamycin A exhibits potent *in vitro* cytotoxic activity, efficacious antitumor activity (48), and inhibits procaryotic RNA and protein synthesis earlier and to a greater extent than DNA synthesis. Although studies on the single electron oxidation of fredericamycin A and its role in generating oxygen free radicals have been detailed in support of a nondiscriminant mode of action (49), more recent investigations (50) have disputed the results of the original studies. In addition, 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 (51). This latter observation is in spite of the report that

Figure 7



Isolation
 Pandey, R. C.
J. Antibiot., **34**, 1389 (1981).
 Structure Determination
 Silverton, J. V.; Pandey, R. C.
J. Am. Chem. Soc., **104**, 4478 (1982).
 Antitumor Activity
 Warnick-Pickle, D. J.
J. Antibiot., **34**, 1402 (1981).
 Mechanism of Action
 Ross, W. E.
Cancer Chemother., **24**, 167 (1989).

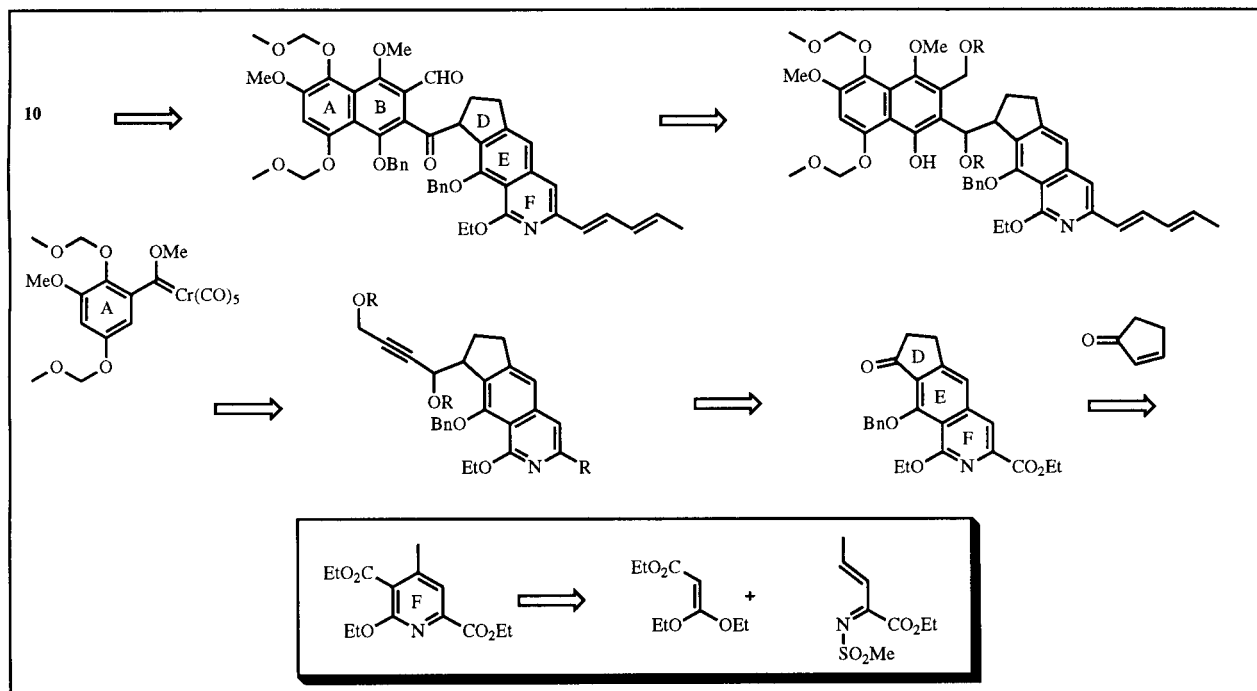
the agent may not interact directly or detectably with DNA (48) suggesting direct enzyme inhibition or selective stabilization of a tertiary complex of DNA, topoisomerase, and **10**. In recent efforts we have detailed a convergent total synthesis of **10** in efforts to provide the natural product and key agents necessary to address the origin of its biological properties. These studies and the resulting synthetic approach are complementary to the initial (52) and recently described (53-56) total syntheses of racemic **10**.

