Molecular Design, Chemical Synthesis, Kinetic Studies, Calculations, and Biological Studies of Novel Enediynes Equipped with Triggering, Detection, and Deactivating Devices. Model Dynemicin A Epoxide and *cis*-Diol Systems

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Abstract: A series of enediyne model systems of the dynemicin A type equipped with triggering and modulating/signaling devices were designed, synthesized, and studied. Specifically, compounds **16**, **18**, **25**, and **27** were synthesized via ring closures involving intramolecular acetylide additions to carbonyl groups followed by deoxygenation. Compounds **16** and **25** underwent cycloaromatization to systems **28** and **29**, respectively, upon acid treatment. These conversions were observed with significant changes in the UV and fluorescence spectra of the compounds involved. Compounds **18** and **27**, upon activation with base (DBU or basic buffer solution), were converted to free amino epoxides **30** and **31** which were further transformed into *cis*-diols **8** and **9**, respectively, by exposure to silica gel in wet benzene. Kinetic studies used to determine the free energies of activation ($\Delta G^{\ddagger}$) for the cycloaromatization of **8** (22.6 kcal/mol, 30 °C) and **9** (25.7 kcal/mol, 37 °C) to products **32** and **33**, respectively. *Ab initio* calculations regarding the reactivity of these systems were in agreement with the experimental findings. The isolation of compounds **8**, **9**, **30**, and **31** provide strong support for the postulated intermediates in the dynemicin A reaction cascade. The physical, chemical, and biological profiles of the reported compounds may provide the basis for further applications in mechanistic, biological, and medical studies.

Introduction

Dynemicin A (**1**) is a newly discovered enediyne-containing antitumor antibiotic isolated from the fermentation broth of *Micromonospora chersina* with an intriguing molecular structure and mechanism of action.[1] In addition to its *in vivo* antibacterial activity,[1] **1** exhibits potent antitumor properties against a variety of cancer cell lines and prolongs significantly the life span of mice inoculated with P388 leukemia and B16 melanoma cells.[2] The chemical structure of **1** was determined by spectroscopic and X-ray crystallographic analysis of its triacetate derivative.[2] The absolute stereochemistry of **1** was assigned by Langley and coworkers[3] from molecular modeling studies with DNA. This assignment is supported by our results with synthetic, optically active model compounds.[4]

Conjugation of a 10-membered ring enediyne core with an anthraquinone moiety[5] makes **1** a uniquely distinct member of the enediyne family.[6] It has been confirmed that the anthraquinone moiety of **1** both binds into the minor groove of DNA[7] via intercalation and provides for the activation of the agent via bioreduction.[8]

The elegance of the mechanism of action of dynemicin (**1**) can be seen in Scheme I, which features a cascade of reactions. After binding of **1** to the targeted DNA sequence and undergoing bioreduction, the resulting activated intermediate (**2**) rearranges, opening the epoxide and forming the quinone methide intermediate **3**. Attack by nucleophiles, such as water and thiols, present in living systems, converts **3** to **4**. The hydroquinone **4** then undergoes a Bergman cycloaromatization reaction[9] to give the benzenoid diradical **5**. Abstraction of hydrogens from the sugar phosphate backbone of DNA by this reactive diradical, transforms **5** into **6** with concomitant DNA strand breaking.

Biological assays with **1** demonstrate that it is activated by either NADPH or thiols and that the preferential cutting site is on the 3′ side of purine bases of DNA (e.g., 5′-GC, 5′-GT, and 5′-AG).[7] The final adducts **6** (Nu = water, methyl thioglycolate) have been isolated and characterized.[7,10] Further support for this mechanism comes from molecular mechanics calculations[3,11] that indicate the important role of epoxide opening and formation of the *cis*-opened intermediate **4** in the action of **1**. The conformation of **4** is such that the termini of the enediyne moiety are brought within suitable bond forming distance. Nonetheless, questions still remain about the existence and stability of the postulated intermediates in this reaction cascade.

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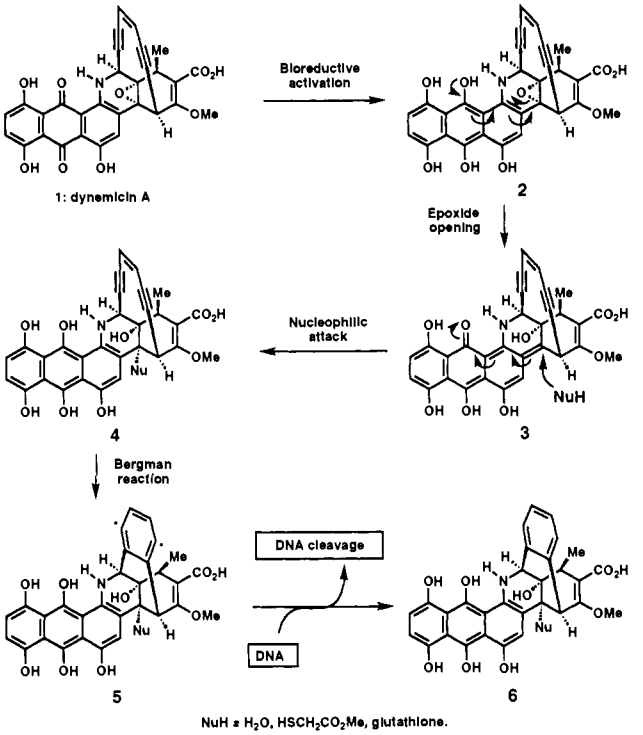
Scheme I[a]



[a] Proposed mechanism of action of dynemicin A.

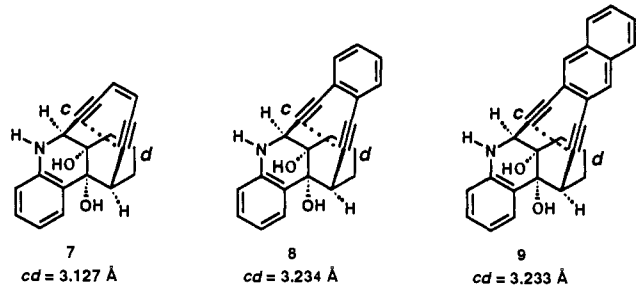


Figure 1. Structures of dynemicin A diol model systems with different reactivity toward Bergman cycloaromatization. The distances between the remote acetylenic carbons (*cd*) were obtained by molecular mechanics calculations (MMX).

Reports from these laboratories include the following: (a) chemical simulation of the dynemicin A (**1**) reaction cascade by synthetic model systems[12] and (b) novel designed enediynes of the dynemicin A type possessing potent and selective cytotoxic properties.[13] In this article, we present the results of a project aimed at design, synthesis, and kinetic studies of novel enediynes equipped with triggering, signaling, and deactivating devices. The last device permitted the isolation of model epoxide and *cis*-opened diol systems of the dynemicin A type[14] and allowed studies on the relative rates of cycloaromatization of **7**, **8**, and **9** (Figure 1).

Results and Discussion

Molecular Design and Theoretical Considerations on the Reactivity of Enediynes. We have demonstrated that the *cis*-opened system **7** (Figure 1) and its protected analogs undergo spontaneous Bergman cycloaromatization.[12] Trapping experiments with different hydrogen-atom sources supported the intermediacy of benzenoid diradicals in this reaction cascade.

A structure–reactivity relationship was developed for cyclic enediynes using molecular mechanics calculations and data derived from X-ray crystallographic analysis.[16] The distance between the acetylene termini was found to be correlated with ground-state strain energy and therefore provided a good indicator of compound reactivity (increased strain implies increased reactivity). In particular, compounds with *cd* distances in the critical range of 3.2 ± 0.1 Å were found to cyclize spontaneously.

Molecular mechanics calculations (MMX)[15] predicted that the distance between the remote acetylenic carbons (*cd*) in **7** (3.127 Å, Figure 1) will fall below the critical value of 3.3 Å,[16] consistent with spontaneous cyclization of **7** at room temperature. The *cd* distances calculated for compounds **8** (3.234 Å) and **9** (3.233 Å) are close to that of **7** (Figure 1), but conjugation of additional aromatic rings with the enediyne moiety in **8** and **9** prevent them from undergoing spontaneous cycloaromatization at room temperature. This may be expected due to a reduced gain in resonance stabilization energy in the cycloaromatization of **8** or **9** *vis-a-vis* **7**. Thus, the reactivities of **8** and **9** present novel exceptions to the *cd* distance criterion. This result motivated us to study the geometry and energetics of this process systematically, using Hartree–Fock *ab initio* methods (*vide infra*).

Strictly speaking, the reactivity of a given enediyne compound toward Bergman cycloaromatization is determined by the free energy of activation ($\Delta G^{\ddagger}$). Although, the *cd* distance criterion mentioned above is an empirical measure of the stability of enediyne compounds toward cycloaromatization (derived from the study of a series of monocyclic enediyne systems[16] and supported by results with a number of other synthetic compounds[9e,f,16,17]), it must be pointed out that the *cd* distance rule pertains only to the strain energy of ground state. Therefore, it is not surprising that "exceptions" to the rule exist,[18] particularly in polycyclic systems or in systems where stabilization of the transition state is possible. For a quantitative measurement of reactivity, one must consider the total free energy difference between the ground state and the transition state ($\Delta G^{\ddagger}$) for each individual reaction. Various enthalpic factors, such as resonance, solvation, and strain energy, should also be taken into account as well as the entropic factors of activation ($\Delta S^{\ddagger}$). Different reactivities of arenediynes and related systems, arising from differences in resonance energy, have been reported,[14,19,20] and solvent effects on the cycloaromatization of arenediynes have also been noted recently.[20]

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(15) PC model from Serena Software, Bloomington, IN, was used. This package contains the MMX force field, which is derived from the MM2 force field and the p-VESCF routines of MMP1 (MM2 and MMP were developed by N. L. Allinger).

