Stereochemical and Conformational Effects on the Cycloaromatization of Dynemicin A-Related Molecules

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Abstract: A series of compounds was investigated in order to determine the factors that govern the cycloaromatization reaction exhibited by dynemicin A and related molecules. It was determined that the stereochemistry at C10a dictated the thermal reactivity of compounds equipped with an exo-epoxide. Structures containing an α-substituent were unreactive while those possessing a β-substituent underwent cyclization at 80 °C. Molecular mechanics and dynamics calculations indicate that this reactivity difference is due to a steric interaction that develops as the α-substituted compounds undergo a conformational change that appears to be necessary for aromatization to occur. Additionally, a C10a α-substituted endo-epoxide was synthesized and shown to undergo cycloaromatization under mild acidic conditions *via* an epoxide opening.

Introduction

Dynemicin A (**1**) is unique among the enediyne antibiotics in that it contains not only a cyclic enediyne but an anthraquinone chromophore.[1,2] Unlike other members of this class, it exhibits antibacterial and antitumor activity with low toxicity. Thus, in an in vivo mouse leukemia assay, it significantly prolongs lifespan. This pharmacological activity is believed to be related to dynemicin A's ability to cleave DNA following its intercalation into DNA with its anthraquinone ring. This mode of binding positions the enediyne portion in the minor groove, where its chemistry with DNA takes place.[3-5] Dynemicin A's ability to be activated by reducing agents[3,6,7] leads to a proposed mechanism of activation in which the reduction of the anthraquinone precedes an epoxide opening reaction. This results in an intermediate capable of undergoing a cycloaromatization reaction under physiological conditions.[3-5,8] An intermediate diradical is believed to abstract a hydrogen atom from the backbone of DNA leading ultimately to strand scission.

The unusual structure and chemistry of dynemicin A led us to initiate synthetic and structural studies in this area. These resulted in syntheses of di- and tri-*O*-methyl dynemicin A methyl esters.[9] During the course of our investigations several compounds were found to possess novel chemical properties. We therefore set out to determine the factors that govern the reactivity of these compounds. The results of these studies are presented in this Article.

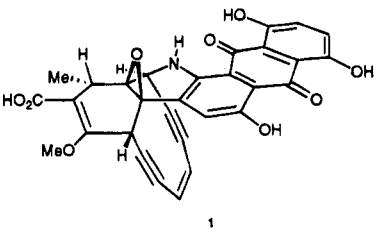

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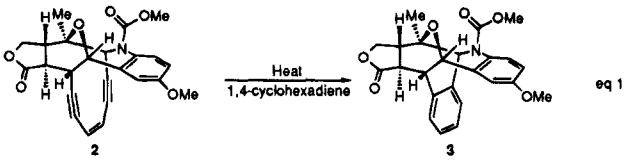
Figure 1. Structure of dynemicin A.

Results and Discussion

The key observation generating these studies is outlined in eq 1. The epoxide **2** when heated in the presence of 1,4-cyclohexadiene underwent cycloaromatization to give the aromatized product **3**.[10-12] This was somewhat unexpected as the



2 **3** eq 1

product is formally the epoxide of a bridgehead bicyclo[3.3.1]-nonene. Although these systems are expected to be less strained than their olefinic counterparts, MM3 calculations[13-17] show that the bridgehead epoxides are approximately 10 kcal mol^{-1}

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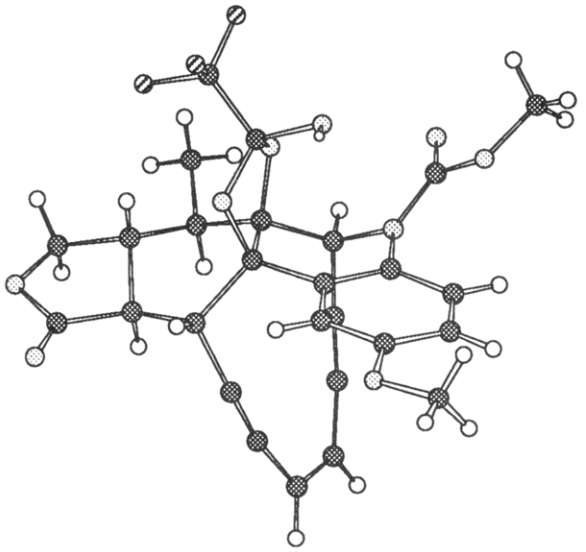

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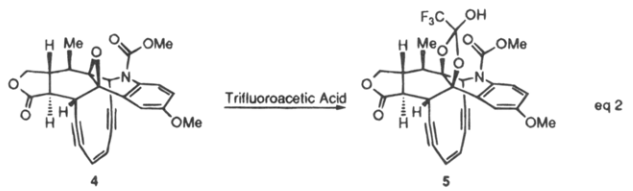
Figure 2. Chem3D representation of the crystal structure of compound **5**.

more strained than nonbridgehead epoxides when situated on a bicyclo[3.3.1]nonane structure.

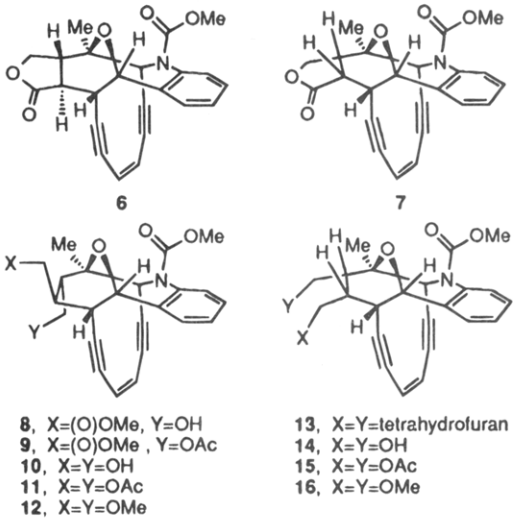
A second surprising result is shown in eq 2. In this instance compound **4** was expected to aromatize when treated with protic acids. However, when trifluoroacetic acid was used the ortho-acid **5** was produced.[10-12] The structure of this compound has



4 5

been confirmed by X-ray crystallographic analysis (Figure 2). Its stability is stunning in light of the fact that the C12−C17 distance is 3.280 Å, which is within the range that would be expected to lead to cyclization at room temperature.[18] Furthermore, when the ortho-acid **5** was heated a new compound was produced, but again cycloaromatization had not occurred. The new structure showed the same mass as the starting material, but its ^{1}H NMR spectrum was slightly different. It has been assigned the structure of the anomeric ortho-acid.[11] If the factors governing these aromatization reactions could be deciphered, then it might be possible to use this knowledge to facilitate the design of new structures capable of cleaving DNA under physiological conditions.

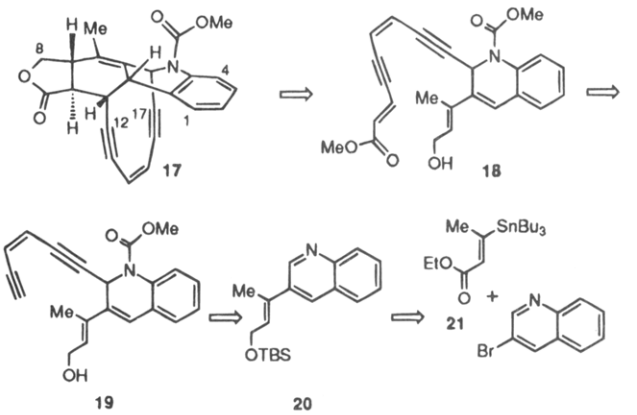
Synthesis. In order to investigate these phenomena, several structural variants of dynemicin A were designed (Figure 3). Each of these contains what will be referred to as an exo-epoxide, defined as an epoxide that is spiro to, rather than fused to, the ten-membered ring containing the enediyne. Given the observation above, it was anticipated that this epoxide would provide for thermal control over the cyclization reaction. To further investigate, substituents were varied from electron-donating to electron-withdrawing and then altered to provide for the possibility of hydrogen bonding in two cases (**10**, **14**).



8, X=(O)OMe, Y=OH
9, X=(O)OMe , Y=OAc
10, X=Y=OH
11, X=Y=OAc
12, X=Y=OMe
13, X=Y=tetrahydrofuran
14, X=Y=OH
15, X=Y=OAc
16, X=Y=OMe

Figure 3. Proposed exo-epoxide-containing structural variants of dynemicin A.

Scheme 1



17 18 19 20 21

The syntheses of the proposed compounds were envisioned to pass through a common intermediate **17** (Scheme 1), which therefore became our first synthetic target.

The vinyl tin reagent **21** was produced using methodology developed by Piers and co-workers.[19] Addition of tributytin copper(I) to ethyl tetrolate led to the desired product with no detectable regioisomers. Furthermore, this methodology proved compatible to a scaleup that has been performed on 20 g of ethyl tetrolate in 59% yield. The key to success is to maintain vigorous stirring upon addition of solid copper bromide−dimethyl sulfide to the solution of lithium tributyltin. Coupling of this vinyl tin to 3-bromoquinoline under palladium catalysis in refluxing toluene for 24 h gave the desired product **22** in 58% (16% recovered vinyl tin), provided that an additional portion of tetrakis(triphenylphosphine)palladium was added every 6−8 h (Scheme 2). Reduction of the ester with diisobutylaluminum hydride (DIBAL-H) gave the corresponding alcohol that could be protected as the *tert*-butyldimethylsilyl ether to give vinyl quinoline **20** in 75% yield for the two steps.

The route described above constitutes a slight departure from the one used in the syntheses of di- and tri-*O*-methyl dynemicin A methyl ester in that the vinyl tin reagent in the latter cases was derived from 2-butyne-1-ol.[10] Although the coupling reaction works comparably with either reagent, the difficulties associated with the production of the vinyl tin from the alcohol (mediocre regioselectivity and difficult separation of isomers) renders the method used here superior.

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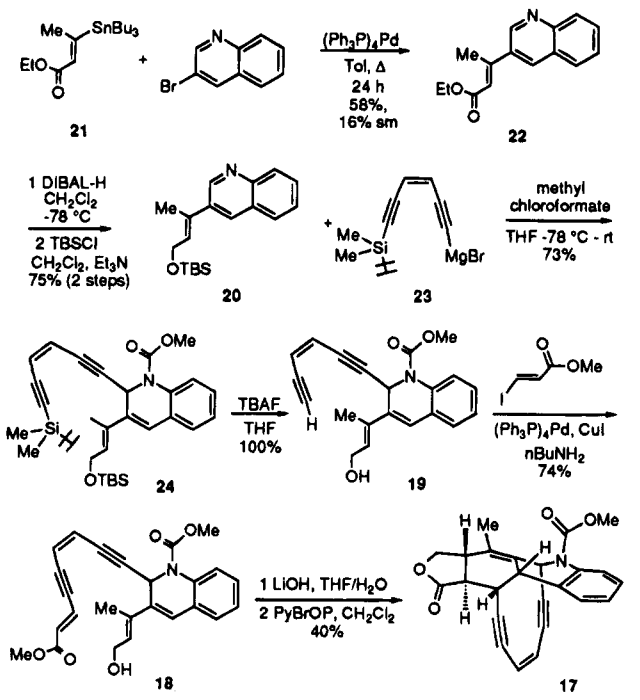
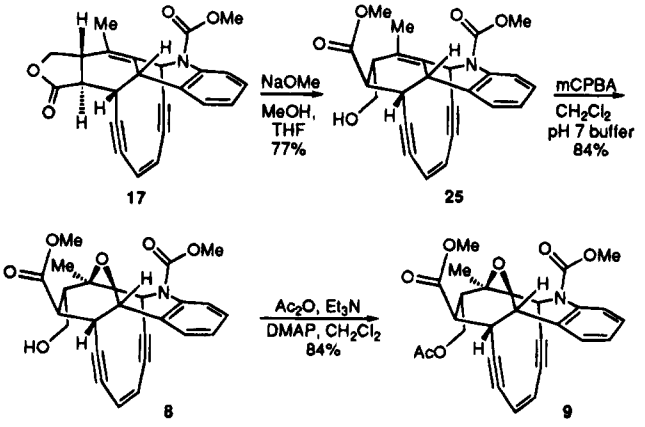
Scheme 2



Scheme 3



The remainder of the synthesis of the target intermediate **17** was straightforward (Scheme 2). The enediyne portion of the system could be incorporated as a single unit using the monoprotected enediyne previously prepared in these laboratories.[10] Thus, addition of the Grignard reagent **23** to a solution of vinyl quinoline and methyl chloroformate at −78 °C followed by warming to rt gave the dihydroquinoline **24** in 73% yield. Treatment of the bis-silyl compound with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) provided the doubly deprotected compound **19** quantitatively. Coupling of the terminal acetylene to the known iodoacrylate[10] using standard Pd(0)-based chemistry[20] produced the fully elaborated skeleton in 74% yield. Saponification of the methyl ester and treatment of the crude seco-acid with bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP)[21] in methylene chloride at "high" dilution (1 mM) gave the desired target **17** in 40% yield for the two steps.