Our efforts provided the first total synthesis of natural and *ent*-fredericamycin A as well as a set of key partial structures of the natural product. The key steps of the convergent approach to **10** rest on the implementation of a regioselective 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 (Scheme 3). 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. The incorporation of readily removed protecting groups at the unactivated phenol sites assured a

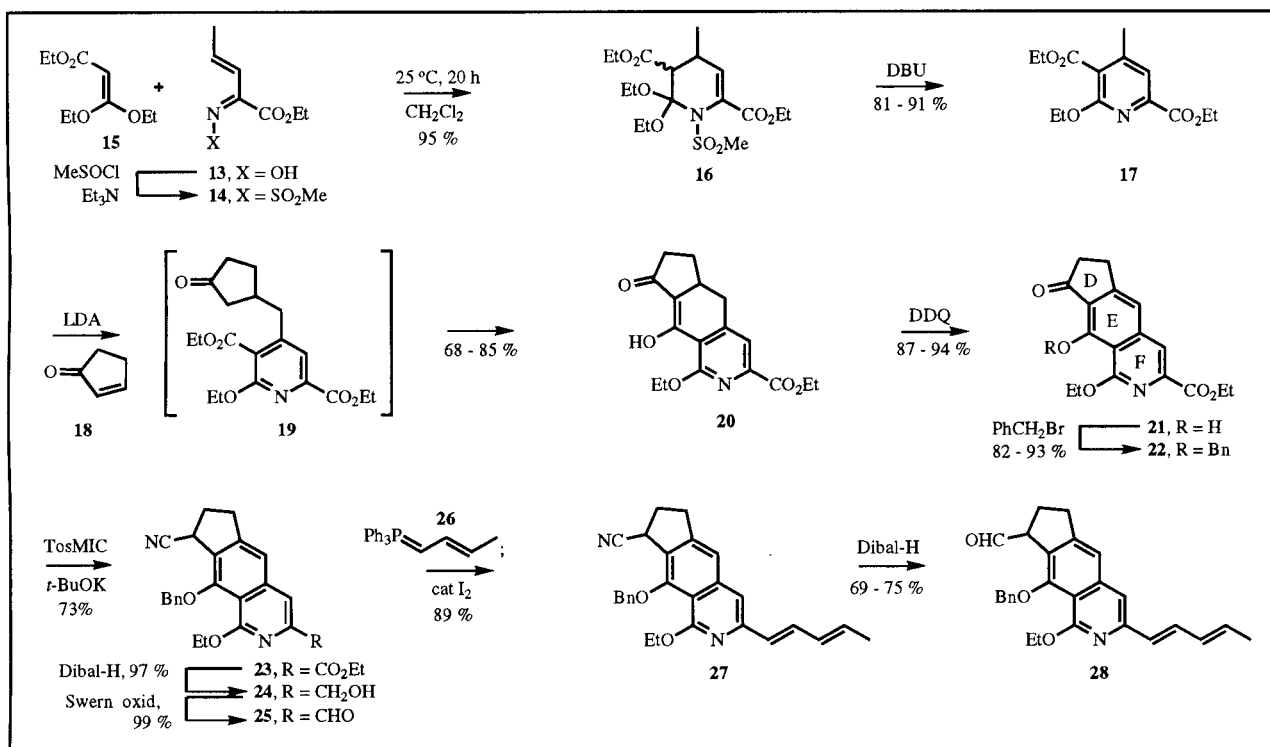
simple and high yielding deprotection of the resolved penultimate intermediate.

Our approach was based on a concise, four step synthesis of **21** employing a key LUMO_{diene}-controlled Diels-Alder reaction of the *N*-sulfonyl-1-aza-1,3-butadiene **14** followed by a single-step Michael addition-Claisen condensation for annulation of the DE ring system and the further elaboration of this precursor **21** to the fully functionalized DEF ring system of fredericamycin A. Room temperature (25 °C) Diels-Alder reaction of **14** and **15** (CH₂Cl₂, 25 °C, 20 h, 95% based on **15**) provided the adduct **16** as a 1:1 mixture of C3-diastereomers in superb conversions (Scheme 4). The noncomplementary addition of the strong electron-withdrawing C2-ethoxycarbonyl group further lowers the inherent low lying LUMO of the *N*-sulfonyl-1-aza-1,3-butadiene to the extent that even the modestly reactive dienophile **15** participates in a room temperature [4 + 2] cycloaddition reaction. This unusually facile reaction at 25 °C precludes the need for conventional thermal reaction conditions and the competitive tautomerization of **14** that occurs at elevated temperatures, *i.e.* 100 °C. The crude diene **14** prepared from oxime **13** by low temperature, homolytic rearrangement of the *in situ* generated *O*-sulfinate (CH₃SOCl, Et₃N, CCl₄, 0 °C, 10 min) was used directly in the reaction with **15** and was obtained as a 7:3 mixture of *trans* and *cis* isomers of which only the *trans* isomer productively reacts at 25 °C. It is notable that this diene, while sensitive,