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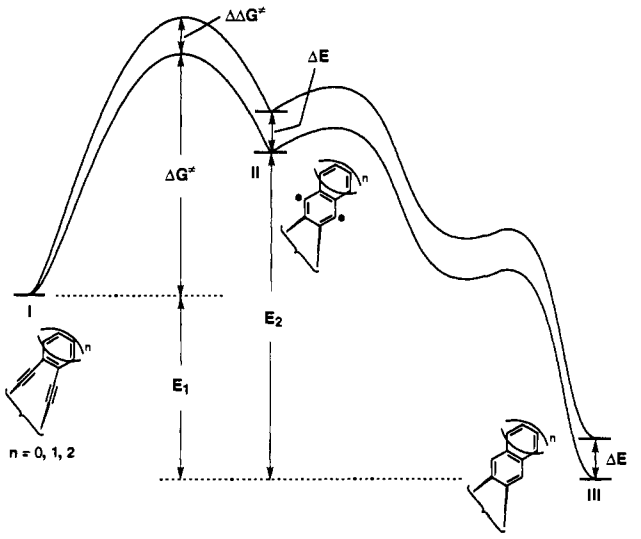


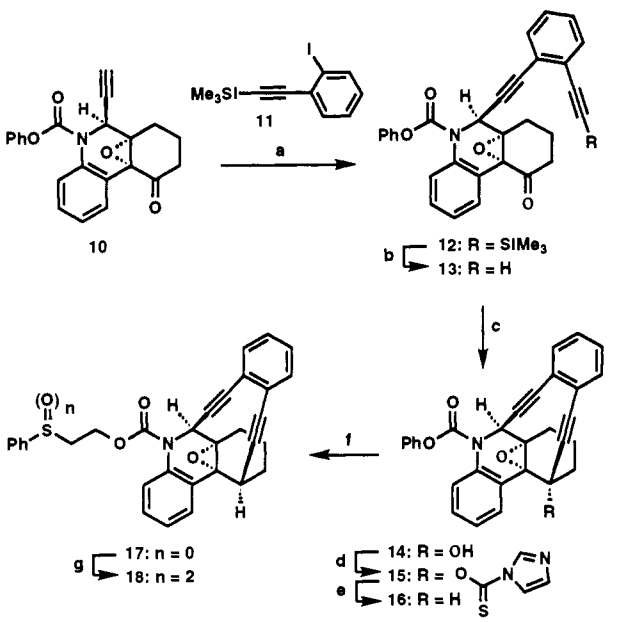
Figure 2. Postulated potential energy diagrams for cycloaromatization of compounds I to form products III *via* radical intermediates II.

A qualitative analysis of the contribution of resonance energy to activation energy of the cyclization process is given in Figure 2. Assuming that Bergman cycloaromatization of **I** to form diradical intermediate **II** has a late transition state, the potential energy of this transition state should be closer to that of **II**. The next process is a hydrogen atom abstraction by **II** to form **III**. The energy difference (E_2) between **II** and **III** should be nearly the same for all compounds in this series regardless of how many aromatic rings are initially conjugated with the diyne moiety (n = 0–2). Recalling the resonance energies of benzene (36 kcal/mol), naphthalene (61 kcal/mol), and anthracene (84 kcal/mol),[21] the energy difference (E_1) between substrate **I** and product **III** will depend on how much resonance energy is gained by formation of an additional fused aromatic ring to the existing framework. Assuming the Hammond postulate, a change in resonance energy gained (ΔE) in the final products will reflect a potential energy difference in the transition states.

Synthesis of Designed Enediynes. Synthesis of the targeted compounds was achieved using a modification of the general methodology developed previously in these laboratories.[12b,c] Scheme II presents the synthesis of compound **18** starting from the known intermediate **10**.[12b,c] Coupling of **10** with (2-iodophenyl)trimethylsilylacetylene (**11**),[22] catalyzed by Pd(0)–Cu(I), afforded **12** (75%), which was converted to compound **13** by removal of the trimethylsilyl group (LiOH, THF–H_2O) in 84% yield. Intramolecular acetylide addition to the ketone was effected by treatment of **13** with slight excess of lithium diisopropylamide (LDA) in toluene at –78 °C, producing **14** in excellent yield (89%). Removal of the tertiary hydroxyl group in **14** was performed by a two-step sequence via intermediate **15**, leading to deoxygenated product **16** (76% yield). Installation of the triggering device was accomplished by (a) displacement of the phenoxy group of **16** with sodium 2-phenylthioethoxide in THF to form **17** (98%) and (b) subsequent oxidation of **17** to the corresponding sulfone **18** with *m*-chloroperbenzoic acid (*m*CPBA, 81% yield). Compound **18** was quite stable under neutral conditions and demonstrated reasonable stability to tertiary amines (e.g., Et_3N, 25 °C).

The synthesis of compound **27** is depicted in Scheme III. This construction proceeded via a similar sequence to that outlined in Scheme II, the major modification being the manner in which the enediyne chain was attached to **10**. This change was necessary due to the difficulty in preparing a naphthyl analog of **11**. Thus, **10** was coupled with 2,3-bis(((trifluoromethyl)sulfonyl)oxy)-naphthalene (**19**)[23] to give **20** (84%) which further reacted with trimethylsilylacetylene under the influence of the usual catalyst system to form **21** (97%). Compound **27** showed a similar chemical reactivity profile as that of **18**.

Scheme II[a]



[a] Reagents and conditions: (a) 1.0 equiv of **11**, 0.05 equiv of $Pd(PPh_3)_4$, 0.2 equiv of CuI, 2.0 equiv of Et_3N, PhH, 40 °C, 2 h, 75%; (b) 10.0 equiv of LiOH, THF–H_2O (10:1), 25 °C, 40 min, 84%; (c) 1.2 equiv of LDA, PhMe, –78 °C, 10 min, 89%; (d) 3.0 equiv of $Imid_2C{=}S$, DMAP (catalyst), CH_2Cl_2, 25 °C, 7 days, 81%; (e) 1.3 equiv of $^nBu_3SnH$, AIBN (catalyst), PhMe, 25 °C, 1 h, 94%; (f) 2.0 equiv of $PhSCH_2CH_2ONa$, THF, 25 °C, 10 min, 98%; (g) 2.5 equiv of *m*CPBA, CH_2Cl_2, 25 °C, 30 min, 81%.

Acid-Induced Cycloaromatizations. Compounds **16** and **25** were chosen in order to investigate the physical and chemical profiles of the designed systems. Upon exposure of **16** and **25** to *p*-toluenesulfonic acid in the presence of a hydrogen-atom donor (e.g., 1,4-cyclohexadiene) at room temperature (25 °C), **28** and **29** were isolated in 79% and 49% yields, respectively (Scheme IV). The formation of **28** and **29** may be explained by initial, acid-mediated, epoxide opening to give the corresponding N-protected *cis*-diols of **8** and **9** (Figure 1), followed by Bergman cycloaromatization and hydrogen-atom abstraction. The tendency of the N-protected *cis*-diols to undergo spontaneous cycloaromatization at room temperature in contrast to the isolable free amines **8** and **9** (Figure 1, *vide infra*) is not presently understood. Compound **16** and its cyclization product, **28**, demonstrated very similar UV (Figure 3, top) and fluorescence profiles. However, rather major changes were observed in the comparison of **25** with **29**. The UV spectrum of **29** (Figure 3, bottom) showed a set of vibrationally split absorption peaks above 320 nm, typical of the anthracene ring system. Fluorescence spectra of **25** and **29** (Figure 4) reflected differences, both in the wavelength and the relative intensity of the peaks. These

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(22) Compound **11** was obtained by reaction of 1,2-diiodobenzene with trimethylsilylacetylene under the catalytic influence of tetrakis(triphenylphosphine)palladium and cuprous iodide in benzene in 54% yield.

(23) Compound **19** was prepared in 92% yield by mixing 2,3-dihydroxynaphthalene and trifluoromethylsulfonyl anhydride in the presence of 2,6-lutidine in dichloromethane.

(24) The aromatic signal (d = 7.05 ppm, doublet) of 4-methoxybenzaldehyde was clearly separated from the signals of substrates and products in this reaction and remains unchanged during the reaction course.

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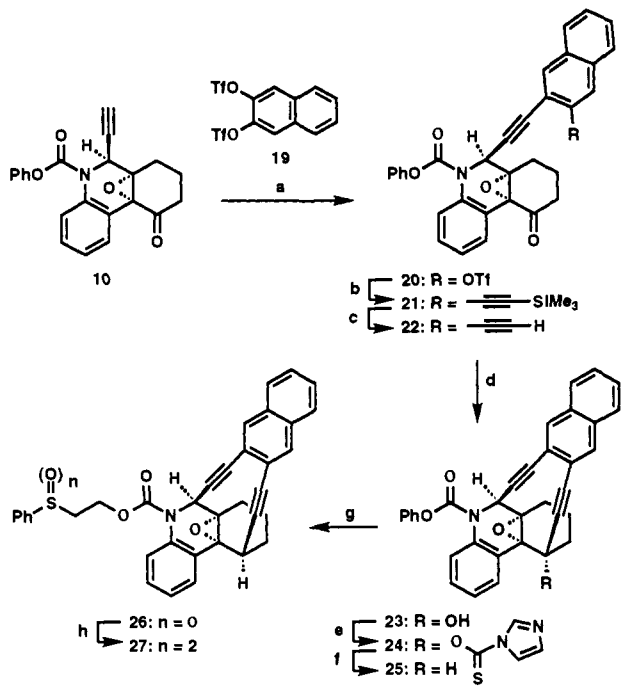
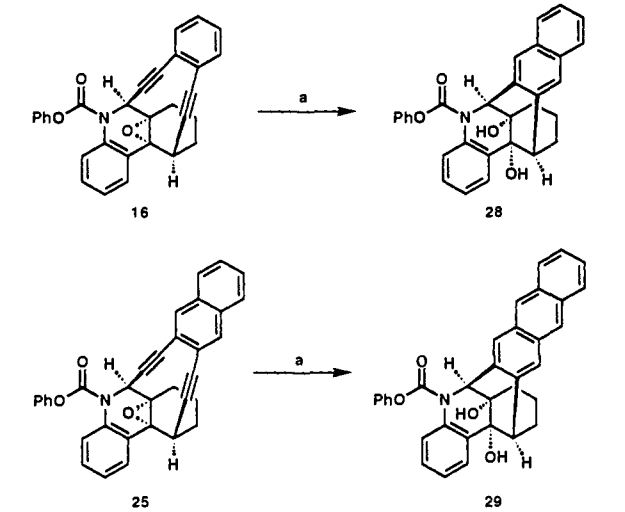
Scheme III[a]



[a] Reagents and conditions: (a) 1.0 equiv of **19**, 0.05 equiv of $Pd(PPh_3)_4$, 0.2 equiv of CuI, 2.0 equiv of Et_3N, CH_3CN, 25 °C, 1 h, 84%; (b) 5.0 equiv of trimethylsilylacetylene, 0.05 equiv of $Pd(PPh_3)_4$, 0.2 equiv of CuI, 2.0 equiv of Et_3N, CH_3CN, 25 °C, 20 h, 97%; (c) 10.0 equiv of LiOH, THF–H_2O (10:1), 25 °C, 40 min, 96%; (d) 1.2 equiv of LDA, PhMe, –78 °C, 10 min, 79%; (e) 3.0 equiv of $Imid_2C{=}S$, DMAP (catalyst), CH_2Cl_2, 25 °C, 7 days, 91%; (f) 1.3 equiv of $^nBu_3SnH$, AIBN (catalyst), PhMe, 25 °C, 1 h, 93%; (g) 2.0 equiv of $PhSCH_2CH_2ONa$, THF, 25 °C, 10 min, 83%; (h) 2.5 equiv of *m*CPBA, CH_2Cl_2, 25 °C, 30 min, 86%.