With the common intermediate in hand, the steps required to construct the proposed compounds were initiated. The *trans*-lactone **17** was epoxidized using trifluoroperacetic acid (generated from urea−hydrogen peroxide complex and trifluoroacetic anhydride[22]) buffered with solid sodium phosphate dibasic to provide an unstable epoxide in approximately 20% yield. Due to its instability, the epoxide was immediately subjected to thermolysis conditions (see below).

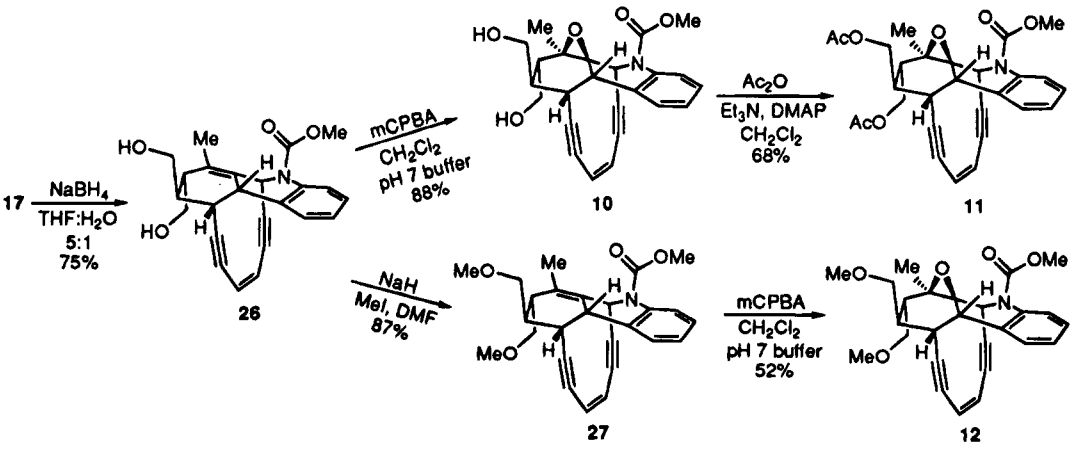
The methyl esters **8** and **9** were obtained by methanolysis of the lactone **17** (Scheme 3). Initial attempts to carry out this transformation were hampered by the production of significant quantities of *cis*-lactone **28**. This undesired reactivity was traced to the presence of hydroxide in the methoxide. However, treatment of the lactone with "dry" sodium methoxide in 1:1 MeOH:THF gave the desired hydroxy ester **25** in 77%. Epoxidation of the ester **25** using *m*-chloroperbenzoic acid (mCPBA) in methylene chloride buffered with pH 7 phosphate buffer gave the desired epoxide **8** (84%). Compound **9** was produced by acylation of the hydroxy ester **8** (acetic anhydride, triethylamine, (*N,N*-dimethylamino)pyridine, methylene chloride) in 84% yield.

Preparation of the diol derivatives (Scheme 4) began with the reduction of the lactone **17** to the diol using sodium borohydride in 5:1 THF:water in 75% yield.[23] Epoxidation (mCPBA) gave the epoxy diol **10** in 88%. Acylation as described above produced the diacetate **11** in 68% yield.

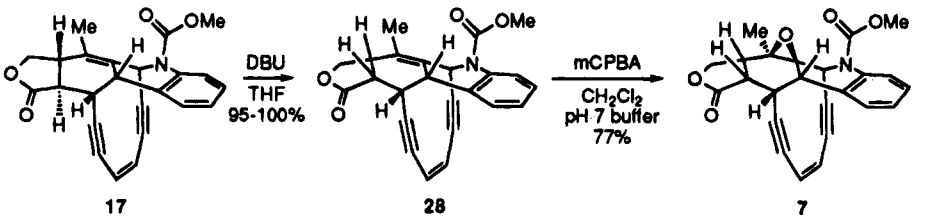
The dimethyl ether **12** was produced by treating the diol **26** with excess sodium hydride and iodomethane in dimethylformamide (87%), followed by epoxidation under the standard conditions (52%).

The preparation of the *cis*-substituted series of compounds (Scheme 5) began with the epimerization of lactone **17** using diazabicycloundecene (DBU) in THF (95−100%). Epoxidation of the *cis*-lactone was accomplished with mCPBA to give epoxide **7** in 77% yield. No attempt was made to construct the

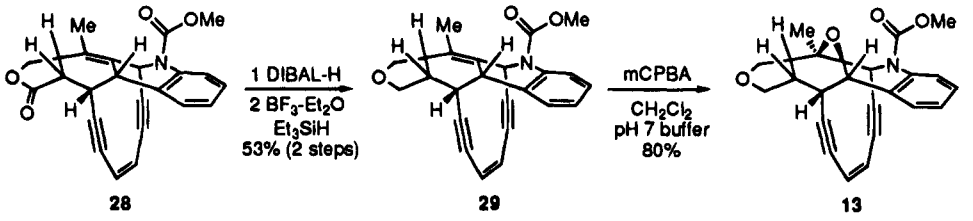
Scheme 4



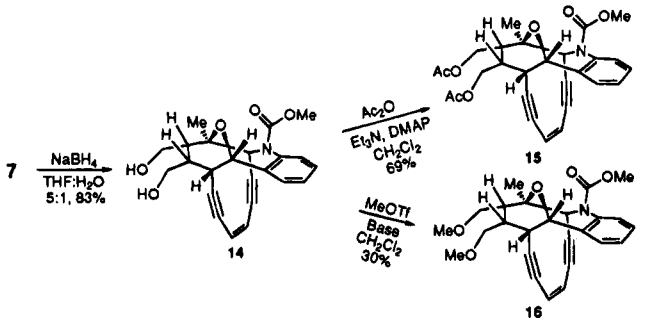
Scheme 5



Scheme 6



Scheme 7



methyl esters corresponding to compounds **8** and **9** as previous studies on a related system indicated that relactonization was a facile process. The tetrahydrofuran, however, could be synthesized by treatment of the *cis*-lactone **28** with DIBAL-H in methylene chloride at −78 °C, followed by treatment with BF_3−Et_2O and triethylsilane (53% for the two steps).[24] Epoxidation proceeded smoothly (80%) under standard conditions to give the desired compound **13** (Scheme 6).

The synthesis of the *cis*-diol derivatives required a slight modification (Scheme 7). The diol derived from reduction of the *cis*-lactone could not be epoxidized under the usual conditions. This may be due to a coordination of the epoxidizing agent on the α-face of the diol, leading to attack of the enediyne and then to decomposition. However, treating the *cis*-lactone epoxide **7** with sodium borohydride in THF:water (5:1) gave the epoxy-diol **14** in 83% yield.[23] This compound could either be acylated under standard conditions (69%) or methylated using trifluoromethanesulfonate and 2,6-di-*tert*-butyl-4-methylpyridine (30%) to provide compounds **15** and **16**, respectively. The sodium hydride, iodomethane conditions used in the *trans*-series gave a mixture of compounds, none of which appeared to be consistent with the desired product, when applied to the *cis*-diol derived from reduction of compound **28**.

Thermolysis. The results of the thermolysis studies are shown in Table 1 and Figure 4. In general, reactions were conducted at 8 mM substrate in toluene with 62 equiv of 1,4-cyclohexadiene. With the exception of the lactones, the reaction temperature was 80 °C. The immediately apparent trend is that the *trans*-substituted compounds undergo cycloaromatization while the *cis*-substituted ones do not.

Table 1. Thermolysis Studies

compd	temp (°C)	time (h)	products	yield (%), ratio
	Trans-Substituted			
lactone **6**	110	6	**30**	40
hydroxy methyl ester **8**	80	12	**31**:**8**	95, 1:3
acetate methyl ester **9**	80	12	**32**:**9**	>80, 1:3
diol **10**	80	12	**33**:**10**	95, 1:1.3
diacetate **11**	80	12	**34**:**11**	>80, 1:2
DiMe ether **12**	80	12	**35**:**12**	>80, 1:3
	cis-Substituted			
lactone **7**	110	22	**7**	>90
tetrahydrofuran **13**	80	12	**13**	>90
diol **14**	80	12	**14**	>90
diacetate **15**	80	12	**15**	>90
DiMe ether **16**	80	12	**16**	>90

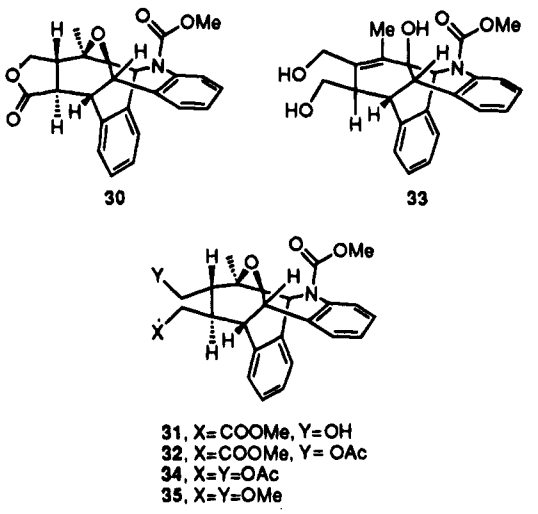


Figure 4. Products obtained from thermolysis of dynemicin A structural variants.

In the case of the diols the results were unexpected. Although an aromatized product, **33**, is formed under the thermolysis conditions, the epoxide is no longer intact. Several lines of evidence support this structural assignment. First, an analysis of the ^1H NMR revealed that the signal corresponding to the methyl group had moved from 1.51 to 1.88 ppm, consistent

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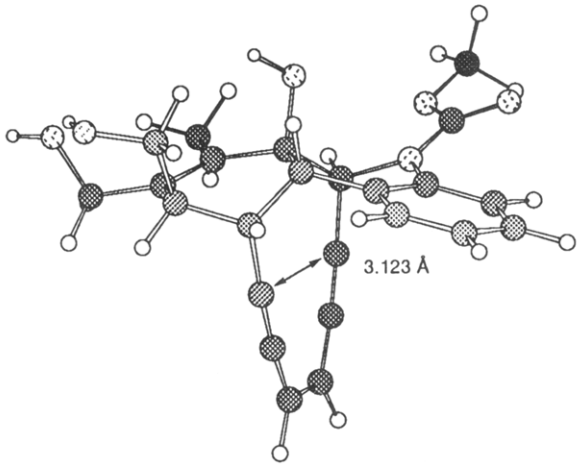


Figure 5. Energy minimized (MM3) model of the elimination product derived from **10**.

with a vinyl methyl group. (Conversely, in the case of the hydroxy methyl ester **8**, the corresponding methyl resonance shifted from 1.52 to 1.18 ppm upon aromatization. The upfield shift is consistent with the methyl group occupying a position above the newly formed aromatic ring and thus being shielded by the ring current.) Furthermore, the mass spectrum showed an ion with the mass corresponding to the loss of OH, which would be expected for a compound containing an allylic hydroxyl.

The elimination of epoxide **10** raises the question of timing: Did the aromatization take place first followed by an elimination or did the epoxide eliminate and then cyclize? Molecular mechanics calculations indicate that once elimination has occurred the C12−C17 distance should decrease from 3.327 to 3.123 Å (Figure 5), indicating that cycloaromatization will be more facile. In an attempt to determine if the epoxide opening step was rate limiting, compound **10** was subjected to identical thermolysis conditions in acetonitrile and dimethyl sulfoxide. (As a control, the cycloaromatization of the hydroxy methyl ester **8** was shown to be insensitive to acetonitrile as solvent.) In acetonitrile the reaction was slower than in toluene and provided a ~5:1.5:1 (80% mass recovery) mixture of compounds after 12 h. The major compound was identified as starting material, while the minor one of the remaining two was the eliminated, aromatized product **33**. The third compound was assigned the structure of the aromatized product with an intact epoxide (^{1}H NMR singlet 1.15 ppm). In dimethyl sulfoxide the eliminated, cyclized product **33** was produced in greater than 90% yield. These results support the hypothesis that there is an intramolecular hydrogen bond (between the C10 hydroxyl and the epoxide) that is present in toluene and assists in the elimination. In acetonitrile and dimethyl sulfoxide, however, the hydrogen bond is disrupted and solvent polarity becomes the more important factor. Acetonitrile is not sufficiently polar to stabilize the transition state leading to elimination relative to the transition state leading to cyclization, and therefore, both products are observed. By virtue of its greater polarity, dimethyl sulfoxide is capable of stabilizing the transition state leading to elimination and compound **33** is the only product observed.