Scheme 3



Scheme 4



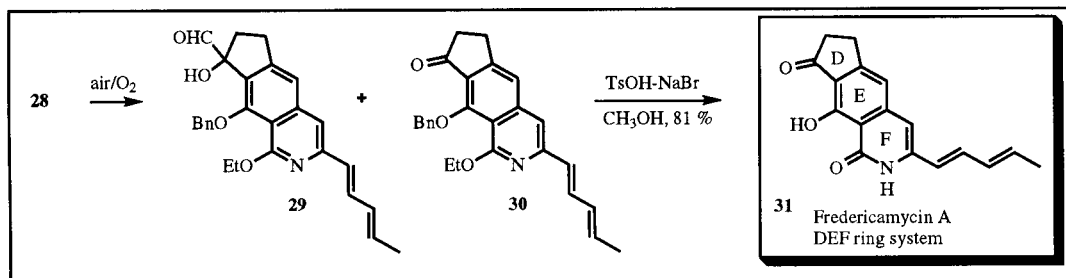
is stable to imine hydrolysis during a rapid aqueous workup and could be occasionally purified by flash chromatography indicating that hydrolysis or tautomerization is much less facile than the diene structure might suggest.

The [4 + 2] cycloadduct **16** was converted directly to pyridine **17** by treatment with DBU (80-91%). Treatment of **17** with LDA followed by cyclopentenone (**18**) and finally EtOH under carefully defined reaction conditions provided **20** derived from a single-step Michael addition-Dieckmann condensation. The intermediate Michael adduct **19** could be isolated and characterized (96%) and subsequently converted to **20** (NaH, THF, cat. EtOH, 25 °C) but was more conveniently obtained simply by extending the Michael addition reaction time. DDQ oxidation of **20** to the naphthol **21** (87-94%) followed by protection of the free phenol as its benzyl ether provided **22** (82-93%) and completed the preparation of the carbon skeleton of an appropriately functionalized DEF ring system.

In our approach, we elected to introduce the pentadienyl side chain prior to the alkyne and its subsequent use in the key chromium carbene benzannulation reaction. Not only was this anticipated to provide fully elaborated advanced intermediates and simplify the final stages of the synthesis but, by design, would also allow the preparation of the fully functionalized lower DEF subunit of

fredericamycin A. This preparation of key partial structures of the natural product for biological assessment was instrumental in our decision to install the pentadienyl side chain at this juncture of the synthesis. Treatment of **22** with TosMIC (*t*-BuOK, EtOH, CH₂Cl₂, 73%) provided the homologated nitrile **23** in excellent conversions. Selective ester reduction of **33** achieved by treatment with Dibal-H (97%) followed by Swern oxidation of **24** (oxalyl chloride-DMSO, 99%) provided the aldehyde **25**. The subsequent introduction of the pentadienyl side chain was best accomplished with the Wittig reagent **26** (THF, 89%) which provided a 8:40:12:40 ratio of *cis-cis*, *cis-trans*, *trans-cis*, and *trans-trans* isomers, respectively. Exposure of this mixture to I₂ (0.05 equiv) in CH₂Cl₂ or CHCl₃ led to isomerization to a clean 85:15 mixture of the desired *trans,trans-27* and *cis,trans-27* (95-100% recovery). Careful chromatography could be employed to provide a further enrichment of the desired *trans,trans-27* (22:1), but proved unnecessary since this further enrichment was routinely accomplished in the purification of subsequent intermediates. In handling **27** and related intermediates, we noted that both prolonged exposure to light and slow or careful chromatography on SiO₂ led to consumption or lower recovery of agent. Although this was not unambiguously established, cursory studies revealed light or acid-catalyzed electrocyclicization of the *trans,cis* isomer