Scheme IV[a]



[a] Reagents and conditions: (a) 1.2 equiv of $TsOH{\cdot}H_2O$, wet PhH-1,4-cyclohexadiene (4:1), 25 °C, 4 h, **28**, 79%; **29**, 49%.

spectroscopic profiles make the naphthalenediyne system an attractive chemical probe for mechanistic and distribution studies.

Isolation of Epoxides 32 and 33, *cis*-Diols 8 and 9, and Kinetic Studies. The triggering device installed on the nitrogen atom of **30**, **18**, and **27** (Scheme V) is stable under neutral conditions and exhibits reasonable stability to weak organic amine bases. These compounds can be activated, however, with stronger inorganic (e.g., Cs_2CO_3) or organic (e.g., DBU) bases as well as basic buffered solutions. Treatment of **30** with an excess of Cs_2CO_3 in the presence of 18-crown-6 in CH_3CN gave the unstable free

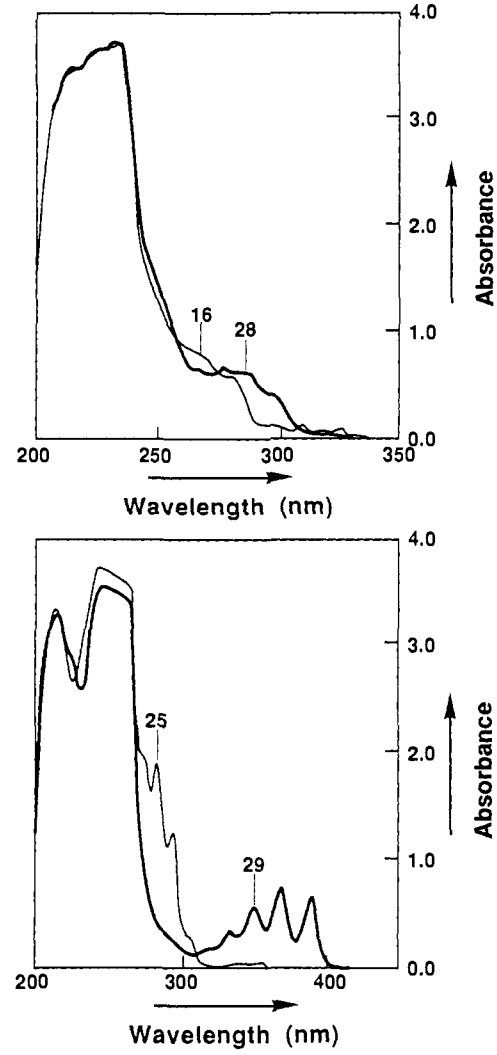


Figure 3. Ultraviolet (UV) spectra of benzenediyne **16** and cycloaromatization product **28** (top) and naphthalenediyne **25** and cycloaromatization product **29** (bottom). Spectra were recorded in EtOH at 25 °C.

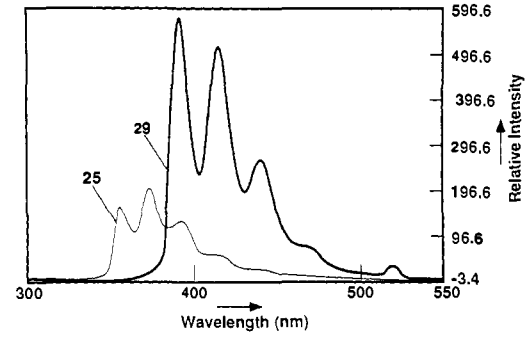
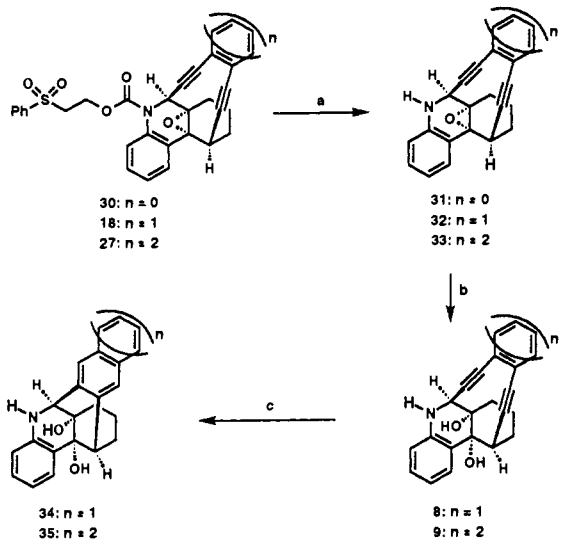


Figure 4. Fluorescence spectra of arenediyne **25** and cycloaromatization product **29**. Spectra were recorded in EtOH (1 μM) at 25 °C, excitation at 260 nm.

amine epoxide **31**.[12a] In contrast with **31**, **32** (50%) and **33** (64%) were isolated from the reaction of **18** and **27**, respectively, with DBU in benzene at room temperature after purification by chromatography. Both **32** and **33** were found to be extremely sensitive to acid, and epoxide opening could be performed by exposing them to silica gel in wet benzene. Thus, **32** was converted to **8** in high yield as indicated by TLC (1 h) but was isolated in pure form in only 34% yield (the low isolation yield is due to the subsequent cycloaromatization of **8**). The more stable *cis*-diol **9**, formed under similar conditions, was isolated in quantitative yield exhibiting a relatively high degree of resistance toward

Scheme V[a]



[a] Reagents and conditions: (a) 2.0 equiv of DBU, PhH, 25 °C, 0.5–2 h, **31**, not isolable, high yield based on TLC (ref 12a); **32**, 50%; **33**, 64%; (b) silica gel, wet PhH, 25 °C, 2–3 h, **8**, 34%; **9**, 100%; (c) for **8** → **34**: PhH-1,4-cyclohexadiene (4:1), 25 °C, 2 h, 70%; for **9** → **35**: PhH-1,4-cyclohexadiene (4:1), 65 °C, 2 h, 72%.

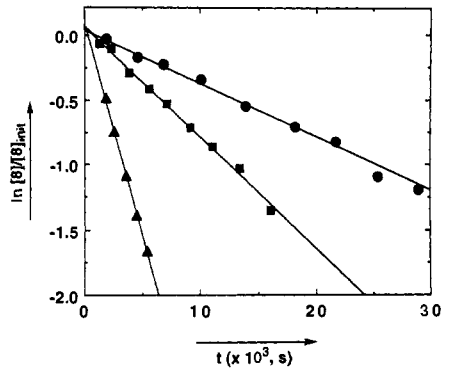


Figure 5. Thermolysis of benzenediyne **8** in THF-d_8 at 10 (○), 20 (■), and 30 (△) °C as monitored by ^{1}H NMR.

Table I. Rate Constants (k_{obs}) and Half-Lives ($t_{1/2}$) of Decomposition of Compound **8** in THF-d_8 at Various Temperatures as Measured by ^{1}H NMR

T (°C)	k_{obs} (s^{-1})	correlation coefficient	$t_{1/2}$ (h)
10	4.06×10^{-5}	0.994	4.92
20	8.57×10^{-5}	0.996	2.47
30	3.29×10^{-4}	1.000	0.67

cycloaromatization at room temperature (*vide infra*). Stirring **8** in a mixture of benzene/1,4-cyclohexadiene (4:1) at room temperature (25 °C) for 2 h resulted in formation of the cycloaromatization product **34**. On the other hand, heating at 65 °C for 2 h was required for the conversion of **9** to **35** (Scheme V), reflecting the difference in the free energy of activation for the two processes.

Kinetic studies were carried out for the cycloaromatization reactions of compounds **8** and **9** in THF-d^8 at different temperatures. Disappearance of substrate was monitored by ^{1}H NMR spectroscopy using 4-methoxybenzaldehyde[24] as an internal standard. A free energy of activation ($\Delta G^{\ddagger}$) of 22.6 kcal/mol (30 °C) was derived from the kinetic data for the cycloaromatization of **8** measured at 10, 20, and 30 °C (Figure 5; Table I). Kinetic measurements for compound **9** were conducted at higher temperatures (37, 50, 60, and 70 °C) leading to a free energy of activation ($\Delta G^{\ddagger}$) of 25.7 kcal/mol at 37 °C (Figure 6; Table II).

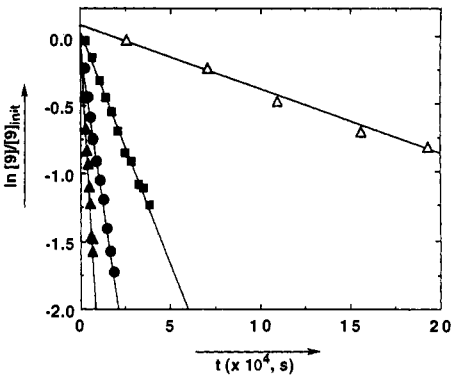


Figure 6. Thermolysis of naphthalenediyne **9** in THF-d_8 at 37 (△), 50 (■), 60 (○), and 70 (▲) °C as monitored by ^{1}H NMR.

Table II. Rate Constants (k_{obs}) and Half-Lives ($t_{1/2}$) of Decomposition of Compound **9** in THF-d_8 at Various Temperatures as Measured by ^{1}H NMR

T (°C)	k_{obs} (s^{-1})	correlation coefficient	$t_{1/2}$ (h)
37	4.67×10^{-6}	0.991	45.6
50	3.48×10^{-5}	0.993	6.03
60	8.54×10^{-5}	0.994	1.86
70	2.24×10^{-4}	0.988	0.80

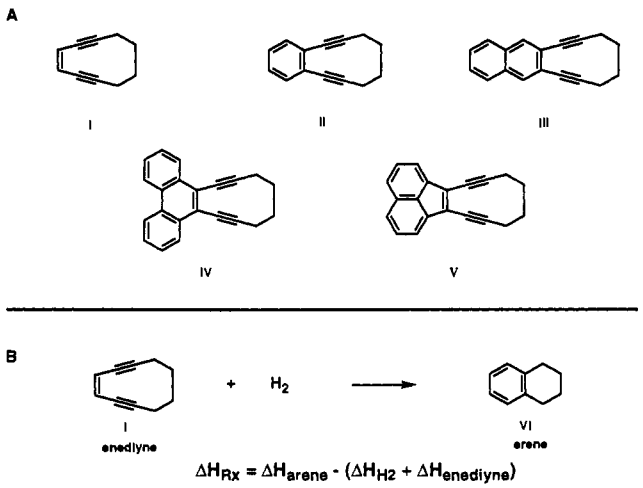


Figure 7. Structures of compounds I–V (A) and cycloaromatization reaction of enediyne I (B).