The *cis*-diol **14** neither eliminated nor cyclized. In this compound it appears that the hydrogen bond is not present. Furthermore, the elimination product may suffer significant $A^{1,2}$ -strain between the hydroxymethyl substituents at C7a and C10a. This strain might also manifest itself in the transition state leading to elimination. Despite the apparent $A^{1,2}$ -interaction, the model predicts that the intra-acetylene distance (C12−C17) will decrease from 3.339 to 3.107 Å once elimination has occurred. In a preliminary experiment, when the *cis*-diol was heated to 110 °C, the ^{1}H NMR of the crude reaction mixture indicated the formation of a new compound in which the methyl peak experienced the downfield shift characteristic of a vinyl methyl. It thus appears that for the diols, the observed reactivity stems from the facility of the epoxide elimination.

Calculations. Two possible explanations were considered for the reactivity differences observed with the *cis*- and *trans*-isomers. First, there could be an electronic interaction that stabilizes the *cis*-compounds or destabilizes the *trans*-compounds, or the effect could be acting (inversely) upon the transition state. Second, there could be a steric interaction that acts in a similar fashion to the above mentioned electronic interaction.

An examination of the MM3 minimized model of the *cis*-lactone **7** indicated there may in fact be a relevant electronic interaction. In this model, the distance between the carbonyl carbon and the closest acetylene carbon is 2.982 Å (Figure 6). Gleiter and co-workers have recently shown that in macrocyclic transannular diacetylene compounds, the acetylenes interact

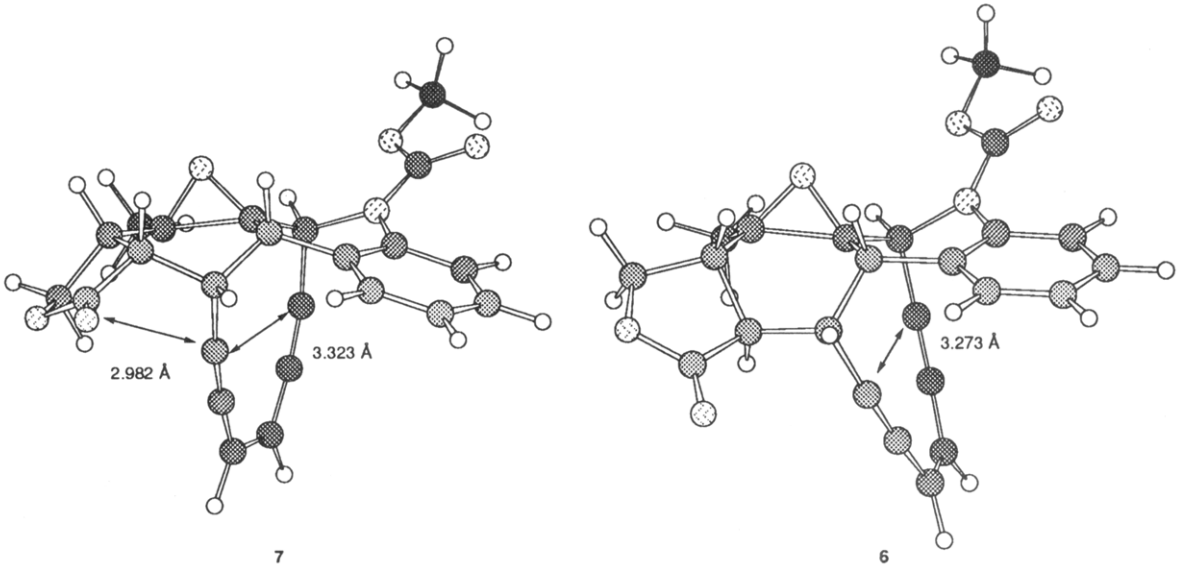


Figure 6. Energy minimized (MM3) models of the *cis*- and *trans*-lactones **7** and **6**.

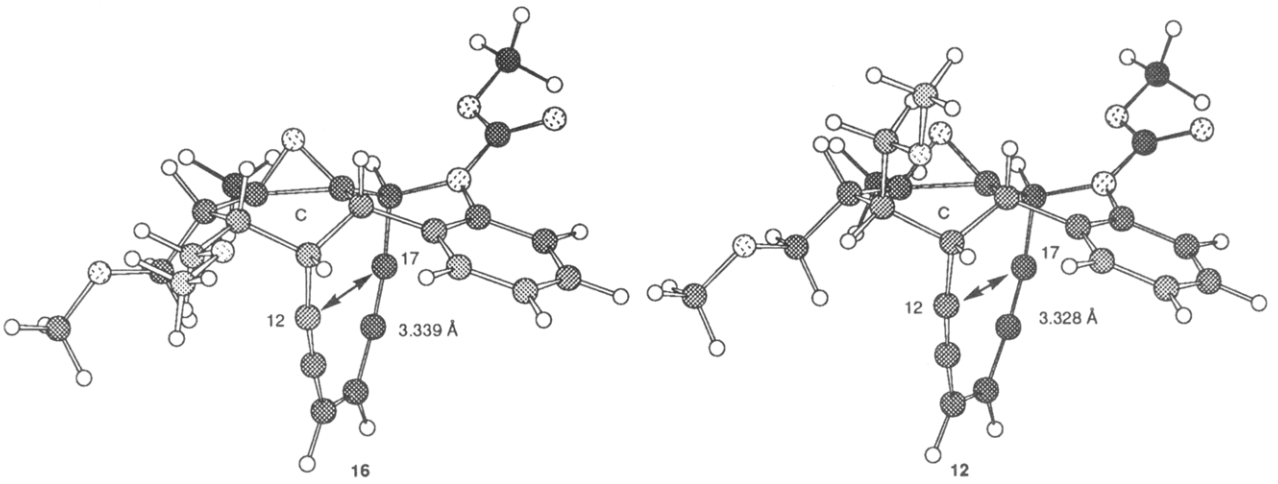


Figure 7. Energy minimized (MM3) models of the bis-methyl ethers **16** and **12**.

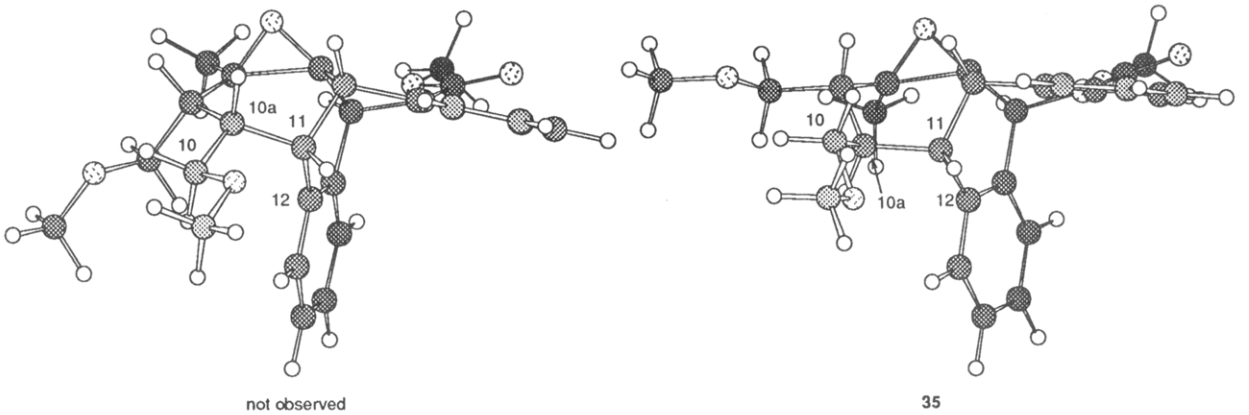


Figure 8. Energy minimized (MM3) models of the aromatic products from the bis-methyl ethers **16** (not observed) and **12** (compound **35**).

when the distance between them is 3 Å or less.[25] The possibility existed that there was an electronic interaction between the acetylene and the lactone carbonyl that was somehow inhibiting the cyclization. However, the experiments with the tetrahydrofuran **13** reveal that although the proposed interaction cannot be ruled out, it does not appear to be a major factor in the reactivity of the *cis*-lactone.

In the diol derivatives **14**−**16** (in which the carbonyl no longer exists) there could be a destabilizing interaction between the oxygen lone pairs and the radical center that develops as the compound proceeds along the reaction coordinate. Once again the results with the tetrahydrofuran **13**, in which the ring constraint prevents the described interaction, indicate that this possibility is unlikely.

With the electronic explanations fading from favor, a molecular mechanics examination of the dimethyl ethers was undertaken. Unfortunately, the molecular mechanics methods used are not capable of calculating the structure or energy of the diradical intermediates. Therefore the energy minimized (MM3) aromatic product was used for comparison to determine what changes would have to take place in passing from starting material to product. Although it is impossible to determine the precise pathway by which the reaction proceeds using these methods, the results appear to be relevant to the problem.

The minimized structures of the *cis*- and *trans*-dimethyl ethers are shown in Figure 7. The two structures are almost identical with the exception of the relevant stereocenter. The conformation of the C ring is a half chair in both, and the C12−C17 distances are 3.339 and 3.328 Å for **16** and **12**, respectively. Although the distance is less in the *trans*-substituted compound, it is not sufficiently diminished to account for the significant reactivity differences observed. Furthermore, the calculated energies are within 1 kcal mol^{-1} of each other with the *cis*-substituted compound actually being higher in energy. Therefore, the ground state destabilization hypothesis appears invalid.

The minimized (MM3) structures of the aromatic products (Figure 8) reveals significant differences. The model of the *trans*-substituted compound indicates that the C ring should adopt a boat conformation. The methoxymethylene substituent that is in an axial position in the half chair rotates outward to occupy a pseudoequatorial position in the boat. The basis for this conformational change can be traced to the need to form a bond between C12 and C17 so as to generate the aromatic nucleus. In particular, the C12−C11−C10a−C10 dihedral angle decreases from 179.9° to 138.8°. Similarly, the dihedral angle C11H−C11−C10a−C10aH increases from 52.8° to 95.7° yet the bond lengths and angles remain the same (within 0.1 Å and 1°, respectively). In order to accommodate the changes that occur, the C ring takes on a boat conformation.

In contrast, the model of the *cis*-substituted aromatized product shows that the C ring remains in a half chair. The calculated energy of this system is 7 kcal mol^{-1} higher than the corresponding *trans*-system. This is striking as the enediynes are predicted to differ in energy by less than 1 kcal mol^{-1}. Examination of the various contributions to the energy of the molecule indicates that the majority of the energy difference resides in angle bending (~5 kcal mol^{-1}) with an additional 1

(25) Gleiter, R.; Kratz, D.; Schafer, W.; Schelmann, V. *J. Am. Chem. Soc.* **1991**, *113*, 9258−9264. This distance is close to that which Nicolaou has proposed as a predictor of enediyne cycloaromatization reactivity at room temperature. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. T.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

Table 2. Structural Parameters Derived from Energy Minimized (MM3) Models

compound	C ring conformation	intra-acetylene distance (Å)
trans-lactone **6**	Boat	3.273
trans-lactone aromatic product **30**	Boat	N/A
trans-bis-methyl ether **12**	Half chair	3.328
trans-bis-methyl ether aromatic product **35**	Boat	N/A
cis-lactone **7**	Half chair	3.323
cis-lactone aromatic product[a]	Half-chair	N/A
cis-bis-methyl ether **16**	Half chair	3.339
cis-bis-methyl ether aromatic product[a]	Half chair	N/A

[a] Compounds not observed experimentally.