Scheme 5



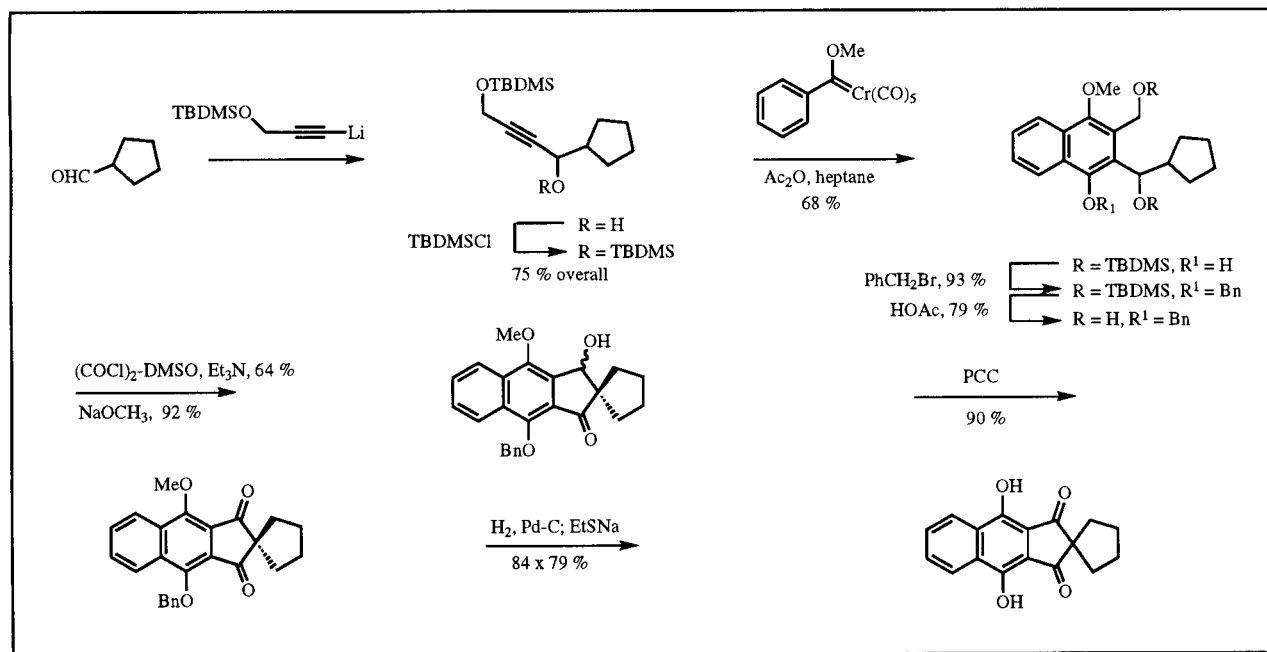
may be responsible for this consumption but could be minimized or avoided by protecting the agents from exposure to light especially during chromatography and minimizing their contact time with chromatographic supports.

This set the stage for introduction of the alkyne side chain for use in the chromium carbene benzannulation reaction. Dibal-H reduction of the nitrile **27** (69-75%) provided cleanly the aldehyde **28** but only when the reaction was conducted in the noncoordinating solvent toluene and no reaction was observed in THF. Initial modest conversions were improved substantially by the choice of workup conditions necessary to promote hydrolysis of the resulting imine (pH 4 phosphate buffer, 25 °C, 20 min) and, importantly, with the rigorous exclusion of air (O₂) throughout the hydrolysis, workup, and chromatographic purification. The aldehyde **28** proved to be remarkably prone to benzylic oxidation and simply subjecting it to chromatographic purification without the precaution of