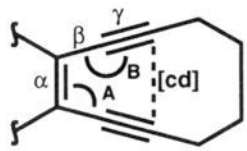
Computations

In order to understand better the structure–activity relationship in arenediyne cyclizations, *ab initio* Hartree–Fock computations were performed on **I–V** (Figure 7, Table III). Geometries were optimized at the minimal basis set STO-3G level of theory and single point energies were evaluated at the split-level basis set, 6-31G(D)//STO-3G (Table III). Cyclization enthalpies were calculated from the equation $\Delta H_{Rx} = \Delta H_{arene} - (\Delta H_{diyne} + \Delta H_{H_2})$ (Figure 7B).

The distance *cd* between the two termini of the arenediyne does not vary significantly across the series **I–V** (*cd* = 3.33 ± 0.05 Å). In general, the geometry of the 10-membered ring does not change in these compounds. Therefore, arguments of ground-state strain offer little insight and cannot predict differences in reactivity.

Two factors do alter significantly in this series: the double bond character of the α-bond and the cyclization enthalpy. The former appears both in a bond length to bond order comparison and in an analysis of possible contributing resonance structures due to the polynuclear aromatic ring. The latter comes from the calculated reaction series. For the linear arenes **I–III**, α-bond

Table III. Calculated Geometries and Cyclization Energies for Compounds I–V



	geometry[a]						cyclization energy[b]	
compd	[cd]	α	β	γ	A	B	STO-3G	STO-3G/6-31G(D)
I	3.32	1.33	1.46	1.18	118.0	167.3	150.7	124.3
II	3.30	1.42	1.46	1.18	116.1	168.8	136.3	111.7
III	3.30	1.45	1.46	1.18	115.4	169.3	129.5	106.1
IV	3.29	1.36	1.46	1.18	116.7	168.6	139.4	112.6
V	3.38	1.36	1.45	1.18	119.4	165.3	151.3	123.6
av	3.32	1.38	1.46	1.18	117.1	167.9		
±S	0.018	0.025	0.002	0.000	0.64	0.80		
% var	0.5	1.8	0.1	0.0	0.5	0.5		

[a] Distances are in Å, angles are in deg. [b] Energies are in kcal/mol.

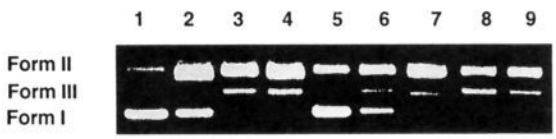


Figure 8. Supercoiled DNA interaction with selected enediynes. ΦX174 DNA was incubated for 48 h at 37 °C with compounds **8**, **9**, **18**, **27**, and **30–33** in buffer (50 mM Tris-HCl, pH 8.5) and analyzed by electrophoresis (1% agarose gel, ethidium bromide stain): lane 1, DNA control; lane 2, **18** [10.0 mM]; lane 3, **32** [10.0 mM]; lane 4, **8** [10.0 mM]; lane 5, **27** [10.0 mM]; lane 6, **33** [10.0 mM]; lane 7, **9** [10.0 mM]; lane 8, **31** [0.1 mM]; lane 9, **30** [1.0 mM]. Key: I, form I DNA; II, form II DNA; III, form III DNA.

order and cyclization enthalpy both decrease from **I** to **III**; for the analogous structures, **7–9**, reactivity decreases from **7–9**. On the basis of the presumed transition-state structure and the relatively constant value for the energy of a $C_{(arom)}$–H bond, most of the difference in cyclization enthalpy must already be present in the rate-determining transition state. This conjecture is supported by the close agreement between the $\Delta\Delta H°$ of 5.4 kcal/mol for **II** and **III** and the $\Delta\Delta G^{\ddagger}$ of 3.1 kcal/mol for **8** and **9**.

Cyclization enthalpy is not simply a function of ring size but depends mostly on the α-bond order. The calculated cyclization enthalpies of **IV** and **V** demonstrate this clearly. Assuming the general importance of the cyclization enthalpy in predicting reactivity, then **IV** should show a reactivity similar to **8**, and **V** should be as reactive as **7**. This conclusion may be used to design extended polynuclear or heterocyclic arenediynes, with selective intercalation properties, and to moderate their reactivity through the site of annelation of the cyclic diyne.

DNA Cleavage and Cytotoxicities Studies. The DNA cleaving properties of the synthesized enediynes were examined and compared with the parent systems **30** and **31** as previously described.[13] Incubation of ΦX174 supercoiled DNA with enediynes **8**, **9**, **18**, **27**, and **30–33** under basic conditions (pH 8.5) at 37 °C for 48 h resulted in significant single- and double-strand DNA cleavages with formation of form II and form III DNA's (Figure 8). Noteworthy in these experiments is the diminished activities of the benzenediyne and naphthalenediyne systems toward DNA damage. This is in agreement with their chemical profiles toward cycloaromatization to form the diradical species.

The cytotoxicities of compounds **30**, **18**, and **27** against a variety of tumor cell lines were determined (Table IV) according to previously published procedures.[13] The lower potencies of compounds **18** and **27**, as compared to that of **30** were consistent with the relative reactivities of these compounds toward cycloaromatization. Particularly striking differences in potencies were observed with the most sensitive Molt-4 leukemia cells.

Table IV. Cytotoxicities of Enediynes **30**, **18**, and **27**

		IC_{50} (M)		
cell type	cell line	**30**	**18**	**27**
pancreatic carcinoma	Capan-1	3.9×10^{-7}	1.5×10^{-6}	6.2×10^{-6}
melanoma	M-14	7.8×10^{-7}	3.1×10^{-6}	1.5×10^{-6}
melanoma	M-21	1.5×10^{-6}	6.2×10^{-6}	3.1×10^{-6}
ovarian carcinoma	Ovcar-3	1.9×10^{-7}	1.2×10^{-5}	3.1×10^{-5}
lung carcinoma	UCLA P-3	2.0×10^{-7}	6.2×10^{-6}	3.1×10^{-6}
melanoma	SK-Mel-28	7.8×10^{-7}	1.2×10^{-5}	3.1×10^{-6}
astrocytoma	U-87 UG	3.1×10^{-7}	3.1×10^{-6}	3.1×10^{-6}
T-cell leukemia	Molt-4	1.0×10^{-11}	1.0×10^{-7}	1.0×10^{-8}

Conclusion

The studies described in this article were inspired by the chemistry and biology of the novel enediyne antitumor antibiotic dynemicin A (**1**). They include molecular design, chemical synthesis, kinetic studies, and theoretical calculations as well as biological investigations. From the results obtained it is concluded that annelation of aryl systems such as benzene and naphthalene on the enediyne moiety has a retarding effect on the cycloaromatization rate of the designed enediynes. The deactivation effect allowed the isolation and characterization of *cis*-opened diol systems of the type postulated in the cascade of reactions proposed for the mechanisms of the DNA cleaving action of dynemicin A (**1**). Theoretical calculations provided explanations for the observed reactivity and supported the postulated mechanism of action of dynemicin A (**1**). The observed dependence of cyclization rate on α-bond order will allow the design of new targets with novel aromatic frameworks. Finally, the biological and spectroscopic properties of the designed molecules may make them useful biological tools and potential leads for further developments.

Experimental Section

General Techniques. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and were not corrected. NMR spectra were recorded on a Bruker AC-250, AM-300, or AMX-500 instrument. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Low-resolution mass spectra (MS) or high-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under positive fast atom bombardment (FAB^+) conditions.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light, 7% ethanolic phosphomolybdic acid, and heat as developing agents. Preparative thin-layer chromatography (preparative TLC) was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise

noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

2-Iodo((trimethylsilyl)ethynyl)benzene (11). To a degassed solution of (trimethylsilyl)acetylene (3.53 mL, 25 mmol), triethylamine (5.2 mL, 37.3 mmol), and 1,2-diiodobenzene (10.0 g, 30.3 mmol) in dry benzene (50 mL) cooled in an ice–water bath (0 °C) was added tetrakis(triphenylphosphine)palladium (290 mg, 0.25 mmol) and cuprous iodide (760 mg, 4.0 mmol). The resulting mixture was stirred at 25 °C until TLC indicated the formation of a bis-coupling product. The reaction mixture was diluted with ethyl ether (100 mL), washed with saturated aqueous ammonium chloride (2 × 100 mL), and saturated aqueous sodium bicarbonate (100 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash column chromatography (silica, petroleum ether) to give the product **11** (4.05 g, 54%): pale yellow oil; R_f = 0.56 (silica, petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.0, 1.1 Hz, 1 H, aromatic), 7.45 (dd, J = 7.7, 1.7 Hz, 1 H, aromatic), 7.26 (td, J = 7.6, 1.1 Hz, 1 H, aromatic), 6.97 (td, J = 7.7, 1.7 Hz, 1 H, aromatic), 0.27 (s, 9 H, Si(CH_3)$_3$); IR ($CHCl_3$) ν_{max} 3060, 2958, 2160, 1459, 1250, 1017, 862, 755 cm^{-1}; HRMS for $C_{11}H_{13}ISi$ (M^+), calcd 299.9831, found 299.9838.

***N*-[(Phenyloxy)carbonyl]-6-[[(2-(trimethylsilyl)ethynyl)phenyl]ethynyl]-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (12).** To a solution of ketone epoxide **10**[12b,c] (670 mg, 1.86 mmol) and cuprous iodide (71 mg, 0.37 mmol) in dry, degassed benzene (20 mL) was added triethylamine (0.40 mL, 2.87 mmol), and then the resulting mixture was stirred at 25 °C for 10 min followed by addition (via syringe) of a mixture of **11** (0.50 g, 1.67 mmol) and tetrakis(triphenylphosphine)palladium (107 mg, 0.09 mmol) in dry, degassed benzene (5 mL) prepared in a separate flask (25 °C, 20 min). The reaction mixture was heated at 40 °C for 2 h, poured into a mixture of saturated aqueous ammonium chloride (50 mL) and saturated aqueous sodium bicarbonate (50 mL), and extracted with ethyl ether (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash column chromatography (silica, 33% ethyl ether in petroleum ether) to give the product **12** (740 mg, 75%): colorless gum; R_f = 0.42 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 7.7 Hz, 1 H, aromatic), 7.54–7.04 (m, 12 H, aromatic), 5.99 (s, 1 H, C*H*N), 2.78–2.70 (m, 2 H, CH_2), 2.40–2.27 (m, 2 H, CH_2), 2.09–1.90 (m, 2 H, CH_2), 0.27 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.0, 151.0, 136.0, 132.5, 132.4, 129.9, 129.3, 128.8, 128.4, 128.3, 128.1, 127.6, 126.0, 125.7, 125.3, 124.1, 123.1, 121.5, 103.1, 98.7, 86.4, 84.6, 75.0, 57.5, 48.3, 38.8, 24.0, 18.2, 0.0; IR ($CHCl_3$) ν_{max} 2958, 1715, 1491, 1377, 1320, 1251, 1203, 1021, 864, 844, 758 cm^{-1}; HRMS for $C_{33}H_{29}NO_4SiCs$ (M + Cs^+), calcd 664.0920, found 664.0907.