Table 3. Structural Parameters Derived from Molecular Dynamics Calculations

compound	minimum	maximum	mean	median	std dev
	C12–C17 (distance in Å)				
trans-**12**	2.943	3.636	3.309	3.306	0.114
cis-**16**	3.048	3.731	3.340	3.337	0.106
	Dihedral Angle (value in deg)[a]				
trans-**12**	−23.82	92.73	58.12	59.88	12.87
cis-**16**	51.307	97.69	74.04	73.93	7.79

[a] See text for angle definitions.

kcal mol^{-1} from bond stretching. Thus, it appears that while the *trans*-substituted systems undergo a conformational change during the cycloaromatization, the *cis*-substituted compounds undergo a series of bond angle distortions instead.

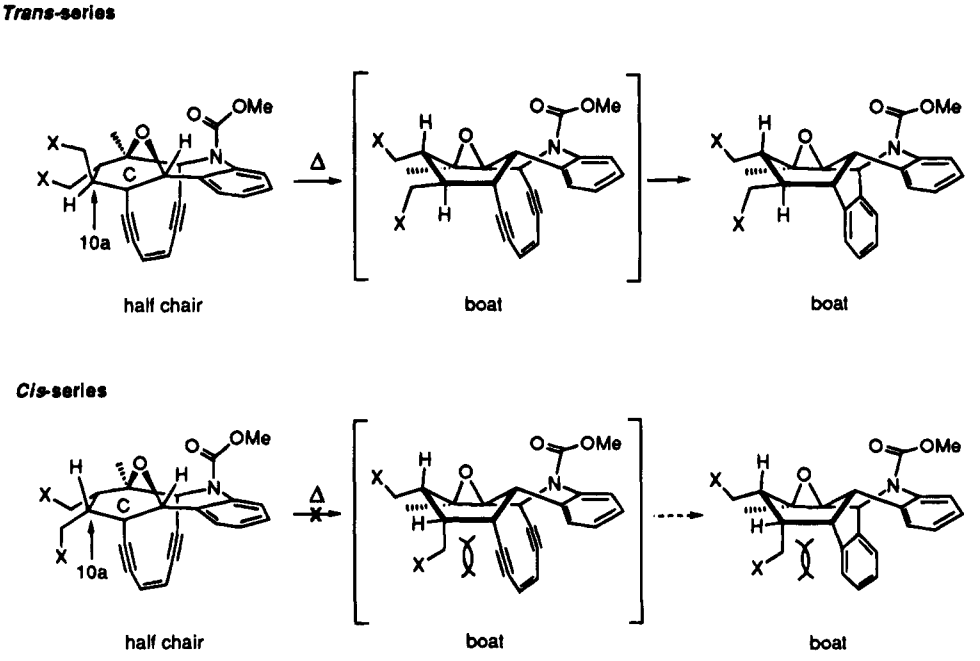
A comparison between the C ring conformation and the intra-acetylene distance was next performed for a number of calculated structures (Table 2). The salient features are the following: (1) in the *trans*-lactone **6** the C ring is in a boat in the ground state and the intra-acetylene distance is the shortest of those examined and (2) all of the experimentally observed aromatic products are predicted to have their C ring in a boat conformation. These results indicate that the transformation to a boat conformation in the C ring is one pathway that may lead to a decrease in the intra-acetylene distance. Furthermore, the *trans*-dimethyl ether is not significantly different, with respect to the intra-acetylene distance, than the other compounds examined. Where the *trans*-substituted ether does differ from the *cis*-substituted compounds is in the changes that accompany the conformational change from the half chair in the enediyne to the boat in the aromatic product (Figures 7 and 8).

As mentioned above, in the *trans*-compound the methoxymethylene is predicted to occupy an axial position in the starting material and to move to a pseudoequatorial one in the product. In the *cis*-substituted system the methoxymethylene already occupies the equatorial position in the enediyne. If the C ring were to take on a boat conformation, the substituent would then be in an axial position. Furthermore, as the transformation to a boat proceeds, the C10–C10a bond begins to eclipse the C11–C12 bond. The energetics associated with these interactions may prevent the *cis*-substituted compounds from reaching the conformation necessary to undergo a cycloaromatization (Scheme 8).

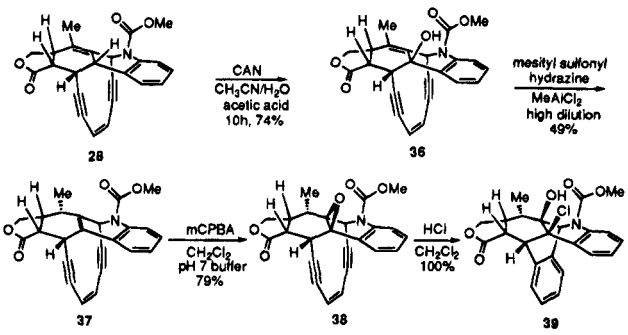
If the cyclization is dependent upon access to the boat conformation, then these compounds demonstrate a "stereochemical switch" for the cycloaromatization reaction. Thus, their ability to reach the required conformation for aromatization is governed by the stereochemistry at C10a. In compounds that have a substituent at C10a in the β orientation (Scheme 8) the conformational change is allowed, and the subsequent cyclization reaction proceeds. Note that it is not necessary that the molecule reach the boat conformation, just that it be able to proceed along that path to some undetermined point. In the case of a substituent at C10a in the α orientation, however, the developing steric and torsional interactions hinder access to the boat conformation and therefore prevent the cyclization from occurring.

As a further test of the conformational hypothesis, a molecular dynamics simulation was conducted on compounds **12** and **16**.[26] The results are summarized in Table 3. Although the mean C12–C17 distance is approximately equal in both structures, the minimum for the *trans*-compound is quite short. The angular differences are more pronounced. In the *trans*-dimethyl ether **12** the C10–C10a–C11–C11H angle was examined, while in the *cis*-compound **16** the angle C10aH–C10a–C11–C11H was considered. Although these angles are not identical, they were chosen in order to facilitate a direct comparison. Values near 60° in either case correspond to a half chair, while

Scheme 8



Scheme 9



those near 0° represent a boat conformation. The *trans*-compound reaches a boat conformation during the molecular dynamics simulation, while the *cis*-compound does not. Furthermore, an examination of the *trans*-structures in which the dihedral angle is between 30° and −30° gives an average C12−C17 distance of 3.217 Å (as compared to 3.309 for the entire set). Moreover, this set contains the structures with the shortest distance (2.943 Å). A second insight gained from these calculations is that the *trans*-epimer is more flexible in the region of the C ring. This point is demonstrated by the standard deviation of the examined angle. While the value for this parameter is 7.79° in the *cis*-substituted compound **16**, it is 12.87° for the corresponding *trans*-compound **12**.

A similar conformational transformation may also be used by dynemicin A. In both models[4,5] and in the X-ray structure of the natural product,[2] the methyl group is found in a pseudoaxial position with a close contact with the neighboring acetylene. This conformation is enforced by the presence of the epoxide. However, once the epoxide is opened the ring can undergo a conformational change from a pseudoboat to a pseudochair. This allows the methyl group to move from an axial to an equatorial position. The energy release facilitates the transition of the activated form of the natural product into a conformation that can cyclize at room temperature. This analysis leads to the prediction that epi-methyl and desmethyl dynemicin A may not cycloaromatize as readily as the natural product.

Despite the reticence of the *cis*-substituted enediynes to cycloaromatize, it appeared that if the epoxide could be opened then the cyclization of these substrates should occur readily. Once the bond angles at the bridge reach the normal sp^3-hybridized angle (109°) the C12−C17 distance decreases to the point where the cycloaromatization is expected to be facile. This prediction was supported both by the calculations on the *trans*-diol discussed above and by an observation of Magnus and coworkers.[27] In their system the reduction of a carbonyl to an alcohol in a ten-membered ring enediyne resulted in a significant enhancement of the rate of cycloaromatization. Unfortunately, preliminary attempts to open the exo-epoxide of *cis*-lactone **7** failed (TMSOTf;[28] *p*-toluenesulfonic acid; diethyl aluminum tetramethylpiperidide[29]). We therefore turned our attention to the endo-epoxide since its opening should be facilitated by virtue of its benzylic nature.

Thus, the *cis*-lactone **27** was oxidized in 74% yield using CAN in the presence of acetic acid (Scheme 9).[30] Due to the poor solubility of the benzylic alcohol **36** the requisite transposition reaction was conducted at a concentration of 1 mg/mL in the presence of methylaluminum dichloride and mesityl sulfonyl hydrazine in methylene chloride.[10] This gave the desired product in 49% yield after high performance liquid chromatography.

The transposed olefin was epoxidized (mCPBA, pH 7 phosphate buffer) to give compound **38** in 79% yield. In one instance, the pH 7 phosphate buffer was replaced with pH 4 phosphate buffer. The more acidic medium resulted in spontaneous epoxide opening to the chlorohydrin and subsequent cycloaromatization at ambient temperature. To further investigate this chemistry, the epoxide was treated with anhydrous HCl in THF and methylene chloride. In methylene chloride the aromatized product **39** was produced in quantitative yield.

Presumably the events that occur are as follows: After protonation, the epoxide opens to give the benzylic cation at C11a. This cation is trapped by the chloride ion present. Once both C6a and C11a are fully sp^3 hybridized, the cyclization reaction is anticipated to occur readily. This is based both on the observed reactivity of dynemicin A as well as the calculated structure of a related compound shown in Figure 5. This altered reactivity can be traced to the changes in bond angles that accompany the rehybridization. The tetrahedral bond angle forces C12 and C17 closer to each other, and this may account for the ease of cyclization.

A review of studies in the di- and tri-*O*-methyl dynemicin A methyl ester syntheses indicates that a methoxy substituent on the aromatic ring prevented similar chemistry from occurring in that system. An inductive effect of the oxygen substituent appears to be the cause. As the methoxy is meta to the reactive benzylic site its electron-donating capability is attenuated. Instead its electron-withdrawing, inductive property decreases reactivity at the benzylic site. Thus, the methoxy group is seen to dictate the chemistry of the system in a subtle way.

Conclusions

These studies have shown that for the dynemicin A analogs described herein, the stereochemistry at C10a has a significant effect on their ability to cycloaromatize. When the configuration of the C10a substituent is β, the compounds undergo cycloaromatization at 80 °C. However, when it is α, the compounds fail to undergo thermally activated cycloaromatization. These results appear to stem from a conformational change in the C ring as the molecule proceeds along the reaction coordinate. In the latter case a steric interaction develops between the substituent and the enediyne that inhibits the conformational change and thus prevents cyclization.

Stereochemical and conformational factors can thus play a significant role in influencing the reactivity of bicyclic enediynes. Although insights into these factors have been gained with the dynemicin analogs **8**−**16**, the still unexplained stability of the ortho-ester **5** (eq 2) serves as a reminder that the factors that govern the cycloaromatization chemistry can be quite subtle.

Experimental Section

General Experimental Methods. Procedures. All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen or argon. Air and moisture sensitive compounds were introduced *via* syringe or cannula through a rubber septum. Cooling was performed using the following baths: Ice−water (0 °C), ice−methanol (−10 °C), dry ice−carbon tetrachloride (−23 °C), dry ice−acetone (−78 °C).

(26) Molecular dynamics simulations were carried out using the MM3 force field at a temperature of 353 K. After a 10 ps equilibration the molecule was observed for 50 ps. Intermediate structures were saved every 0.05 ps. The SHAKE algorithm was employed to constrain C−H bonds.

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Physical Data. Melting points were measured with a Mel-Temp apparatus and were uncorrected. Infrared spectra (IR) were recorded using a Nicolet 5PC FT-IR spectrometer (υ max in cm^{-1}). Samples were prepared as thin films by evaporation onto a salt plate (NaCl) or as solutions in noted solvents using a NaCl solution cell. ^1H NMR spectra were recorded on either a Bruker AM-500 (500 MHz) or AM-400 (400 MHz) spectrometer as noted at ambient temperature. Data were reported as follows: chemical shift in ppm using residual protio solvent as internal standard (7.24 for $CDCl_3$) on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in hertz, and integration. ^{13}C NMR spectra were recorded on a Bruker AM-500 (125 MHz) or AM-400 (100 MHz) spectrometer and were reported in ppm using solvent resonance as internal standard (77.0 for $CDCl_3$). All ^{13}C spectra were determined with complete proton decoupling. In cases where line broadening was observed due to slow interconversion of carbamate rotamers, ^1H and ^{13}C NMR spectra were recorded at 333 K. Partial ^{13}C spectra are reported for compounds that exhibit absent or overlapping signals. Mass spectra were obtained using either a JEOL AX-505 or SX-102.