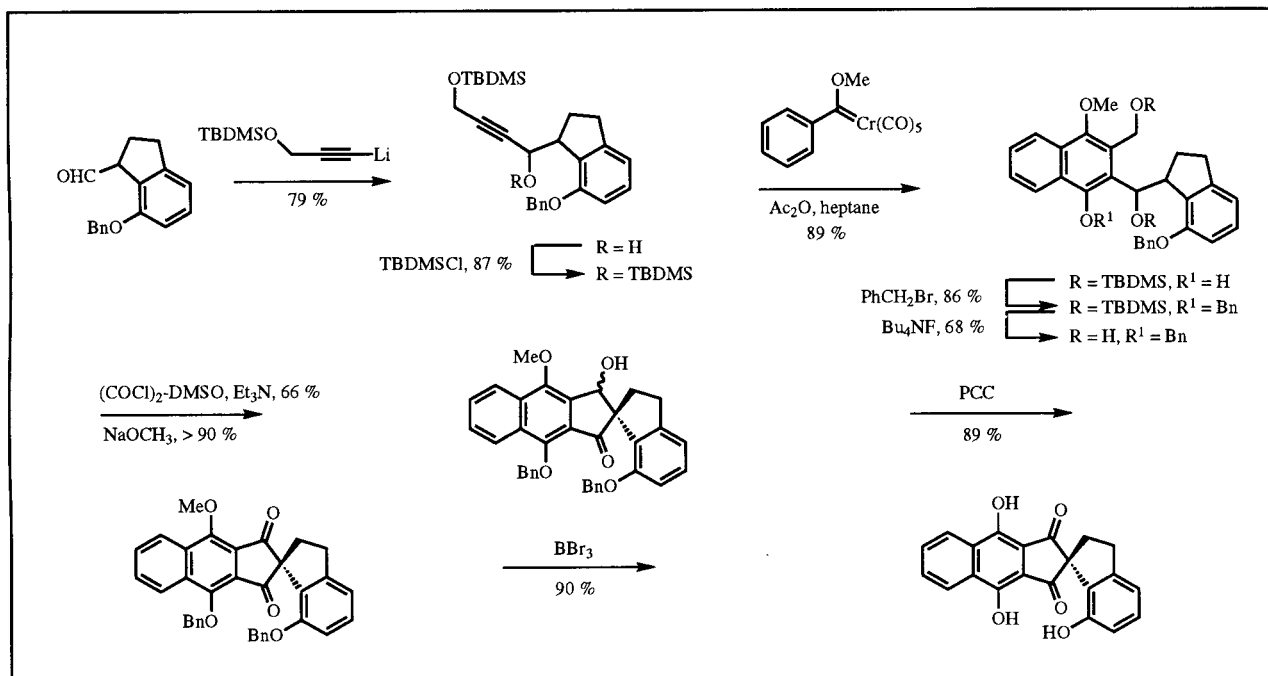
rigorously excluding air (O₂) resulted in rapid conversion to the α -hydroxyaldehyde **29** and the oxidative decarbonylation product **30** (Scheme 5). The nitrile **27** exhibited similar behavior but was sufficiently stable such that special precautionary efforts were not required for its handling or purification. Thus, although the aldehyde **28** could be isolated and characterized, it could also be isolated crude from the reduction reaction in an exceptionally clean form (> 95%) in good yields ($\leq 70\%$) and used directly in the subsequent alkyne addition reaction with improvements in the overall conversions. With **30** in hand, deprotection of the benzyl ether and pyridone ethyl ether was examined (TsOH, NaBr, CH₃OH, reflux, 81%) and found to cleanly provide **31**. In addition to providing the fully functionalized DEF ring system, this insured that the pyridone ethyl ether could be readily deprotected.

Prior to addressing the natural product itself, we first examined the viability of the chromium carbene benzan-