***N*-[(Phenyloxy)carbonyl]-6-[[(2-ethynyl)phenyl]ethynyl]-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (13).** To a solution of **12** (680 mg, 1.28 mmol) in THF–H_2O (10:1, 110 mL) was added lithium hydroxide monohydrate (108 mg, 2.57 mmol), and the reaction mixture was stirred at 25 °C for 40 min. The reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash column chromatography (silica, 33% ethyl ether in petroleum ether); to afford **13** (496 mg, 84%): white solid; mp 134–136 °C (from ethyl ether–petroleum ether); R_f = 0.29 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (dd, J = 7.9, 1.4 Hz, 1 H, aromatic), 7.55–7.01 (m, 12 H, aromatic), 5.97 (s, 1 H, C*H*N), 2.96 (s, 1 H, CC*H*), 2.80–2.70 (m, 2 H, CH_2), 2.42–2.26 (m, 2 H, CH_2), 2.09–1.88 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.5, 151.0, 136.0, 132.4, 129.8, 129.3, 128.8, 128.5, 128.4, 128.3, 127.6, 125.8, 125.7, 124.9, 124.6, 123.1, 121.5, 86.6, 84.2, 81.6, 81.1, 75.4, 57.6, 48.2, 38.8, 23.9, 18.5; IR ($CHCl_3$) ν_{max} 3289, 2927, 1716, 1490, 1377, 1321, 1203, 754 cm^{-1}; HRMS for $C_{30}H_{21}NO_4Cs$ (M + Cs^+), calcd 592.0525, found 592.0525.

Compound 14. A solution of **13** (1.24 g, 2.7 mmol) in dry toluene (40 mL) cooled at −78 °C was treated with lithium diisopropylamide (2.16 mL of a 1.5 M solution in cyclohexane, 3.24 mmol). After 10 min at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL) and extracted with ethyl ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 50% ethyl ether in petroleum ether) to furnish **14** (1.10 g, 89%): white solid; mp 97–99 °C (dec, from ethyl ether); R_f = 0.12 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (dd, J = 8.0, 1.5 Hz, 1 H, aromatic), 7.49–7.12 (m, 12 H, aromatic), 5.84 (s, 1 H, C*H*N), 2.37 (dd, J = 15.3, 8.2 Hz, 1 H, CH_2), 2.26–1.92 (m, 4 H, CH_2), 1.77–1.70 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 150.9, 135.8, 131.5, 130.2, 129.3, 129.1, 128.7, 128.3, 128.1, 127.8, 127.7, 127.3, 126.2, 125.7, 125.2, 121.5, 96.0, 93.4, 90.2, 88.7, 73.6, 72.9, 64.2, 50.2, 34.7, 23.3, 19.2; IR ($CHCl_3$) ν_{max} 3452, 2951, 1717, 1492, 1381, 1324, 1203, 758 cm^{-1}; HRMS for $C_{30}H_{21}NO_4Cs$ (M + Cs^+), calcd 592.0525, found 592.0531.

Compound 15. A solution of **14** (780 mg, 1.7 mmol), thiocarbonyldiimidazole (905 mg, 5.26 mmol), and DMAP (103 mg, 0.84 mmol) in dichloromethane (6 mL) was stirred at 25 °C for 1 week. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography (silica, 67% ethyl ether in petroleum ether) to give **15** (780 mg, 81%): white solid; mp 132–134 °C (dec, from ethyl ether); R_f = 0.28 (silica, 67% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1 H, aromatic), 7.73 (dd, J = 8.1, 1.2 Hz, 1 H, aromatic), 7.65 (s, 1 H, aromatic), 7.55–7.02 (m, 13 H, aromatic), 5.64 (s, 1 H, C*H*N), 3.13–3.09 (m, 1 H, CH_2), 2.46 (dd, J = 14.9, 7.1 Hz, 1 H, CH_2), 2.36–2.15 (m, 3 H, CH_2), 1.86–1.79 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.2, 150.9, 137.2, 136.2, 131.0, 130.3, 130.1, 129.6, 129.4, 129.0, 128.9, 128.3, 126.8, 126.5, 126.2, 125.9, 125.5, 121.5, 117.8, 100.3, 90.1, 89.1, 85.6, 74.4, 63.7, 50.1, 28.1, 22.9, 18.6; IR ($CHCl_3$) ν_{max} 3061, 3016, 2958, 1724, 1491, 1446, 1384, 1322, 1284, 1205, 994, 973, 958, 755 cm^{-1}; HRMS for $C_{34}H_{23}N_3O_4SCs$ (M + Cs^+), calcd 702.0464, found 702.0443.

Compound 16. A solution of **15** (690 mg, 1.21 mmol) in dry toluene (20 mL) was treated with *n*-Bu_3SnH (0.40 mL, 1.49 mmol) in the presence of catalytic amount of AIBN at 25 °C for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (silica, 33% ethyl ether in petroleum ether) to provide **16** (504 mg, 94%): white crystalline solid; mp 216–218 °C (dec, from ethyl ether); R_f = 0.44 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.8, 1.1 Hz, 1 H, aromatic), 7.52 (br s, 1 H, aromatic), 7.37 (t, J = 7.7 Hz, 2 H, aromatic), 7.30 (dd, J = 7.4, 1.1 Hz, 1 H, aromatic), 7.26–7.13 (m, 8 H, aromatic), 5.61 (s, 1 H, C*H*N), 3.87 (t, J = 2.8 Hz, 1 H, CH_2CH-), 2.49 (dd, J = 15.0, 7.8 Hz, 1 H, CH_2), 2.32–2.19 (m, 1 H, CH_2), 2.08–1.98 (m, 2 H, CH_2), 1.90–1.82 (m, 1 H, CH_2), 1.65–1.55 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 150.9, 135.6, 130.0, 129.2, 128.9, 128.8, 128.6, 128.3, 128.1, 127.7, 127.2, 126.8, 125.6, 125.2, 121.5, 96.9, 90.7, 90.6, 88.8, 70.1, 60.7, 49.7, 28.9, 22.7, 22.6, 15.5; IR ($CHCl_3$) ν_{max} 2952, 2937, 1720, 1493, 1379, 1324, 1299, 1273, 1253, 1235, 1164, 1147, 1025, 991, 914 cm^{-1}; UV (EtOH) λ_{max} (log e) 282 (3.55), 260 (sh, 3.74), 237–210 (br, 4.36–4.32) nm; HRMS for $C_{30}H_{21}NO_3Cs$ (M + Cs^+), calcd for 576.0576, found 576.0611.

Sulfide 17. To a suspension of NaH (30 mg of 60% dispersion in mineral oil, 0.75 mmol) in dry THF (1 mL) was added 2-(phenylthio)-ethanol (0.10 mL, 0.74 mmol) followed by stirring at 25 °C for 5 min. The resulting solution was added (via syringe) to a solution of **16** (164 mg, 0.37 mmol) in dry THF (3 mL). After stirring at 25 °C for 10 min, the reaction mixture was diluted with ethyl ether (5 mL), poured into H_2O (10 mL), and extracted with ethyl ether (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 33% ethyl ether in petroleum ether) to furnish **17** (183 mg, 98%): colorless gum; R_f = 0.36 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.8, 1.4 Hz, 1 H, aromatic), 7.39–7.13 (m, 12 H, aromatic), 5.47 (br s, 1 H, C*H*N), 4.41–4.15 (m, 2 H, OCH_2), 3.81 (t, J = 2.6 Hz, 1 H, C*H*CH_2), 3.25–3.06 (m, 2 H, CH_2S), 2.42 (dd, J = 14.7, 6.9 Hz, 1 H, CH_2), 2.25–2.13 (m, 1 H, CH_2), 2.03–1.92 (m, 2 H, CH_2), 1.82–1.78 (m, 1 H, CH_2), 1.62–1.53 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 154.4, 135.7, 134.9, 130.1, 129.9, 129.6, 129.1, 128.8, 128.5, 128.4, 128.2, 128.0, 127.7, 127.1, 127.0, 126.6, 124.9, 96.9, 90.8, 90.7, 88.6, 70.3, 64.6, 60.7, 49.4, 32.4, 29.0, 22.7, 22.6, 15.5; IR ($CHCl_3$) ν_{max} 3057, 3018, 2948, 1704, 1494, 1393, 1321, 1272, 1027, 759 cm^{-1}; HRMS for $C_{32}H_{25}NO_3SCs$ (M + Cs^+), calcd 636.0609, found 636.0622.

Sulfone 18. To a solution of **17** (90 mg, 0.18 mmol) in dichloromethane (2 mL) was added *m*CPBA (55%, 168 mg, 0.54 mmol) followed by stirring at 25 °C for 30 min. The reaction mixture was poured into saturated aqueous sodium bicarbonate (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 75% ethyl ether in petroleum ether) to provide **18** (78 mg, 81%): white solid; mp 81–83 °C (from ethyl ether–petroleum ether); R_f = 0.29 (silica, 75% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.10 (m, 13 H, aromatic), 5.41 (br, 1 H, C*H*N), 4.60–4.30 (m, 2 H, OCH_2), 3.81 (br s, 1 H, C*H*ClH_2), 3.50 (br, 2 H, CH_2S), 2.41 (dd, J = 14.6, 6.8 Hz, 1 H, CH_2), 2.27–2.13 (m, 1 H, CH_2), 2.08–1.92 (m, 2 H, CH_2), 1.87–1.79 (m, 1 H, CH_2), 1.59 (br t,

J = 9.0 Hz, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 169.5, 138.8, 135.3, 134.0, 133.6, 130.0, 129.8, 129.4, 128.9, 128.6, 128.3, 128.2, 128.0, 127.7, 127.1, 126.8, 125.1, 96.8, 90.7, 90.5, 88.7, 70.1, 60.6, 59.4, 55.1, 49.4, 28.9, 22.7, 22.5, 15.5; IR ($CHCl_3$) ν_{max} 2950, 1700, 1425, 1400, 1310, 1265, 1150, 750 cm^{-1}; HRMS for $C_{32}H_{25}NO_5SCs$ (M + Cs$^+$), calcd 668.0508, found 668.0531.