Chromatography. Analytical thin layer chromatography (TLC) was performed using EM reagent 0.25 mm silica gel 60-F plates. Components were visualized by illumination with ultraviolet light (254 nm) and by staining with one of the following reagents: *p*-anisaldehyde in ethanol−sulfuric acid, 7% phosphomolybdic acid in ethanol, ceric ammonium molybdate in 10% sulfuric acid, or potassium permanganate in water. Preparative TLC was performed using EM 0.5 mm silica gel 60-F plates which were preeluted with the indicated solvent. Flash column chromatography was performed as previously described.[31] High performance liquid chromatography (HPLC) was performed using a Waters 510 liquid chromatograph equipped with a μporasil column (1 × 25 cm).

Solvents and Reagents. Solvents were distilled and/or stored over 4 Å molecular sieves prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal/benzophenone ketyl. Acetonitrile, triethylamine, diisopropylamine, and benzene were distilled from calcium hydride. Methanol was distilled from $Mg(OMe)_2$. Methylene chloride was distilled from phosphorus pentoxide. Organolithium reagents were titrated against 2,6-di-*tert*-butyl-4-methylphenol in ether at 0 °C using 1,10-phenanthroline as indicator. Bis(acetonitrile)palladium (II) chloride was prepared by refluxing palladium(II) chloride in acetonitrile.[32] Tetrakis(triphenylphosphine)palladium(0) was prepared according to the *Inorganic Syntheses* procedure.[33] Deuterochloroform was stored over granular anhydrous potassium carbonate. All other reagents were used as obtained from commercial sources or purified according to standard procedures.[34]

Ethyl (*E*)-3-(Tributylstannyl)-2-buteneoate (21). A solution of lithium diiisopropylamide was prepared by the addition of *n*-BuLi (2.5 M in hexane, 92.8 mL, 232 mmol, 1.3 equiv) to a solution of diisopropylamine (32.3 mL, 232 mmol, 1.3 equiv) in 1.7 L of tetrahydrofuran at 0 °C. The solution was stirred for 15 min at 0 °C, after which tributyltin hydride (62.4 mL, 232 mmol, 1 equiv) was added. After an additional 45 min of stirring the reaction was cooled to −78 °C. Solid copper bromide−dimethyl sulfide (47.7 g, 232 mmol, 1.3 equiv) was added, with vigorous stirring, to the yellow solution which became dark orange. After 15 min a solution of ethyl tetrolate (20 g, 178.4 mmol, 1 equiv) in 50 mL of tetrahydrofuran was added *via* cannula. The reaction was stirred for 3 h at −78 °C and then quenched with saturated ammonium chloride that had been adjusted to pH 8 with ammonium hydroxide. The reaction was warmed to ambient temperature and diluted with ether. Separation of layers and washing of the ethereal layer with saturated ammonium chloride (pH 8) was continued until the aqueous phase no longer appeared blue and then once with brine. After extracting the combined aqueous layers once with ether, the combined organic solutions were dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. The crude material was purified by funnel column chromatography over silica gel eluting with a gradient of hexane to 3% ether/hexane. The product was isolated in 56% yield: R_f 0.44 (10% ethyl acetate/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (q, J = 1.7 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.37 (d, J = 1.9 Hz, 3H), 1.49−1.43 (m, 6H), 1.33−1.26 (m, 12H), 0.89 (m overlapping, 3H) 0.87 (t, J = 7.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 164.4, 128.1, 59.5, 29.0, 27.3, 22.4, 14.4, 13.6, 9.4; IR (neat) 2957, 2926, 2872, 2855, 1714, 1599, 1464, 1419, 1377, 1365, 1257, 1176, 1099, 1072, 1039, 960, 864, 690, 663 cm^{-1}; MS (FAB) *m/e* calcd for $C_{18}H_{37}O_2Sn$ 405.1819, found 405.1842; 405 ($[M + H]^+$).

3-(2-Carbethoxy-1-methylethenyl)quinoline (22). 3-Bromoquinoline (11.4 mL, 84.2 mmol, 1 equiv) and the vinyl tin reagent **21** (42.4 g, 105.2 mmol, 1.25 equiv) were dissolved in 300 mL of toluene. The solution was degassed with argon for 20 min. Tetrakis(triphenylphosphine)palladium (1.96 g, 1.7 mmol, 0.02 equiv) and approximately 50 mg of 2,6-di-*tert*-butyl-4-methylphenol were added. The solution was refluxed for 24 h in the dark. An additional portion of tetrakis-(triphenylphosphine)palladium (650 mg) was added every 8 h. The reaction was cooled to ambient temperature and filtered through a pad of Celite. The filtrate was diluted with ether and washed three times with 15% aqueous ammonium hydroxide and once with brine. After drying over magnesium sulfate the solvent was removed *in vacuo*. The product was purified by column chromatography eluting with a gradient of hexane to 40% ether/hexane. This procedure provided 11.7 g of pure product (58%) as well as 6.7 g of unreacted vinyl tin reagent: mp 62−63 °C; R_f 0.12 (30% ethyl acetate:hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, J = 2.2 Hz, 1H), 8.19 (d, J = 2.2 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.72 (m, 1H), 7.56 (m, 1H), 6.29 (d, J = 1.3 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 2.67 (d, J = 1.3 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.9, 148.4, 148.1, 134.6, 133.2, 130.1, 129.2, 128.2, 127.4, 127.2, 118.8, 60.1, 17.8, 14.3; IR ($CHCl_3$) 2984, 1709, 1632, 1620, 1493, 1370, 1335, 1289, 1273, 1233, 1198, 1175, 1142, 1044, 783, 762, 756, 747, 739, 669 cm^{-1}; MS (EI) *m/e* calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1094; 241 ($[M]^+$), 212 ($[M - C_2H_5]^+$), 196 ($[M - C_2H_5O]^+$); orange solid.

3-(2-(Hydroxymethyl)-1-methylethenyl)quinoline. Neat DIBAL-H (21.6 mL, 121.25 mmol, 2.5 equiv) was diluted to 1 M with methylene chloride. The enone **22** (11.7 g, 48.5 mmol, 1 equiv) was cooled to −78 °C in 138.5 mL of methylene chloride, and the DIBAL-H solution was added slowly. The dark red reaction was stirred at −78 °C for 2 h after which 20 mL of methanol was added cautiously (reaction can foam violently) and warmed to ambient temperature. Approximately 300 mL of saturated sodium potassium tartrate was added. After stirring at ambient temperature for 3 h the reaction was diluted with ethyl acetate. The aqueous fraction was extracted three times with ethyl acetate, and the combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the crude product, which was purified by funnel column chromatography over silica gel using a gradient (30% ethyl acetate/hexane to 60:30:10 ethyl acetate:hexane:methanol) as eluant to give 7.45 g (77%) of pure product: mp 62−64 °C; R_f 0.13 (1:1 ethyl acetate: hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 8.96 (d, J = 2.2 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.62 (dd, J = 8.3, 6.9 Hz, 1H), 7.48 (dd, J = 8.0, 7.1 Hz, 1H), 6.18 (t, J = 6.3 Hz, 1H), 4.41 (d, J = 6.4 Hz, 2H), 3.69 (bs, 1(OH)), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.0, 135.3, 134.0, 131.9, 129.6, 129.2, 128.8, 127.9, 127.7, 126.9, 59.5, 15.7; IR ($CHCl_3$) 3611, 3270, 3067, 3011, 2971, 2874, 1572, 1493, 1385, 1360, 1343, 1235, 1213, 1129, 1098, 1003, 959, 911, 860, 837 cm^{-1}; MS (EI) *m/e* calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0999; 199 ($[M]^+$), 184 ($[M - CH_3]^+$). Anal. Calcd for $C_{13}H_{13}NO$: C 78.14 H 6.54 N 6.93. Found C 78.39 H 6.53 N 7.04; yellow solid.

3-(3-*tert*-butyldimethylsiloxy)-1-methyl-1-propenylquinoline (20). Imidazole (3.06 g, 44.9 mmol, 1.2 equiv) was added to a solution of allylic alcohol (7.45 g, 37.4 mmol, 1 equiv) in 187 mL of methylene chloride. *tert*-Butyldimethylchlorosilane (6.18 g, 41 mmol, 1.1 equiv) was added. A white precipitate formed. The reaction was stirred at ambient temperature for 16 h, quenched with saturated sodium bicarbonate, and extracted into ether. The aqueous layer was extracted once with ether, and the combined organic fractions were extracted once with brine. The organic solution was dried over magnesium

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sulfate and filtered, and the solvent was removed under reduced pressure. The crude material was combined with an identically processed reaction on 2.34 g of alcohol. The material was purified by funnel column chromatography eluting with 25% ether/hexane to give 14.94 g (97% combined) of desired product: R_f 0.33 (20% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.0 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.0 (d, J = 2.2 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 8.0, 7.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 6.09 (dd, J = 6.0, 0.8 Hz, 1H), 4.4 (d, J = 6.0 Hz, 2H), 2.1 (d, J = 0.8 Hz, 3H), 0.9 (s, 9H), 0.1 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149, 147, 135, 133, 132, 130, 129, 128.9, 128, 127.8, 126.7, 60.8, 26, 18, 15.9, −5.1; IR (neat) 2955, 2930, 2886, 2857, 1491, 1472, 1464, 1445, 1383, 1358, 1256, 1111, 1086, 1057, 1007, 907, 837, 814, 777, 750 cm^{-1}; MS (EI) *m/e* calcd for $C_{19}H_{27}NOSi$ 313.1862, found 313.1875; 313 ([M]$^+$), 256, 182, 167.

2-(6-(Thexyldimethylsilyl)hexa-1,5-diyn-3-ene)-3-(3-(*tert*-butyldimethylsiloxy)-1-methyl-1-propenyl)quinoline-1(2*H*)-carboxylic Acid Methyl Ester (24). The quinoline **20** (8.05 g, 25.6 mmol, 1 equiv) was dissolved in 250 mL of tetrahydrofuran and cooled to −78 °C. A solution of silyl enediyne Grignard reagent **23**[10] [prepared by treating thexyldimethylsilyl enediyne (58.9 mmol, 1 equiv) with *n*-BuLi (24.7 mL of a 2.5 M solution in hexane, 1.05 equiv) in 59 mL of THF at −78 °C. The resulting yellow solution was then treated with 61.8 mL of a 1 M solution of magnesium bromide in 3:1 ether/benzene] was added *via* cannula. The reaction was stirred for 5 min and methyl chloroformate (40 mL, 51.2 mmol, 2 equiv) was added. After stirring for an additional 5 min at −78 °C the reaction was warmed to ambient temperature over 4 h. Saturated ammonium chloride was added, and the product was extracted into ether. The organic layer was washed two times with saturated ammonium chloride, and the combined aqueous washes were back extracted with ether. The ethereal solution was dried over magnesium sulfate and filtered, and the ether was removed *in vacuo*. The crude material was combined with an identically processed reaction on 6.89 g of quinoline. The product was purified by funnel column chromatography eluting with a gradient of hexane to 5% ether/hexane to give 34.9 g (73%) of pure product: R_f 0.55 (20% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (bs, 1H), 7.2 (td, J = 6.3, 1.6 Hz, 1H), 7.15 (dd, J = 7.7, 1.6 Hz, 1H), 7.08 (td, J = 7.6, 1.0 Hz, 1H), 6.5 (s, 1H), 6.4 (bs, 1H), 6.0 (bt, J = 4.7 Hz, 1H), 5.68 (d, J = 11.1 Hz, 1H), 5.62 (dd, J = 11.0, 1.8 Hz, 1H), 4.42 (td, J = 14, 5 Hz, 2H), 3.8 (s, 3H), 1.9 (s, 3H), 1.65 (m, 1H), 0.9 (s, 15H), 0.9 (d, J = 7 Hz, 6H), 0.17 (s, 6H), 0.1 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 137.1, 133.8, 131.2, 129, 127.5, 127, 124.5, 123.9, 121, 119.7, 119.6, 102.8, 102.5, 93.7, 80.2, 77.2, 60.8, 53.3, 45.5, 34.5, 25.9, 23.3, 20.7, 18.6, 18.3, 13.9, −2.5, −5.1; IR (neat) 2957, 2861, 2150, 1713, 1489, 1462, 1439, 1377, 1331, 1294, 1246, 1219, 1194, 1144, 1129, 1107, 1053, 1024, 839, 775, 673 cm^{-1}; MS (EI) *m/e* calcd for $C_{35}H_{51}NO_3Si_2$: 589.3407, found 589.3395; 589 ([M]$^+$), 444; CI 607, [M + NH_4]$^+$, 479, 372, 314.