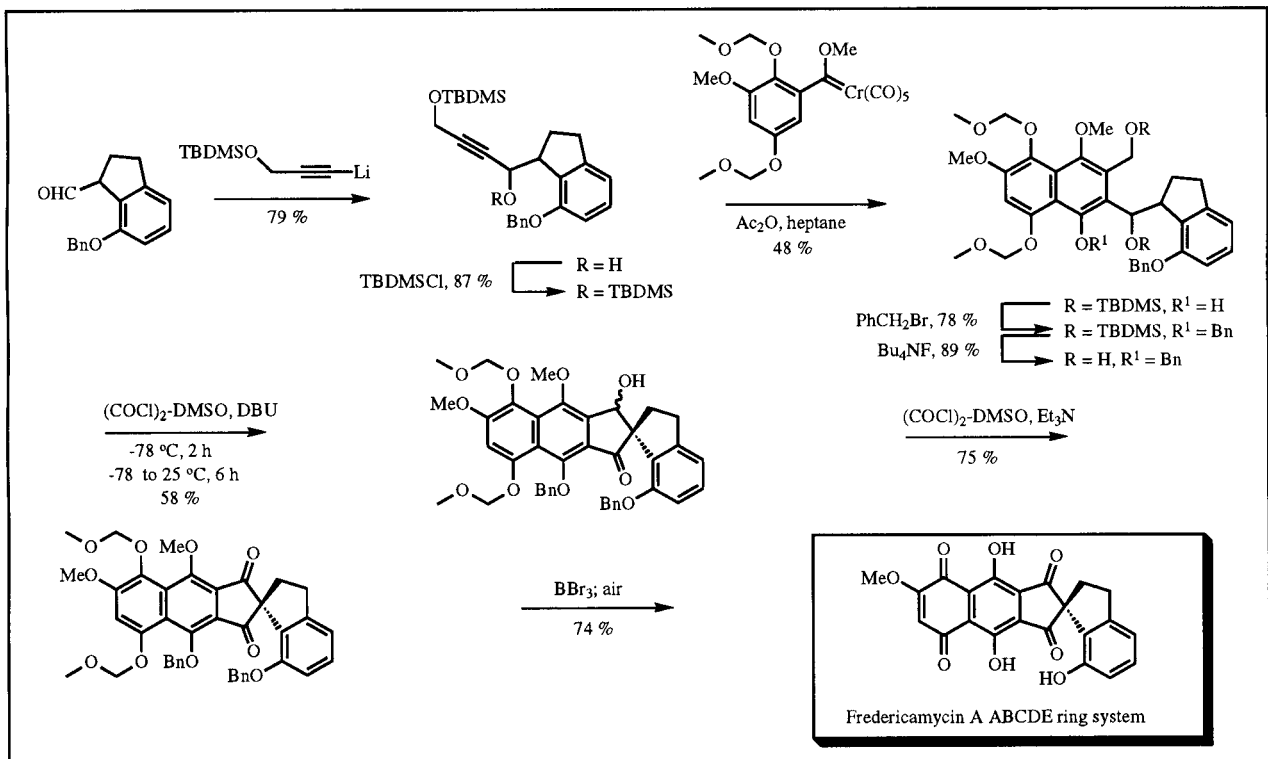
Scheme 6



Scheme 7



Scheme 8



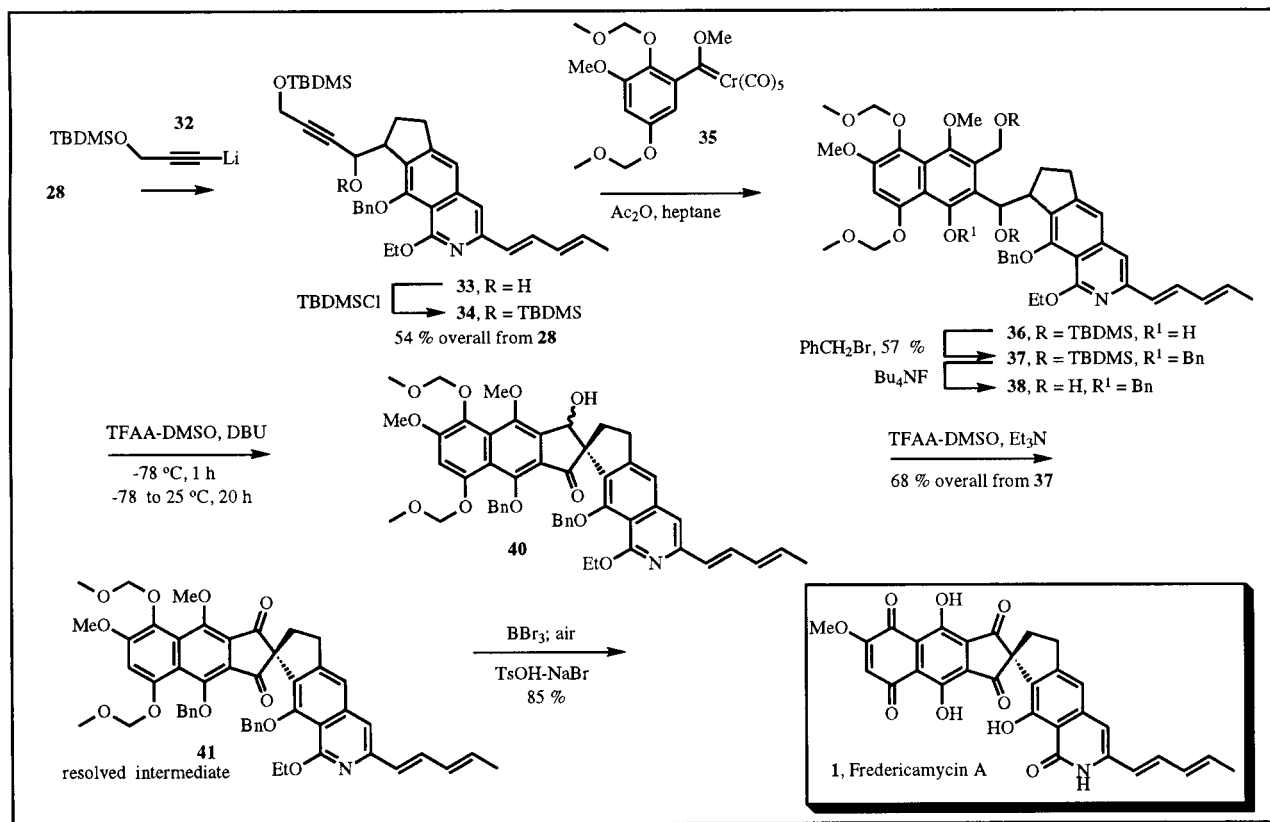
nulation approach to introduction of the fredericamycin AB ring system and the subsequent key aldol closure for introduction of the spiro[4.4]nonene CD ring system (43). Regiospecific benzannulation reaction of the unfunctionalized chromium carbene complex with appropriate alkynes was found to occur effectively when conducted in heptane (80 °C) in the presence of Ac_2O (1 equiv) under conditions that do not acylate the product phenol without the detection of products derived from subsequent TBDMSOH elimination (Schemes 6-7). This was in sharp contrast to the reactions run in the absence of Ac_2O which proceeded at much slower rates, afforded competitive reaction products, and provided much lower conversions to the desired benzannulation products. In addition to the rate acceleration, the reactions run in the presence of Ac_2O proved much cleaner providing few or no minor byproducts. By this approach, two key substructures of the fredericamycin ABCD and ABCDE ring system were prepared (Schemes 6-7). Importantly, the final stage of the anticipated natural product total synthesis was effectively addressed at this juncture of our efforts. The protocols for a potentially problematic oxidative conversion of the benzannulation reaction products to the key keto aldehyde intermediates and their simple aldol closure for creation of the spirocenter were developed.