2,3-Bis(((trifluoromethyl)sulfonyl)oxy)naphthalene (19). To a solution of 2,3-naphthalenediol (10 g, 62.5 mmol) and 2,6-lutidine (21.8 mL, 187 mmol) in dichloromethane (100 mL) was slowly added (trifluoromethane)-sulfonyl anhydride (21 mL, 125 mmol) at 0 °C. After stirring at 25 °C for 3 h, the reaction mixture was diluted with ethyl ether (300 mL), washed with saturated aqueous ammonium chloride (200 mL), 5% aqueous HCl (200 mL), and saturated aqueous sodium bicarbonate (200 mL). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from ethyl ether–petroleum ether to give **19** (24.4 g, 92%): white crystalline solid; mp 82–83 °C; R_f = 0.63 (silica, 25% benzene in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81–7.75 (m, 4 H, aromatic), 7.56–7.51 (m, 2 H, aromatic); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.0, 131.8, 128.7, 128.1, 122.2, 116.1; IR ($CHCl_3$) ν_{max} 3059, 1600, 1462, 1431, 1221, 1138, 885 cm^{-1}; HRMS for $C_{12}H_6F_6O_6S_2$-Cs (M + Cs$^+$), calcd 556.8564, found 556.8553. Anal. Calcd for $C_{12}H_6F_6O_6S_2$: C, 33.97; H, 1.43. Found: C, 33.98; H, 1.50.

***N*-[(Phenyloxy)carbonyl]-6-[[3-(((trifluoromethyl)sulfonyl)oxy)-2-naphthyl]ethynyl]-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (20).** To a mixture of **10**[12b,c] (1.00 g, 2.78 mmol) and cuprous iodide (106 mg, 0.56 mmol) in dry, degassed CH_3CN (20 mL) was added triethylamine (0.80 mL, 5.74 mmol) at 0 °C followed by stirring at 25 °C for 10 min. To this mixture was added (via syringe) a mixture of **19** (1.30 g, 3.07 mmol) and tetrakis(triphenylphosphine)-palladium (160 mg, 0.14 mmol) in dry, degassed CH_3CN (5.0 mL) prepared in a separate flask (25 °C, 20 min). The resulting mixture was stirred at 25 °C for 1 h, poured into a mixture of saturated aqueous ammonium chloride (50 mL) and saturated aqueous sodium bicarbonate (50 mL), and extracted with ethyl ether (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash column chromatography (silica, benzene) to furnish **20** (1.47 g, 84%): white solid; mp 157–158 °C (from ethyl ether–petroleum ether); R_f = 0.35 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, J = 7.9, 1.4 Hz, 1 H, aromatic), 7.96 (s, 1 H, aromatic), 7.83–7.80 (m, 2 H, aromatic), 7.64 (s, 1 H, aromatic), 7.62–7.55 (m, 3 H, aromatic), 7.42–7.36 (m, 3 H, aromatic), 7.30–7.12 (m, 4 H, aromatic), 6.07 (s, 1 H, C*H*N), 2.83–2.69 (m, 2 H, CH_2), 2.50–2.39 (m, 2 H, CH_2), 2.06–1.95 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.5, 151.0, 146.3, 135.8, 135.2, 132.8, 131.6, 130.3, 129.4, 128.8, 128.6, 128.0, 127.9, 127.7, 127.5, 126.0, 125.8, 121.5, 119.9, 119.4, 117.3, 114.6, 89.4, 79.5, 74.3, 57.6, 48.4, 38.7, 23.8, 17.9; IR ($CHCl_3$) ν_{max} 3062, 3021, 2948, 1722, 1491, 1423, 1377, 1207, 1141, 753 cm^{-1}; HRMS for $C_{33}H_{22}F_3NO_7SCs$ (M + Cs$^+$), calcd for 766.0123, found 766.0123. Anal. Calcd for $C_{33}H_{22}F_3NO_7S$: C, 62.56; H, 3.50; N, 2.21. Found: C, 62.51; H, 3.50; N, 2.26.

***N*-[(Phenyloxy)carbonyl]-6-[[3-((trimethylsilyl)ethynyl)-2-naphthyl]-ethynyl]-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (21).** To a mixture of **20** (1.59 g, 2.51 mmol), tetrakis-(triphenylphosphine)palladium (290 mg, 0.25 mmol), and cuprous iodide (96 mg, 0.50 mmol) in dry, degassed CH_3CN (50 mL) cooled at 0 °C was added (trimethylsilyl)acetylene (1.64 mL, 11.6 mmol) and triethylamine (1.60 mL, 11.5 mmol). The resulting mixture was stirred at 25 °C for 20 h, poured into a mixture of saturated aqueous ammonium chloride (50 mL) and saturated aqueous sodium bicarbonate (50 mL), and extracted with ethyl ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash column chromatography (silica, 25% ethyl ether in petroleum ether) to afford **21** (1.42 g, 97%): colorless gum; R_f = 0.53 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (dd, J = 7.9, 1.4 Hz, 1 H, aromatic), 7.94 (s, 1 H, aromatic), 7.71–7.10 (m, 13 H, aromatic), 6.03 (s, 1 H, C*H*N), 2.80–2.72 (m, 2 H, CH_2), 2.45–2.29 (m, 2 H, CH_2), 2.09–1.90 (m, 2 H, CH_2), 0.30 (s, 9 H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.1, 151.0, 136.0, 132.8, 132.7, 132.3, 132.0, 130.0, 129.5, 129.3, 128.6, 128.3, 127.5, 127.4, 126.1, 125.7, 123.1, 121.6, 121.5, 120.5, 120.3, 115.3, 103.4, 98.1, 85.8, 84.8, 75.1, 57.6, 48.3, 38.9, 24.0, 18.3, 0.0; IR ($CHCl_3$) ν_{max} 3056, 3019, 2958, 2155, 1721, 1490, 1377, 1319, 1256, 1203, 845, 753 cm^{-1}; HRMS for $C_{37}H_{31}NO_4SiCs$ (M + Cs$^+$), calcd 714.1077, found 714.1077.

***N*-[(Phenyloxy)carbonyl]-6-[3-ethynyl-2-naphthylethynyl]-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (22).** To a solution of **21** (1.42 g, 2.44 mmol) in a mixture of THF–H_2O (10:1, 220 mL) was added lithium hydroxide monohydrate (205 mg, 4.88 mmol) followed by stirring at 25 °C for 40 min. The reaction mixture was diluted with H_2O (200 mL) and extracted with ethyl ether (2 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by flash chromatography (silica, 33% ethyl ether in petroleum ether) to provide **22** (1.20 g, 96%): colorless gum; R_f = 0.35 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J = 7.9, 1.4 Hz, 1 H, aromatic), 7.92 (s, 1 H, aromatic), 7.80 (s, 1 H, aromatic), 7.72–7.68 (m, 2 H, aromatic), 7.60–7.10 (m, 10 H, aromatic), 6.19 (s, 1 H, C*H*N), 2.95 (s, 1 H, CC*H*), 2.86–2.74 (m, 2 H, CH_2), 2.45–2.28 (m, 2 H, CH_2), 2.10–1.90 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.6, 150.9, 135.9, 132.7, 132.3, 132.2, 132.1, 129.9, 129.3, 128.8, 127.5, 127.4, 125.8, 125.7, 123.1, 121.4, 120.9, 120.5, 86.0, 84.3, 81.7, 80.4, 75.4, 57.6, 48.2, 38.7, 23.8, 18.4; IR ($CHCl_3$) ν_{max} 3294, 2957, 1714, 1489, 1378, 1320, 1256, 1202, 1069, 753 cm^{-1}; HRMS for $C_{34}H_{23}NO_4Cs$ (M + Cs$^+$), calcd 642.0681, found 642.0660.

Compound 23. A solution of **22** (829 mg, 1.63 mmol) in dry toluene (20 mL) cooled at −78 °C was treated with lithium diisopropylamide (1.30 mL of a 1.5 M solution in cyclohexane, 1.95 mmol). After 10 min at −78 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride (3 mL), poured into H_2O (50 mL), and extracted with ethyl ether (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 50% ethyl ether in petroleum ether) to give **23** (653 mg, 79%): white solid; mp 139–142 °C (dec, from ethyl ether); R_f = 0.14 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (dd, J = 8.0, 1.5 Hz, 1 H, aromatic), 7.75 (s, 1 H, aromatic), 7.71 (s, 1 H, aromatic), 7.70–7.63 (m, 2 H, aromatic), 7.48–7.11 (m, 10 H, aromatic), 5.61 (s, 1 H, C*H*N), 2.41 (dd, J = 15.1, 8.2 Hz, 1 H, CH_2), 2.30–2.05 (m, 3 H, CH_2), 2.01–1.93 (m, 1 H, CH_2), 1.77–1.70 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 151.0, 136.0, 132.2, 131.9, 131.5, 130.5, 129.3, 129.1, 128.3, 127.9, 127.7, 127.5, 126.3, 125.7, 125.2, 122.7, 122.0, 121.6, 95.4, 93.5, 90.0, 88.7, 73.7, 73.0, 64.3, 50.2, 34.7, 23.5, 19.3; IR ($CHCl_3$) ν_{max} 3452, 3016, 2953, 1714, 1491, 1380, 1323, 1203, 751 cm^{-1}; HRMS for $C_{34}H_{23}NO_4Cs$ (M + Cs$^+$), calcd 642.0681, found 642.0694. Anal. Calcd for $C_{34}H_{23}NO_4$: C, 80.14; H, 4.55; N, 2.75. Found: C, 80.43; H, 4.19; N, 2.89.

Compound 24. A solution of **23** (693 mg, 1.36 mmol), thiocarbonyldiimidazole (727 mg, 4.08 mmol), and DMAP (83 mg, 0.68 mmol) in dichloromethane (5 mL) was stirred at 25 °C for 1 week, and then the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (silica, 67% ethyl ether in petroleum ether) to give **24** (770 mg, 91%): white solid; mp 146–148 °C (dec, from ethyl ether); R_f = 0.27 (silica, 67% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1 H, aromatic), 7.88 (s, 1 H, aromatic), 7.78–7.01 (m, 16 H, aromatic), 5.56 (s, 1 H, C*H*N), 3.17–3.10 (m, 1 H, CH_2), 2.50 (dd, J = 14.3, 7.1 Hz, 1 H, CH_2), 2.40–2.20 (m, 3 H, CH_2), 1.90–1.79 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 179.3, 150.9, 136.4, 132.3, 131.1, 130.8, 130.5, 129.5, 129.4, 128.3, 128.0, 127.9, 127.8, 127.0, 126.5, 125.9, 125.4, 122.1, 121.6, 121.5, 100.4, 89.8, 89.6, 89.2, 85.6, 74.4, 63.8, 50.2, 28.0, 23.1, 18.6; IR ($CHCl_3$) ν_{max} 3016, 2957, 1724, 1490, 1384, 1321, 1281, 1203, 751 cm^{-1}; HRMS for $C_{38}H_{25}N_3O_4$-SCs (M + Cs$^+$), calcd 752.0620, found 752.0620.