2-(Hexa-1,5-diyn-3-enyl)-3-(3-hydroxy-1-methyl-1-propenyl)quinoline-1(2*H*)-carboxylic Acid Methyl Ester (19). Tetrabutylammonium fluoride (87.3 mL of a 1 M solution in THF, 2.5 equiv) was added to a solution of the silyl enediyne **24** in 350 mL of THF at 0 °C. The black reaction was stirred at 0 °C for 1 h. Saturated ammonium chloride was added, and the reaction was warmed to ambient temperature. The product was extracted into ether and washed two times with water. The combined aqueous layers were extracted with ether. After drying over magnesium sulfate the organic layers were filtered, and the solvent was removed at reduced pressure. The crude oil was purified by funnel column chromatography over silica gel (30−40% ethyl acetate:hexane) to give 11.66 g (99%) of pure product: R_f 0.43 (40% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 7.6 (d, J = 8.1 Hz, 1H), 7.23 (t, J = 1.0 Hz, 1H), 7.21 (d, J = 0.7 Hz, 1H), 7.1 (td, J = 8.0, 1.4 Hz, 1H), 6.57 (s, 1H), 6.39 (d, J = 1.9 Hz, 1H), 6.12 (t, J = 6.4 Hz, 1H), 5.71 (dd, J = 10.9, 1.3 Hz, 1H), 5.64 (dd, J = 16.9, 2.1 Hz, 1H), 4.38 (d, J = 6.1, 2H), 3.82 (s, 3H), 3.04 (d, J = 2.2 Hz, 1H), 1.95 (s, 3H), 1.2 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 154.0, 137.6, 134.3, 133.3, 127.9, 127.8, 127.7, 127.1, 124.5, 124.1, 121.9, 121.2, 119.1, 94.4, 84.7, 80.9, 80.5, 59.9, 53.3, 46.2, 13.9; IR (neat) 3291, 2955, 2250, 2094, 1705, 1489, 1441, 1381, 1333, 1296, 1252, 1194, 1144, 1129, 1053, 1034, 1020, 976, 911, 764, 733, 648 cm^{-1}; MS (EI) *m/e* calcd for $C_{21}H_{19}NO_3$: 333.1365, found 333.1374; CI 333 ([M]$^+$), 351, [M + NH_4]$^+$, 316, [M + NH_4 − NH_3 − H_2O]$^+$.

2-(8-Methoxycarbonyl)octa-1,5-diyn-3(*Z*),7(*E*)-enyl-3-(3-hydroxy-1-methyl-1-propenyl)quinoline-1(2*H*)-carboxylic Acid Methyl Ester (18). Iodomethacrylate (11.87 g, 56 mmol, 1.6 equiv), *n*-butylamine (13.8 mL, 140 mmol, 4 equiv), and tetrakis(triphenylphosphine)-palladium (2.0 g, 1.75 mmol, 0.05 equiv) were dissolved in 275 mL of benzene. The yellow solution was degassed with argon for 20 min. The hydroxy acetylene **19** (11.66 g, 35.0 mmol, 1 equiv) in 50 mL of benzene was similarly degassed. Copper iodide (1.3 g, 7 mmol, 0.2 equiv) was added to the solution of iodoacrylate, and the acetylene solution was added *via* cannula. The brown reaction was stirred in the dark for 16 h, diluted with ethyl acetate, and washed with saturated ammonium chloride until the aqueous layer was no longer blue (at least three times). The combined aqueous fractions were washed once with ethyl acetate. After washing with brine, the organic layers were dried over magnesium sulfate and filtered. After solvent removal *in vacuo* the material was purified by funnel column chromatography eluting with 35−40% ethyl acetate/hexane which provided 10.8 g (74%) of pure product: R_f 0.125 (40% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 333 K) δ 7.61 (d, J = 8.1 Hz, 1H), 7.21 (td, J = 6.6, 1.4 Hz, 1H), 7.16 (dd, J = 7.6, 1.6 Hz, 1H), 7.08 (td, J = 7.3, 1.0 Hz, 1H), 6.78 (dd, J = 15.9, 2.3 Hz, 1H), 6.58 (s, 1H), 6.42 (s, 1H), 6.13 (d, J = 15.9 Hz, 1H), 6.08 (t, J = 6.2 Hz, 1H), 5.80 (dd, J = 10.7, 2.2 Hz, 1H), 5.74 (dd, J = 11.8, 1.8 Hz, 1H), 4.39 (m, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 1.95 (s, 3H), 1.72 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 166.2, 154.0, 137.2, 134.1, 133.1, 130.1, 128.0, 127.9, 127.6, 127.2, 125.0, 124.7, 123.9, 121.9, 121.4, 118.8, 95.7, 95.2, 93.2, 80.7, 59.9, 53.3, 51.7, 46.1, 13.9; IR (neat) 3488, 3017, 2953, 2181, 1709, 1618, 1568, 1489, 1439, 1381, 1250, 1167, 1124, 1105, 1020, 961, 889, 860, 808, 762, 667 cm^{-1}; MS (FAB) *m/e* calcd for $C_{25}H_{23}NO_5Na$ 440.1474, found 440.1462; 440 ([M + Na]$^+$).

2-(8-Carboxyocta-1,5-diyne-3(*Z*),7(*E*)-enyl-3-(2-hydroxy-1-methyl-1-propenyl)quinoline-1(2*H*)-carboxylic Acid Methyl Ester. A solution of the hydroxy ester **18** (10.8 g, 25.9 mmol, 1 equiv) in 260 mL of THF was cooled to 0 °C. A 1 M solution of lithium hydroxide (72.5 mmol, 2.8 equiv) was added. The reaction was stirred for 10 min at 0 °C and then 3 h at ambient temperature. After dilution with ethyl acetate and washing with saturated sodium bisulfate, the layers were separated, and the aqueous fraction was extracted three times with ethyl acetate. The combined organic solutions were washed once with brine, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure. The crude product (9.08 g, 87%) was used directly in the next reaction. Purified for characterization by column chromatography over silica gel eluting with 8:1:1 ethyl acetate:THF:ether, 1% acetic acid: mp 110 °C dec; R_f 0.22 (8:1:1 ether:THF:ethyl acetate, 1% Acetic Acid); ^{1}H NMR (400 MHz, $CDCl_3$ 333 K) δ 7.63 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 5.9 Hz, 1H), 7.18 (d, J = 6.4 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.86 (dd, J = 15.7, 2.2 Hz, 1H), 6.61 (s, 1H), 6.44 (d, J = 2.5 Hz, 1H), 6.16 (d, J = 15.7 Hz, 1H), 6.09 (t, J = 6.0 Hz, 1H), 5.82 (dd, J = 10.8, 2.0 Hz, 1H), 5.77 (dd, J = 10.8, 1.6 Hz, 1H), 4.41 (m, 2H), 3.84 (s, 3H), 1.97 (s, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$ 333 K) δ 183.4, 169.8, 133.9, 133.1, 129.4, 129.3, 127.9, 127.8, 127.7, 127.3, 127.2, 124.8, 123.9, 122.0, 118.8, 96.5, 95.8, 92.9, 80.6, 60.0, 53.6, 45.8, 20.5, 14.0; IR ($CHCl_3$) 3400, 3026, 2957, 1703, 1620, 1491, 1441, 1381, 1335, 1298, 1252, 1217, 1213, 1063, 961, 779, 768, 760, 754, 748, 741, 733, 669 cm^{-1}; MS (FAB (negative ion)) *m/e* calcd for $C_{24}H_{20}NO_5$ 402.1341, found 402.1353; 402 ([M − H]$^-$).

(6*R,7a*S**,10a*R**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-7-methyl-10-oxo-6,11-[3]hexene-[1,5]diynofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (17).** The crude seco-acid (4.5 g, 11.17 mmol, 1 equiv) and triethylamine (7.8 mL, 55.9 mmol, 5 equiv) were dissolved in 4 L of methylene chloride. Bromotripyrolidinophosphonium hexafluorophosphate (PyBrop, 9.88 g, 21.2 mmol, 1.9 equiv) was added dropwise in 40 mL of methylene chloride. The reaction was stirred at ambient temperature for 16 h and then washed with brine. The brine was extracted three times with methylene chloride. The organic fractions were dried over sodium sulfate and filtered, and the solvent was removed on a rotary evaporator. A second batch of material was processed identically and simultaneously. The crude products were combined, stripped onto 30 g of silica gel, and purified by funnel

column chromatography. Elution began with 6:5:1 *tert*-butyl methyl ether:hexane:ethyl acetate. After a yellow band eluted, the solvent was changed to 75:20:5 methylene chloride:hexane:ethyl acetate giving pure product (40%): mp 180 °C dec; R_f 0.41 (1:1 ethyl acetate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.19 (m overlapping, 2H), 6.26 (d, J = 1.8 Hz, 1H), 5.58 (dd, J = 9.5, 2.1 Hz, 1H), 5.50 (dd, J = 9.5, 1.9 Hz, 1H), 4.54 (dd, J = 8.4, 6.7 Hz, 1H), 4.27 (dd, J = 11.1, 8.4 Hz, 1H), 3.85 (td apparent, J = 6.7, 2.1 Hz, 1H), 3.78 (s, 3H), 3.61 (bd, J = 5.9 Hz, 1H), 3.00 (td apparent, J = 13.6, 6.6 Hz, 1H), 2.61 (dd, J = 14.8, 6.7 Hz, 1H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 154.3, 136.3, 134.7, 130.3, 127.3, 127.0, 126.7, 125.8, 125.5, 125.2, 122.2, 104.3, 95.1, 88.0, 82.7, 68.4, 53.3, 49.7, 45.0, 43.6, 29.7, 22.1, 13.5; IR ($CHCl_3$) 3025, 1786, 1700, 1493, 1443, 1372, 1325, 1310, 1298, 1285, 1252, 1233, 1211, 1194, 1180, 1101, 1060, 993, 835 cm^{-1}; MS (EI) *m/e* calcd for $C_{24}H_{19}NO_4$ 385.1314, found 385.1332; 385 ([M]$^+$); off-white solid.

(6*R,6a*S**,7*R**,7a*S**,10a*R**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-6a,7-epoxy-7-methyl-10-oxo-6,11-[1′,2′]benzenofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (30).** A stock solution of trifluoroperacetic acid (TFPA) was prepared by the addition of 2.5 μL of TFAA (0.018 mmol, 1 equiv) to a solution of urea hydrogen peroxide complex (6.6 mg, 0.07 mmol, 4 equiv) in 2 mL of methylene chloride at 0 °C buffered with 8.6 mg of dibasic sodium phosphate. The solution was then warmed to ambient temperature and stirred for 5 min. The *trans*-lactone **17** (7 mg, 0.017 mmol, 1 equiv) was dissolved in 200 μL of methylene chloride and cooled to 0 °C, and 200 μL of the TFPA solution was added. The reaction was stirred for 30 min at 0 °C and then quenched with a 1:1 mixture of triethylamine and saturated aqueous sodium bicarbonate. The product was extracted into ether and washed with brine. The aqueous layers were extracted once with ether, and the combined ethereal solutions were dried over magnesium sulfate. Filtration and solvent removal *in vacuo* gave the crude material which was passed through a plug of silica gel eluting with 9:1 methylene chloride:ether. The resulting epoxide was immediately dissolved in toluene to a final concentration of 0.008 M. The solution was degassed using two cycles of freeze-pump-thaw. 1,4-Cyclohexadiene (62 equiv) was added and the reaction was heated to 110 °C for 6 h. After cooling and solvent removal *in vacuo* the product was purified by thin layer chromatography (2.5 mm, 1:1 ethyl acetate: hexane) to give the cyclized product in 40% yield (2.8 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (bs, 1H), 7.31 (dd, J = 9.1, 4.9 Hz, 1H), 7.16 (m overlapping, 3H), 7.07 (m overlapping, 2H), 6.98 (m, 1H), 5.63 (bs, 1H), 4.54 (dd, J = 8.4, 6.5 Hz, 1H), 4.06 (dd, J = 11.0, 8.5 Hz, 1H), 3.90 (s, 3H), 3.86 (t, J = 3.4 Hz, 1H), 3.01 (d, J = 3.0 Hz, 1H), 2.84 (m, 1H), 2.49 (dd, J = 15.3, 3.0 Hz, 1H), 1.37 (s, 3H); IR (neat) 2922, 2857, 1776, 1699, 1493, 1441, 1369, 1290, 1261, 1182, 1105, 1053, 983, 972, 954, 852, 763, 719, 675 cm^{-1}; MS (EI) *m/e* calcd for $C_{24}H_{21}NO_5$ 403.1420, found 403.1439; 403 ([M]$^+$); white solid.