This was fully implemented in a preparation of the key partial structure constituting the fully functionalized fredericamycin ABCDE ring system (Scheme 8). This led to significant improvements with the implementation of a single-step keto aldehyde generation, subsequent aldol closure and led to the introduction of a uniquely successful single-step deprotection protocol (BBr_3 , -78 °C) for selective removal of the precursor protecting groups without competitive A ring methyl ether cleavage that many recent total syntheses have relied upon.

In these preceding studies (43), we developed a highly convergent approach to the ABC ring system based on the implementation of a regiospecific chromium carbene benzannulation reaction for assemblage of the fully functionalized AB ring system followed by a simple aldol closure for construction of the spiro[4.4]nonene with introduction of ring C. Our successful use of this approach in the preparation of the partial structures of **10** (43) suggested that all elements of this sequence might be fully adaptable to the natural product and we were optimistic that the presence of the F ring and pentadienyl side chain would not compromise its implementation.

Treatment of the sensitive aldehyde **28** with the lithium acetylide **32** and subsequent protection of the resulting

Scheme 9



alcohol **33** provided the alkyne **34** (54%) and a key component for the benzannulation reaction (Scheme 9). Due to the sensitivity of the aldehyde **28** and the chromatographic losses encountered in careful purifications of substrates containing the diene side chain, the three-step conversion of **27** to **34** was generally accomplished without the intermediate purification of **28** or **33** and provided **34** in better overall yield. In agreement with our preceding studies (43), the benzannulation reaction of **34** with the functionalized chromium carbene complex **35** proceeded best in heptane in the presence of Ac₂O (1-2 equiv) under conditions (50 °C, 48 h) that do not acetylate the product phenol and provided **36** as a single regioisomer and as a 3:1 mixture of diastereomers. Notably, this reaction failed to provide **36** in the absence of Ac₂O which, in our preceding studies, was shown to accelerate the benzannulation reaction and may affect the reaction course. Consistent with past observations, the regioselectivity of this reaction may be attributed to the modest steric differences in the alkyne α substituents that dictate the regioselectivity of the initial [2 + 2] chromium metallocyclobutene adduct preferentially placing the large substituent *ortho* to the product phenol. More subtle was the overall effect of the alkyne structure on the successful implementation of the benzannulation reaction of the highly oxygenated chromium carbene complex **35** which incorporates an alkoxy substituent *ortho* to the carbene. As defined in the independent observations of Semmelhack, the facility and reaction course with which such complexes participate in the benzannulation reactions with propargylic substrates is substantially diminished although the use of bulky alcohol protecting groups favors naphthol formation over competitive reactions. This subtle but important contribution to the success of the reaction of **35** through employment of the bulky bis-TBDMS ether **34** together with the modified reaction conditions proved necessary for significant generation of **36**.