Compound 25. A solution of **24** (352 mg, 0.57 mmol) in dry toluene (10 mL) was treated with nBu$_3$SnH (0.20 mL, 0.74 mmol) in the presence of a catalytic amount of AIBN at 25 °C for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatography (silica, 33% ethyl ether in petroleum ether) to afford **25** (260 mg, 93%): white crystalline solid; mp 220–222 °C (dec, from ethyl ether); R_f = 0.52 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 1 H, aromatic), 7.73 (s, 1 H, aromatic), 7.72–7.66 (m, 3 H, aromatic), 7.53 (br s, 1 H, aromatic), 7.50–7.42 (m, 2 H, aromatic), 7.38 (t, J = 7.7 Hz, 2 H, aromatic), 7.30–7.13 (m, 5 H, aromatic), 5.64 (s, 1 H, C*H*N), 3.92 (br s, 1 H, CH$_2$C*H*), 2.53 (dd, J = 15.4, 7.5 Hz, 1 H, CH_2), 2.34–2.22 (m, 1 H, CH_2), 2.12–2.00 (m, 2 H, CH_2), 1.91–1.84 (m, 1 H, CH_2), 1.70–1.60 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 150.9, 135.8, 132.3, 131.7, 130.3, 129.3, 128.6, 128.4, 128.3, 128.1, 127.7, 127.6, 127.3, 127.2, 125.2, 123.8, 122.7, 121.5, 96.4, 90.7, 90.5, 88.8, 70.2, 60.8, 49.8, 28.9, 22.7, 22.6, 15.5; IR ($CHCl_3$) ν_{max} 2931, 1719, 1602, 1493, 1380, 1323, 1299, 1286, 1274, 1147, 1025, 975, 920, 894 cm^{-1}; UV (EtOH) λ_{max} (log e) 304 (3.47), 294 (4.01), 284 (4.26), 267–240 (4.53–4.55), 214 (4.50) nm; HRMS for $C_{34}H_{23}NO_3Cs$ (M + Cs$^+$), calcd 626.0732, found 626.0732.

Sulfide 26. To a suspension of NaH (80 mg of 60% dispersion in mineral oil, 2.0 mmol) in dry THF (3 mL) was added 2-(phenylthio)-

ethanol (0.27 mL, 2.0 mmol) followed by stirring at 25 °C for 5 min. This mixture was added via syringe into a solution of **25** (495 mg, 1.0 mmol) in dry THF (7 mL). After stirring at 25 °C for 10 min, the reaction mixture was diluted with ethyl ether (10 mL), poured into H_2O (20 mL), and extracted with ethyl ether (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 33% ethyl ether in petroleum ether) to give **26** (459 mg, 83%): colorless gum; R_f = 0.46 (silica, 33% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.11 (m, 15 H, aromatic), 5.50 (br s, 1 H, C*H*N), 4.43–4.20 (m, 2 H, OCH_2), 3.85 (t, J = 2.9 Hz, 1 H, C*H*CH$_2$), 3.24–3.10 (m, 2 H, CH_2S), 2.46 (dd, J = 14.7, 6.9 Hz, 1 H, CH_2), 2.27–2.15 (m, 1 H, CH_2), 2.09–1.98 (m, 2 H, CH_2), 1.87–1.78 (m, 1 H, CH_2), 1.65–1.57 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 154.3, 135.8, 134.9, 132.3, 131.8, 130.3, 129.9, 129.1, 128.6, 128.1, 128.0, 127.8, 127.6, 127.5, 127.2, 127.1, 126.6, 126.3, 124.9, 123.8, 122.9, 96.4, 90.7, 90.6, 88.6, 70.3, 64.6, 60.8, 49.5, 32.4, 28.9, 22.8, 22.6, 15.5; IR ($CHCl_3$) ν_{max} 3055, 3018, 2950, 1704, 1494, 1393, 1321, 1272, 753 cm^{-1}; HRMS for $C_{36}H_{27}NO_3SCs$ (M + Cs$^+$), calcd for 686.0766, found 686.0766.

Sulfone 27. To a solution of **26** (125 mg, 0.23 mmol) in dichloromethane (3 mL) was added *m*CPBA (55%, 177 mg, 0.56 mmol) followed by stirring at 25 °C for 30 min. The reaction mixture was poured into saturated aqueous sodium bicarbonate (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica, 75% ethyl ether in petroleum ether) to provide **27** (114 mg, 86%): white solid; mp 114–116 °C (dec, from ether–petroleum ether); R_f = 0.29 (silica, 80% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.10 (m, 15 H, aromatic), 5.48 (br, 1 H, C*H*N), 4.65–4.25 (m, 2 H, OCH_2), 3.85 (br s, 1 H, C*H*CH$_2$), 3.51 (br, 2 H, CH_2S), 2.45 (dd, J = 14.7, 6.9 Hz, 1 H, CH_2), 2.20 (dt, J = 18.0, 8.7 Hz, 1 H, CH_2), 2.12–1.93 (m, 2 H, CH_2), 1.90–1.80 (m, 1 H, CH_2), 1.60 (br t, J = 10.1 Hz, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 166.4, 138.9, 135.5, 134.0, 132.4, 131.8, 130.3, 129.5, 128.7, 128.3, 128.1, 128.0, 127.8, 127.6, 127.3, 127.2, 125.2, 123.8, 122.8, 96.3, 90.7, 90.4, 88.8, 70.1, 60.7, 59.4, 55.2, 49.6, 28.9, 22.7, 22.2, 15.5; IR ($CHCl_3$) ν_{max} 2950, 1720, 1430, 1400, 1315, 1280, 1165, 760, 680 cm^{-1}; UV (MeOH) λ_{max} (log e) 280 (3.66, sh), 261 (4.27) nm; HRMS for $C_{36}H_{27}NO_5SCs$ (M + Cs$^+$), calcd 718.0664, found 718.0665. Anal. Calcd for $C_{36}H_{27}NO_5S$: C, 73.83; H, 4.65; N, 2.39; S, 5.47. Found: C, 73.69; H, 4.68; N, 2.46; S, 5.11.

Compound 28. A solution of **16** (10 mg, 0.023 mmol) in 1,4-cyclohexadiene (0.2 mL) and benzene (0.8 mL) was treated with *p*-toluenesulfonic acid monohydrate (5.2 mg, 0.027 mmol) at 25 °C for 4 h. The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (silica, 50% ethyl ether in benzene) to afford **28** (8.2 mg, 79%): R_f = 0.48 (silica, 50% ethyl ether in benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1 H, aromatic), 7.84–7.79 (m, 1 H, aromatic), 7.72 (dd, J = 7.4, 1.8 Hz, 1 H, aromatic), 7.68–7.65 (m, 1 H, aromatic), 7.53–7.38 (m, 6 H, aromatic), 7.37 (s, 1 H, aromatic), 7.31–7.26 (m, 2 H, aromatic), 7.12–7.01 (m, 2 H, aromatic), 6.05 (s, 1 H, C*H*N), 3.57 (br s, 1 H, CH$_2$C*H*), 3.10–2.80 (br, 1 H, O*H*), 2.42 (dddd, J = 12.8, 12.8, 3.6, 3.6 Hz, 1 H, CH_2), 2.26 (ddd, J = 13.6, 13.6, 6.0 Hz, 1 H, CH_2), 1.90 (dd, J = 13.2, 4.6 Hz, 1 H, CH_2), 1.67 (br, 1 H, O*H*), 1.47 (br t, J = 12.1 Hz, 2 H, CH_2), 0.90 (ddddd, J = 13.6, 13.6, 13.6, 4.6, 4.6 Hz, 1 H, CH_2); IR ($CHCl_3$) ν_{max} 3597, 3567, 3394 (br), 2930, 1689, 1604, 1488, 1379, 1320, 1285, 1261, 1053 cm^{-1}; UV (EtOH) λ_{max} (log e) 297 (sh, 3.52), 288 (3.71), 277 (3.75), 266 (3.73), 236–210 (br, 4.49–4.42) nm; HRMS for $C_{30}H_{26}NO_4$ (M + H$^+$), calcd 464.1862, found 464.1888.

Compound 29. A solution of **25** (10 mg, 0.02 mmol) in 1,4-cyclohexadiene (0.2 mL) and benzene (0.8 mL) was treated with *p*-toluenesulfonic acid monohydrate (4.6 mg, 0.024 mmol) at 25 °C for 4 h. The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (silica, 50% ethyl ether in benzene) to give **29** (5.1 mg, 49%): R_f = 0.46 (silica, 50% ethyl ether in benzene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1 H, aromatic), 8.23 (s, 1 H, aromatic), 8.22 (s, 1 H, aromatic), 7.99–7.88 (m, 2 H, aromatic), 7.75 (dd, J = 7.7, 1.7 Hz, 1 H, aromatic), 7.54 (s, 1 H, aromatic), 7.50–7.40 (m, 5 H, aromatic), 7.30 (d, J = 7.4 Hz, 3 H, aromatic), 7.14–7.00 (m, 2 H, aromatic), 6.11 (s, 1 H, C*H*N), 3.62 (br s, 1 H, CH$_2$C*H*), 2.46 (dddd, J = 10.8, 10.8, 3.3, 3.3 Hz, 1 H, CH_2), 2.30 (ddd, J = 13.6, 13.6, 6.0 Hz, 1 H, CH_2), 1.94 (dd, J = 13.3, 4.6 Hz, 1 H, CH_2), 1.60 (br, 1 H, O*H*), 1.53 (br t, J = 13.5 Hz, 2 H, CH_2), 0.98 (ddddd, J = 13.9, 13.9, 13.9, 4.3, 4.3 Hz, 1 H, CH_2); IR ($CHCl_3$) ν_{max} 3694, 3567, 2952, 1688, 1604, 1488, 1379, 1319, 1296, 1287, 1269, 1060, 909 cm^{-1}; UV (EtOH) λ_{max} (log e) 390 (3.74), 369 (3.78), 351 (3.66), 333 (3.45), 318 (3.20), 267–244 (4.43–4.46), 215 (4.43) nm; HRMS for $C_{34}H_{27}NO_4Cs$ (M + Cs$^+$), calcd 646.0994, found 646.0994.