6*R,7a*S**,10a*S**,11*S**(±)-7a,8,10,10a,11,11a-Hexahydro-7-methyl-10-oxo-6,11-[3]hexene-[1,5]diynofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (28).** Diazabicycloundecene (197 μL, 1.32 mmol, 2 equiv) was added to a solution of the *trans*-lactone **17** (255.7 mg, 0.66 mmol, 1 equiv) in 80 mL of tetrahydrofuran. The reaction was stirred at ambient temperature for 16 h, and the faintly yellow reaction was quenched with 10% HCl and diluted with ether. The organic layer was washed two times with saturated ammonium chloride and once with brine. The combined aqueous washes were back extracted with ether, the etheral solutions were dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. The crude oil was purified by column chromatography over silica gel eluting with 2.5% ethyl acetate:methylene chloride to give 255 mg (100%) of pure product: mp 170 °C dec; R_f 0.29 (50% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$ 333 K) δ 7.43 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 7.21 (dd, J = 6.4, 6.0 Hz, 1H), 6.28 (s, 1H), 5.56 (dd, J = 9.5, 1.7 Hz, 1H), 5.46 (dd, J = 9.5, 1.7 Hz, 1H), 4.55 (dd, J = 9.7, 8.4 Hz, 1H), 4.17 (dd, J = 8, 10 Hz, 1H), 4.03 (m, 1H), 3.79 (s, 3H), 3.69 (bs, 1H), 3.31 (dd, J = 19.5, 9.9 Hz, 1H), 3.08 (dd, J = 9.9, 5.8 Hz, 1H), 1.85 (d, J = 1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$ 333 K) δ 176.4, 154.4, 137.0, 134.7, 130.3, 127.0, 126.0, 125.8, 125.6, 125.0, 124.1, 122.7, 98.0, 96.1, 89.0, 83.0, 71.9, 53.3, 47.6, 43.2, 42.8, 39.6, 30.7, 15.8; IR ($CDCl_3$) 2957, 2257, 1771, 1701, 1605, 1497, 1445, 1377, 1327, 1306, 1292, 1277, 1248, 1217, 1184, 1121, 1092, 1034, 962 cm^{-1}; MS (EI) *m/e* calcd for $C_{24}H_{19}NO_4$ 385.1314, found 385.1321; 385 ([M]$^+$), 326 ([M − $C_2H_3O_2$]$^+$); white solid.

(6*R,6a*S**,7a*R**,7a*S**,10a*S**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-6a,7-epoxy-7-methyl-10-oxo-6,11-[3]hexene-[1,5]diynofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (7).** *m*-Chloroperbenzoic acid (44.8 mg, 0.26 mmol, 2 equiv) was added in one portion to a solution of the *cis*-lactone **28** (51.5 mg, 0.13 mmol, 1 equiv) in 6.5 mL of methylene chloride and 6.5 mL of commercial pH 7 phosphate buffer. The reaction was stirred at ambient temperature for 12 h and quenched with saturated sodium thiosulfate. The product was extracted into ether and the organic layer was washed three times with saturated sodium bicarbonate and once with brine. The aqueous washes were extracted with ether, and the combined ethereal solutions were dried over magnesium sulfate and filtered. After solvent removal *in vacuo,* the crude product was purified by column chromatography eluting with 37.5% ethyl acetate:hexane, and the pure product was isolated (40.4 mg, 77%): R_f 0.38 (1:1 ethyl acetate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (bs, 1H), 7.27 (t apparent, J = 8.8 Hz, 2H), 7.19 (td, J = 7.6, 1.3 Hz, 1H), 5.69 (dd, J = 9.6, 1.7 Hz, 1H), 5.65 (dd, J = 9.6, 1.7 Hz, 1H), 5.6 (bs, 1H), 4.50 (t apparent, J = 9.0 Hz, 1H), 4.38 (dd, J = 11.5, 8.6 Hz, 1H), 3.94 (m, 1H), 3.81 (s, 3H), 3.22 (dt apparent overlapping, J = 11.4, 9.3 Hz, 1H), 3.18 (d overlapping, J = 3.9 Hz, 1H), 2.79 (dd, J = 9.0, 4.8 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 154.1, 136.2, 128.7, 127.3, 125.7, 125.5, 125.3, 125.1, 123.4, 98.4, 93.6, 89.4, 83.8, 70.7, 69.7, 60.6, 53.6, 50.4, 44.8, 41.9, 39.0, 29.2, 17.3; IR (neat) 3026, 2982, 2957, 2200, 1777, 1707, 1495, 1443, 1375, 1329, 1292, 1253, 1225, 1211, 1181, 1144, 1123, 1082, 1053, 1038, 1022, 901, 750, 719 cm^{-1}; MS (EI) *m/e* calcd for $C_{24}H_{19}NO_5$ 401.1263, found 401.1256; 401 ([M]$^+$); white solid.

(6*R,7a*S**,10a*S**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-7-methyl-6,11-[3]hexene-[1,5]diynofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (29).** A solution of the *cis*-lactone **28** (24.5 mg, 0.064 mmol, 1 equiv) in 6.4 mL of methylene chloride was cooled to 0 °C. Diisobutylaluminum hydride (1 M in methylene chloride, 70 μL, 0.07 mmol, 1.1 equiv) was added dropwise. The reaction was stirred at 0 °C for 10 min and then quenched by the addition of 2 mL of methanol. The reaction was warmed to ambient temperature and diluted with ethyl acetate. The organic solution was washed twice with sodium potassium tartrate and once with brine. After extracting the aqueous layers once with ethyl acetate, the combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. The crude lactol was dissolved in 500 μL of methylene chloride. Triethylsilane (15 μL, 0.096 mmol, 1.5 equiv) was added and the resulting solution was cooled to −78 °C. After addition of boron trifluoride etherate (17 μl, 0.14 mmol, 2.2 equiv), the reaction was allowed to warm slowly to ambient temperature (30 min) and then recooled to −78 °C. After quenching with saturated sodium bicarbonate and rewarming, the product was extracted into ethyl acetate. The organic solution was washed twice with saturated sodium bicarbonate and once with brine. After drying over magnesium sulfate, the organic solution was filtered and the solvent removed *in vacuo*. The crude product may be purified by column chromatography over silica gel (3% ethyl acetate/methylene chloride). The product was isolated in 53% yield (12.5 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (bs, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.25 (apparent t overlapping, J = 7.2 Hz, 1H), 7.23−7.17 (m, 1H), 6.26 (bs, 1H), 5.58 (dd, J = 9.5, 1.6 Hz, 1H), 5.42 (dd, J = 9.5, 1.6 Hz, 1H), 4.27 (apparent t, J = 8.2 Hz, 1H), 4.11 (apparent t, J = 8.1 Hz, 1H), 3.94 (dd, J = 9.2, 5.3 Hz, 1H), 3.77 (s, 3H), 3.64−3.59 (m overlapping, 3H), 2.90 (apparent q, J = 9.8 Hz, 1H), 2.83−2.77 (m, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 154.4, 136.8, 133.3, 131.4, 126.51, 126.49, 125.6, 125.3, 121.6, 100.6, 96.5, 88.6, 82.7, 72.8, 71.9, 53.3, 47.3, 44.5, 43.0, 40.5, 32.9, 17.1; MS (FAB + NaI) *m/e* 394 ([M + Na]$^+$), 372 ([M + H]$^+$).

(6*R,7a*S**,10a*S**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-6a,7-epoxy-7-methyl-6,11-[3]hexene-[1,5]diynofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (13).** The *cis*-tetrahydrofuran **29** (5.5 mg, 0.015 mmol, 1 equiv) was dissolved in 625 μL of methylene chloride. An equal volume of pH 7 phosphate buffer was added.

mCPBA (5.2 mg, 0.3 mmol, 2 equiv) was added, and the reaction was stirred vigorously at ambient temperature. Upon the addition of the epoxidizing agent the organic phase turned pink briefly. After 45 min the reaction was quenched with saturated sodium thiosulfate and diluted with ethyl acetate. The organic phase was washed twice with saturated sodium thiosulfate, twice with saturated sodium bicarbonate, and once with brine. After drying over magnesium sulfate, the organic layer was filtered, and the solvent was removed at reduced pressure. The crude material was purified by column chromatography over silica gel (1.5% ethyl acetate/hexane) to yield 4.7 mg (80%) of the desired epoxide: R_f 0.33 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (bs, 1H), 7.28−7.24 (m overlapping, 2H), 7.18 (m, 1H), 5.70 (dd, J = 9.5, 1.8 Hz, 1H), 5.60 (dd, J = 9.5, 1.8 Hz, 1H), 5.33 (bs, 1H), 4.21 (dd, J = 9.1, 7.2 Hz, 1H), 4.04 (m, 2H), 3.93 (dd, J = 11.5, 8.0 Hz, 1H), 3.82 (s, 3H), 3.52 (m, 1H), 3.15 (d, J = 3.2 Hz, 1H), 2.87 (ddd, J = 11.4, 8.7, 8.6 Hz, 1H), 2.50−2.44 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 136.4, 129.8, 126.9, 125.6, 125.4, 125.2, 122.3, 101.6, 93.5, 89.6, 83.3, 73.3, 71.1, 70.5, 61.8, 53.5, 50.7, 45.2, 43.9, 39.7, 32.2, 19.0; IR (neat) 2955, 2876, 2200, 1707, 1495, 1441, 1375, 1327, 1290, 1251, 1194, 1143, 1122, 1103, 1080, 1060, 1018, 937, 758, 731, 667 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{21}NO_4Na$: 410.1368, found 410.1365; 410 ([M + Na]$^+$), 388 ([M + H]$^+$); white powder.

(6*R,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-9-carbomethoxy-8-(hydroxymethyl)-7-methyl-6,10-[3]hexene-[1,5]diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (25).** The *trans*-lactone **17** (52.8 mg, 0.14 mmol, 1 equiv) was suspended in 1.4 mL of a 1:1 mixture of methanol and tetrahydrofuran and cooled to −10 °C. One unmeasured scoop of sodium methoxide was added. The reaction was stirred for 10 min at −10 °C and then at 0 °C for 30 min. Saturated ammonium chloride was added, and the reaction was warmed to ambient temperature. The product was extracted into ether and washed once with saturated ammonium chloride and once with brine. The combined aqueous layers were extracted once with ether. The combined ethereal layers were dried over magnesium sulfate and filtered, and the solvent removed using a rotary evaporator. The product was purified on a 0.5 mm preparative TLC plate eluted with 1:1 ethyl acetate:hexane to provide 38.2 mg (64%) of the pure product: R_f 0.31 (1:1 ethyl acetate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.23 (t overlapping, J = 7.5 Hz, 1H), 7.19 (m, 1H), 6.29 (bs, 1H), 5.57 (dd, J = 9.4, 1.9 Hz, 1H), 5.46 (dd, J = 9.4, 1.7 Hz, 1H), 3.95 (m, 1H), 3.90 (d, J = 4.9 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.56 (bs, 1H), 2.97 (dd, J = 7.2, 2.7 Hz, 1H), 2.77 (bd, J = 6 Hz, 1H), 1.99 (d, J = 1 Hz, 3H), 1.9 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 154.3, 136.4, 134.7, 131.0, 127.2, 126.5, 125.9, 125.5, 125.4, 125.1, 122.3, 102.3, 96.9, 88.0, 82.0, 62.8, 53.3, 52.5, 46.5, 45.5, 42.7, 40.3, 33.6, 15.0; IR (neat) 3494, 1953, 2250, 2200, 1701, 1495, 1441, 1373, 1325, 1292, 1248, 1194, 1165, 1138, 1121, 1100, 1046, 1020, 910, 764, 733, 648 cm^{-1}; MS (EI) *m/e* calcd for $C_{25}H_{23}NO_5$ 417.1576, found 417.1576; 417 ([M]$^+$), 386 ([M − MeO]$^+$); colorless oil.