Subsequent protection of the free phenol **36** as the benzyl ether **37** was accomplished under mild conditions (PhCH₂Br, Bu₄Ni, K₂CO₃, acetone, 25 °C, 57%) notably without competitive elimination of *t*-BuMe₂SiOH *via* orthoquinomethide generation. Deprotection of the benzylic alcohols was effectively accomplished through treatment with Bu₄NF, provided the diol **38** and set the stage for introduction of the spiro CD ring system. Following our prescribed conditions (43), Swern oxidation of the diol **38** to the corresponding keto aldehyde **39** precedes *in situ* base-catalyzed aldol closure to **40**. The success of the Swern oxidation (TFAA-DMSO) proved dependent on the reaction conditions where activation of both alcohols through formation of the bisalkoxysulfonium salt (60 min, -78 °C) preceded introduction of DBU and base-catalyzed elimination of dimethyl sulfide with formal oxidation of

the primary and secondary alcohols. If the base was added prior to complete activation of both alcohols, displacement reactions effectively compete with the desired oxidations. When this Swern oxidation was carried out with a strong base (DBU versus Et₃N) and the reaction time and temperature extended (30 h, -78 to 25 °C), clean base-catalyzed aldol closure to **40** was observed under the reaction conditions. Subsequent Swern oxidation of **40** (TFAA-DMSO, Et₃N) provided our penultimate intermediate **41**. Each of the steps in the transformation of **37** to **41** was so clean that the overall conversion was accomplished without the purification of intermediates and provided **41** in superb conversions (57-68% overall from **37**) with an average yield of approximately 93-94% for each of the 6 reactions.

Two-step deprotection of **41** (BBr₃, CH₂Cl₂; TsOH-NaBr, CH₃OH) with air oxidation following the BBr₃ treatment served admirably to provide **10** (85%) and completed the synthesis of fredericamycin A. Analogous to our earlier observations (43), the BBr₃ treatment cleanly removed the two MOM ethers, the two benzyl ethers, and the activated C4 methyl ether leaving intact the required C6 methyl ether. Partial deprotection of the pyridone *O*-ethyl ether was observed under the conditions of the BBr₃ treatment and this was cleanly and completely removed upon air oxidation and subsequent treatment with TsOH-NaBr. This provided **10** identical in all respects with a sample of authentic material (¹H NMR, IR, UV, MS, TLC).

As a consequence of the potent activity of the natural product and the uncertainty surrounding its mechanism of action, we were especially interested in the evaluation of both enantiomers of fredericamycin A. The comparative examination of the unnatural enantiomer, like key partial structures, is anticipated to provide seminal observations that may distinguish both the site of action and the structural features contributing to the biological effects of the natural product. To this end, the resolution of the penultimate precursor **41** was examined on a series of HPLC chiral phases (ChiralPac OD, OB-H, AD, OT). The best resolution was observed on a ChiralPac OD column. Racemic **41** could be resolved on a HPLC analytical column (0.46 x 25 cm, 10% *i*-PrOH-hexane, 0.9 mL/min flow rate, α = 1.38) and preparatively separated on a semipreparative HPLC column (2 x 25 cm, 20% *i*-PrOH-hexane, 2-6 mL/min, α = 1.14) to afford the two enantiomers (> 99% *ee*). Independent deprotection of the two enantiomers as detailed above provided natural and *ent*-fredericamycin A (> 99% *ee*). The comparison of the circular dichroism spectra of the two enantiomers of the synthetic and natural fredericamycin A permitted the unambiguous assignments of natural and unnatural enantiomers of synthetic **1** as

well as **41**. Like the CD for natural fredericamycin A recorded at a basic pH of 8.0 ($[\Theta]_{396}^{25} + 2.5 \times 10^4$ degrees \cdot cm² \cdot dmol⁻¹, 20% DMF-CH₃OH/blue form), synthetic *ent*-**1** exhibited the same but opposite CD ($[\Theta]_{396}^{25} - 2.4 \times 10^4$ degrees \cdot cm² \cdot dmol⁻¹, 20% DMF-CH₃OH). At acidic pH with the red protonated form of fredericamycin A, the long wavelength CD band becomes considerably less intense, reverses sign, and more closely resembles the CD spectrum of the corresponding enantiomers of **41**.

Importantly, the unnatural enantiomer of fredericamycin A was found to exhibit potent cytotoxic properties in its own right (IC₅₀ 0.04 μg/mL, L1210) comparable to that of the natural enantiomer (IC₅₀ 0.03 μg/mL, L1210). By contrast, both the key partial structures constituting the intact DEF and ABCDE ring systems of **10** were substantially less potent (*ca.* 100x) and both of a comparable cytotoxic potency (L1210 IC₅₀ = 7 and 2 μg/mL, respectively). It is perhaps surprising that the DEF ring system displayed any activity and the relatively nonpotent activity of the ABCDE ring system highlights the importance of the functionalized F ring to the biological properties of fredericamycin A.

Acknowledgments.

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