Amine Epoxide 32. To a solution of **18** (30 mg, 0.056 mmol) in THF (3 mL) was added DBU (17 mL, 0.11 mmol), and the resulting mixture was stirred at 25 °C for 30 min. The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (silica, 20% ethyl ether in benzene containing 0.5% propylamine) to afford **32** (9.2 mg, 50%): R_f = 0.46 (silica, 20% ethyl ether in benzene containing 0.5% propylamine); ^{1}H NMR (300 MHz, C_6D_6) δ 7.47 (dd, J = 7.7, 1.2 Hz, 1 H, aromatic), 7.03 (m, 2 H, aromatic), 6.93 (td, J = 7.7, 0.9 Hz, 1 H, aromatic), 6.70 (td, J = 7.3, 1.0 Hz, 1 H, aromatic), 6.62 (m, 2 H, aromatic), 6.19 (dd, J = 7.9, 1.0 Hz, 1 H, aromatic), 3.74 (d, J = 2.5 Hz, 1 H, C*H*N), 3.53 (t, J = 3.0 Hz, 1 H, C*H*CH$_2$), 3.31 (d, J = 2.1 Hz, 1 H, N*H*), 2.32–2.30 (m, 1 H, CH_2), 2.05–1.90 (m, 3 H, CH_2), 1.58–1.48 (m, 1 H, CH_2), 1.37–1.24 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 135.4, 130.8, 130.7, 129.9, 129.8, 129.4, 128.9, 128.3, 123.4, 119.9, 119.0, 98.7, 95.5, 91.1, 87.6, 71.5, 62.7, 51.9, 43.6, 25.2, 24.2, 16.9; IR ($CHCl_3$) ν_{max} 3360, 2945, 2890, 1620, 1500, 1475, 1450, 1305, 1160, 925, 760 cm^{-1}; HRMS for $C_{23}H_{18}NO$ (M + H$^+$), calcd for 324.1388, found 324.1388.

Amine Epoxide 33. To a solution of **27** (33.2 mg, 0.057 mmol) in THF (5 mL) was added DBU (17 mL, 0.11 mmol), and the resulting mixture was stirred at 25 °C for 2 h. The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (silica, 20% ethyl ether in benzene containing 0.5% propylamine) to give **33** (13.8 mg, 64%): R_f = 0.46 (silica, 20% ethyl ether in benzene containing 0.5% propylamine); ^{1}H NMR (300 MHz, C_6D_6) δ 7.53 (s, 1 H, aromatic), 7.51 (s, 1 H, aromatic), 7.22–7.00 (m, 5 H, aromatic), 6.95 (td, J = 8.0, 1.3 Hz, 1 H, aromatic), 6.73 (td, J = 7.4, 1.0 Hz, 1 H, aromatic), 6.23 (br d, J = 2.5 Hz, 1 H, aromatic), 3.80 (d, J = 2.9 Hz, 1 H, C*H*N), 3.61 (t, J = 3.0 Hz, 1 H, C*H*CH$_2$), 3.35 (br d, J = 2.5 Hz, 1 H, N*H*), 2.40–2.28 (m, 1 H, CH_2), 2.15–1.95 (m, 3 H, CH_2), 1.64–1.55 (m, 1 H, CH_2), 1.40–1.28 (m, 1 H, CH_2); HRMS for $C_{27}H_{20}NO$ (M + H$^+$), calcd 374.1545, found 374.1549.

Diol 8. A mixture of **32** (5 mg, 0.015 mmol) and silica gel (5 mg) in wet benzene (2 mL) was stirred at 25 °C for 3 h. The silica gel was filtered off, the filtrate was concentrated *in vacuo*, and the residue was purified by preparative TLC (silica, 67% ethyl ether in petroleum ether) to give **8** (1.7 mg, 34%): R_f = 0.70 (silica, 66% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.53 (dd, J = 8.0, 1.3 Hz, 1 H, aromatic), 7.40–7.18 (m, 4 H, aromatic), 7.09 (td, J = 7.6, 1.5 Hz, 1 H, aromatic), 6.94 (td, J = 7.8, 1.1 Hz, 1 H, aromatic), 6.59 (dd, J = 7.8, 0.8 Hz, 1 H, aromatic), 4.21 (br, 1 H, N*H*), 4.19 (s, 1 H, O*H*), 4.07 (br s, 1 H, C*H*N), 3.68 (t, J = 1.7 Hz, 1 H, C*H*CH$_2$), 2.28–1.72 (m, 7 H, O*H*, CH_2CH_2CH_2); HRMS for $C_{23}H_{19}NO_2Cs$ (M + Cs$^+$), calcd 474.0470, found 474.0493.

Diol 9. A mixture of **33** (12 mg, 0.032 mmol) and silica gel (10 mg) in wet benzene (2 mL) was stirred at 25 °C for 2 h. The silica gel was filtered off, the filtrate was concentrated *in vacuo*, and the residue was purified by preparative TLC (silica, 75% ethyl ether in petroleum ether) to provide **9** (12.5 mg, 100%): R_f = 0.50 (silica, 75% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, THF-d_8) δ 7.71 (s, 1 H, aromatic), 7.63 (m, 2 H, aromatic), 7.54 (s, 1 H, aromatic), 7.37–7.28 (m, 3 H, aromatic), 6.80 (t, J = 7.9 Hz, 1 H, aromatic), 6.62 (t, J = 7.1 Hz, 1 H, aromatic), 6.38 (d, J = 7.9 Hz, 1 H, aromatic), 5.59 (s, 1 H, N*H*), 4.64 (s, 1 H, C*H*N), 4.18 (s, 1 H, O*H*), 4.01 (s, 1 H, C*H*CH$_2$), 2.30–1.40 (m, 7 H, O*H*, CH_2CH_2CH_2); ^{13}C NMR (CD_3OD+$CDCl_3$, 125 MHz) δ 141.9, 139.9, 138.9, 134.5, 130.1, 129.1, 128.6, 128.3, 128.2, 127.6, 127.3, 126.9, 121.0, 116.6, 104.1, 99.9, 86.5, 84.8, 73.6, 73.4, 55.2, 41.3, 34.5, 28.5, 20.2; IR ($CHCl_3$) ν_{max} 3475, 3390, 2930, 1620, 1480, 1010, 975, 900, 750 cm^{-1}; UV (MeOH) λ_{max} (log e) 285 (3.81, sh), 259 (4.50) nm; HRMS for $C_{27}H_{21}NO_2Cs$ (M + Cs$^+$), calcd 524.0627, found 524.0681.

Compound 34. A solution of **8** (10 mg, 0.029 mol) in 1,4-cyclohexadiene (0.5 mL) and benzene (2 mL) was stirred at 25 °C for 2 h. The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (silica, 75% ethyl ether in petroleum ether) to give **34** (7.0 mg, 70%): R_f = 0.44 (silica, 75% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1 H, aromatic), 7.76–7.74 (m, 1 H, aromatic), 7.67–7.60 (m, 2 H, aromatic), 7.39 (s, 1 H, aromatic), 7.37–7.34 (m, 2 H, aromatic), 6.87 (t, J = 7.7 Hz, 1 H, aromatic), 6.79 (t, J = 7.7 Hz, 1 H, aromatic), 6.30 (d, J = 7.7 Hz, 1 H, aromatic), 4.37 (s, 1 H, C*H*N), 4.29–4.15 (br, 1 H, N*H*), 3.78 (br s, 1 H, O*H*), 3.73 (br s, 1 H, CH$_2$C*H*), 2.83 (br s, 1 H, O*H*), 2.44–2.33 (m, 1 H, CH_2), 2.28 (dd, J = 13.9, 6.0 Hz, 1 H, CH_2), 1.73 (dd, J = 13.6, 4.9 Hz, 1 H, CH_2), 1.21 (br t, J = 6.5 Hz, 2 H, CH_2), 0.93–0.75 (m, 1 H, CH_2); IR ($CHCl_3$) ν_{max} 3444, 3379, 2927, 1605, 1470, 1372, 1293, 1063, 734 cm^{-1}; HRMS for $C_{23}H_{21}NO_2Cs$ (M + Cs$^+$), calcd 476.0627, found 476.0632.

Compound 35. A solution of **9** (2.5 mg, 0.0064 mmol) in 1,4-cyclohexadiene (0.25 mL) and benzene (1 mL) was heated at 65 °C for 2 h. The solvent was removed *in vacuo*, and the residue was purified by preparative TLC (silica, 75% ethyl ether in petroleum ether) to furnish **35** (1.8 mg, 72%): R_f = 0.37 (silica, 50% ethyl ether in petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1 H, aromatic), 8.22 (s, 1 H, aromatic), 7.95–7.90 (m, 2 H, aromatic), 7.88 (s, 1 H, aromatic), 7.63 (dd, J = 7.7, 1.6 Hz, 1 H, aromatic), 7.55 (s, 1 H, aromatic), 7.42–7.38 (m, 2 H, aromatic), 7.63 (dd, J = 7.7, 1.6 Hz, 1 H, aromatic), 7.55 (s, 1 H, aromatic), 7.42–7.38 (m, 2 H, aromatic), 6.89 (td, J = 7.7, 1.6 Hz, 1 H, aromatic), 6.80 (td, J = 7.7, 1.2 Hz, 1 H, aromatic), 6.31 (dd, J = 7.7, 1.2 Hz, 1 H, aromatic), 4.42 (s, 1 H, C*H*N), 4.27–4.12 (br, 1 H, N*H*), 3.73 (br s, 1 H, O*H*), 3.62 (br s, 1 H, CH_2CH), 2.85 (br s, 1 H, O*H*), 2.48–4.12 (br, 1 H, N*H*), 3.73 (br s, 1 H, O*H*), 3.62 (br s, 1 H, CH_2CH), 2.85 (br s, 1 H, O*H*), 2.48–2.37 (m, 1 H, CH_2), 2.31 (dd, J = 13.9, 5.9 Hz, 1 H, CH_2), 1.76 (dd, J = 13.8, 5.0 Hz, 1 H, CH_2), 1.49–1.40 (m, 2 H, CH_2), 0.90 (td, J = 13.9, 4.5 Hz, 1 H, CH_2); IR ($CHCl_3$) ν_{max} 3442, 3380, 2924, 1605, 1469, 1373, 1291, 1063, 733 cm^{-1}; HRMS for $C_{27}H_{23}NO_2Cs$ ($M + Cs^+$), calcd 526.0783, found 526.0783.

Computational Methods. The molecular structures of all stationary points have been determined using *ab initio* techniques, at the restricted Hartree–Fock (RHF) self-consistent field (SCF) level of theory. The calculations were performed using the STO-3G[25a] and 6-31G(D)[25b,c] basis sets. The latter basis set includes a set of six d polarization functions on all heavy atoms. The STO-3G level of theory was used to carry out full geometry optimizations, and the 6-31G(D) basis set was employed for single point energy calculations at these optimized geometries. Geometry optimizations were performed with the aid of analytically determined gradients and the search algorithms contained in GAMESS.[26] Full structural information on all molecules are available as supplementary material.

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