6*R,6a*S**,7*R**,8*S**,9*R**,10*S**-(±)-5,6,8,9,10,10a-Hexahydro-9-carbomethoxy-6a,7-epoxy-8-(hydroxymethyl)-7-methyl-6,10-[3]hexene-[1,5]diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (8).** *m*-Chloroperbenzoic acid (16.6 mg, 0.096 mmol, 2 equiv) was added to a solution of the hydroxy methyl ester **25** (20 mg, 0.048 mmol, 1 equiv) in 4.8 mL of a 1:1 mixture of methylene chloride and pH 7 phosphate buffer. The biphasic reaction was stirred vigorously at ambient temperature for 3 h. The reaction was poured into a separatory funnel containing ether and saturated sodium thiosulfate. The ethereal layer was washed three times with saturated sodium bicarbonate and once with brine. After drying over magnesium sulfate the solution was filtered, and the solvent removed *in vacuo*. The crude material was purified on a 0.5 mm preparative TLC plate eluting with 1:1 ethyl acetate:hexane to give 12.7 mg (60%) of the desired product: mp 162 °C dec; R_f 0.27 (1:1 ethyl acetate:hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (bs, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.25 (m overlapping, 1H), 7.19 (td, J = 7.4, 1.3 Hz, 1H), 5.66 (dd, J = 9.5, 1.8 Hz, 1H), 5.60 (dd, J = 9.5, 1.9 Hz, 1H), 5.33 (bs, 1H), 4.08 (t, J = 5.3 Hz, 1H), 3.99 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.40 (t apparent overlapping, J = 4.0 Hz, 2H) 3.12 (dd J = 9.0, 4.8 Hz, 1H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, partial) δ 172.7, 136.4, 130.4, 126.6, 125.7, 125.4, 125.0, 124.8, 122.8, 101.5, 93.4, 89.9, 84.7, 70.9, 63.1, 61.8, 53.5, 52.6, 50.5, 41.6, 41.5, 40.0, 27.7, 19.1; IR (neat) 3502, 3014, 2955, 2206, 1707, 1495, 1442, 1375, 1329, 1296, 1248, 1219, 1194, 1154, 1142, 1119, 1101, 1078, 1059, 1039, 1016, 756, 729 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{25}H_{23}NO_6Na$ 456.1423, found 456.1432; 456 ([M + Na]$^+$); off-white solid.

(6*R,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8-(acetoxymethyl)-9-carbomethoxy-6a,7-epoxy-7-methyl-6,10-[3]hexene-[1,5]-diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (9).** The hydroxy methyl ester epoxide **8** (9.5 mg, 0.022 mmol, 1 equiv) was dissolved in 1.1 mL of methylene chloride. Triethylamine (6 μL, 0.044 mmol, 2 equiv), acetic anhydride (3 μL, 0.033 mmol, 1.5 equiv), and a few crystals of (*N,N*-dimethyl)aminopyridine were added in sequence. The reaction was stirred at ambient temperature for 20 min and then diluted with ether. The ethereal solution was washed twice with saturated ammonium chloride and once with brine, and the aqueous layers were back extracted with ether. The combined ether layers were dried over magnesium sulfate and filtered, and the solvent was removed at reduced pressure. The crude material was purified by column chromatography over silica gel (35% ethyl acetate/hexane) to give 8.8 mg (86%) of the desired acetate: R_f 0.44 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (bs, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.24 (t overlapping, J = 7.3 Hz, 1H), 7.19 (td, J = 7.5, 1.4 Hz, 1H), 5.67 (dd, J = 9.5, 1.7 Hz, 1H), 5.60 (dd, J = 9.5, 1.9 Hz, 1H), 5.33 (bs, 1H), 4.46 (dd, J = 11.2, 5.9 Hz, 1H), 4.36 (dd, J = 11.1, 9.4 Hz, 1H), 4.08 (m, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.37 (d, J = 4.2 Hz, 1H), 3.26 (dd, J = 9.0, 6.1 Hz, 1H), 3.14 (d, J = 3.2 Hz, 1H), 2.09 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 171.8, 170.6, 136.4, 130.3, 126.7, 125.6, 125.4, 125.1, 124.8, 122.9, 100.7, 93.3, 90.0, 85.3, 70.9, 65.6, 61.7, 53.5, 52.6, 50.5, 41.6, 41.4, 38.6, 27.6, 21.0, 19.3; IR (neat) 3017, 2955, 2200, 1732, 1715, 1495, 1441, 1375, 1329, 1294, 1229, 1194, 1142, 1120, 1074, 1055, 1024, 976, 758, 731 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{27}H_{25}NO_7Na$ 498.1529, found 498.1531; 498 ([M + Na]$^+$), 476 ([M + H]$^+$); colorless oil.

(6*R,6a*S**,7*R**,8*S**,9*S**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(hydroxymethyl)-7-methyl-6,10-[3]hexene-[1,5]diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (14).** *cis*-Lactone epoxide **7** (28.9 mg, 0.072 mmol, 1 equiv) was dissolved in 1.37 mL of a 5:1 tetrahydrofuran:water mixture. Sodium borohydride (27.2 mg, 0.72 mmol, 10 equiv) was added, and the reaction was stirred at ambient temperature for 4 h. After cooling to 0 °C, 2 N sulfuric acid was added slowly until gas evolution had ceased, and then the solution was poured into ethyl acetate and brine. The aqueous layer was washed two times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate and filtered. After solvent removal at reduced pressure, the product was purified by column chromatography eluting with 5% methanol:methylene chloride to give 24.2 mg (83%) of pure product: mp 97 °C dec; R_f 0.07 (1:1 ethyl acetate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (bs, 1H), 7.23 (m overlapping, 2H), 7.18 (td, J = 7.3, 1.4 Hz, 1H), 5.63 (dd, J = 9.6, 1.8 Hz, 1H), 5.57 (dd, J = 9.6, 1.8 Hz, 1H), 5.33 (bs, 1H), 4.31 (dd, J = 11.7, 5.9 Hz, 1H), 3.97 (dd, J = 11, 8.8 Hz, 1H), 3.84 (m overlapping, 1H), 3.81 (s, 3H), 3.79 (m overlapping, 1H), 3.36 (m, 1H), 3.25 (d, J = 4.3 Hz, 1H), 2.91 (bs, 1H(OH)), 2.51 (m overlapping, 1H), 2.45 (bs overlapping, 1H(OH)), 2.31 (m, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 136.5, 130.2, 126.7, 125.6, 125.3, 124.8, 125.7, 122.6, 101.6, 93.2, 90.0, 85.3, 71.7, 64.7, 63.9, 60.8, 53.5, 50.8, 46.7, 43.7, 39.7, 29.2, 20.6; IR (neat) 3430, 3011, 2955, 2200, 1700, 1584, 1495, 1443, 1377, 1329, 1292, 1250, 1196, 1161, 1143, 1100, 1051, 945, 756, 729, 665 cm^{-1}; MS (FAB) *m/e* calcd for $C_{24}H_{23}NO_5$ 406.1654, found 406.1638; 406 ([M + H]$^+$); white solid.

(6*R,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(hydroxymethyl)-7-methyl-6,10-[3]hexene-[1,5]diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (26).** The *trans*-lactone **17** (43 mg, 0.11 mmol, 1 equiv) was suspended in 2.4 mL of a 5:1 mixture of tetrahydrofuran:water. Sodium borohydride (41.6 mg, 1.1 mmol, 10 equiv) was added and the reaction was stirred for 3 h at ambient temperature. After cooling to 0 °C, the reaction was quenched cautiously with 2 N sulfuric acid (gas evolution), and then the solution was poured into brine. The solution was extracted three times with ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate and

filtered, and the solvent was removed using a rotary evaporator. The product was purified by column chromatography (silica gel, 3% methanol:methylene chloride) to give 32.3 mg (75%) of the desired product: mp 145 °C dec; R_f 0.11 (1:1 ethyl acetate:hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.7 Hz, 1H), 7.4 (bs overlapping, 1H), 7.22 (m overlapping, 1H), 7.19 (m, 1H), 6.26 (bs, 1H), 5.55 (dd, J = 9.4, 1.8 Hz, 1H), 5.42 (dd, J = 9.4, 1.7 Hz, 1H), 3.93 (dd, J = 10.9, 4.0 Hz, 1H), 3.86 (dd, J = 10.9, 6.1 Hz, 1H), 3.75 (s, 3H), 3.72 (m overlapping, 2H), 3.67 (dd, J = 4.0, 2.2 Hz, 1H), 3.51 (bs, 1H), 3.0−2.7 (bs, 2H(OH)), 2.19 (dd, J = 6.3, 2.7 Hz, 1H), 2.13 (bs, 1H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 154.5, 136.5, 134.4, 131.7, 128.1, 126.4,126.0, 125.5, 125.3, 121.7, 104.3, 96.7, 88.2, 81.7, 64.7, 63.3, 53.3, 46.7, 43.2, 42.5, 39.3, 33.0, 15.3; IR (neat) 3434, 3011, 2955, 2194, 1692, 1495, 1445, 1375, 1327, 1298, 1217, 1194, 1138, 1118, 1078, 1045, 976, 958, 756, 667 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{23}NO_4Na$ 412.1525, found 412.1541; 412 ([M + Na]$^+$), 390 ([M + H]$^+$); yellow foam.

(6*R,6a*S**,7*R**,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(hydroxymethyl)-6a,7-epoxy-7-methyl-6,10-[3]hexene-[1,5]-diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (10).** The *trans*-diol **26** (20.3 mg, 0.05 mmol, 1 equiv) was suspended in 2.5 mL of methylene chloride. An identical volume of pH 7 phosphate buffer was added. *m*-Chloroperbenzoic acid (17.2 mg, 0.1 mmol, 2 equiv) was added, and the reaction was stirred vigorously for 4 h. After quenching with saturated aqueous sodium thiosulfate, the product was extracted into ethyl acetate. The organic layer was washed twice with saturated sodium bicarbonate and once with brine. The aqueous washes were back extracted with ethyl acetate. The combined organic solutions were dried over magnesium sulfate and filtered, and the solvent was removed *in vacuo*. The product was purified by column chromatography over silica gel (3% methanol:methylene chloride) to give 20.0 mg (98%) of the epoxy-diol: R_f 0.16 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (bs, 1H,), 7.30 (d, J = 7.8 Hz, 1H), 7.23 (m overlapping, 1H), 7.16 (m, 1H), 5.67 (dd, J = 9.5, 1.8 Hz, 1H), 5.57 (dd, J = 9.5, 1.8 Hz, 1H), 5.53 (bs, 1H), 3.9 (m, 2H), 3.80 (s, 3H), 3.73 (bs, 1H), 3.63 (m, 2H), 3.34 (d, J = 4.1 Hz, 1H), 2.52 (bs, 1H), 2.5−2.2 (bs overlapping, 2H(OH)), 2.0 (m, J = 1 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$, partial) δ 136.4, 130.5, 126.6, 125.4, 125.2, 124.9, 122.2, 103.8, 93.2, 89.8, 84.0, 71.3, 64.9, 64.0, 63.0, 53.5, 50.5, 42.1, 39.6, 39.3, 28.5, 19.0; IR (neat) 3434, 3013, 2955, 2200, 1701, 1495, 1375, 1329, 1290, 1250, 1194, 1173, 1142, 1120, 1103, 1037, 756, 729, 709, 667 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{23}NO_5Na$ 428.1474, found 428.1480; 428 ([M + Na]$^+$); yellow oil.

(6*R,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(methoxymethyl)-7-methyl-6,10-[3]hexene-[1,5]diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (27).** The *trans*-diol **26** (14.6 mg, 0.038 mmol, 1 equiv) was dissolved in 380 μL of DMF. Iodomethane (12 μL, 0.19 mmol, 5 equiv freshly filtered through basic alumina) was added. The solution was cooled to 0 °C, and sodium hydride (5 mg, 0.15 mmol, 60% by weight, 4 equiv) was added. The reaction was allowed to warm to ambient temperature. Iodomethane and sodium hydride were added in aliquots as above until thin layer chromatography (1:1 ethyl acetate:hexane) showed complete consumption of starting material. After dilution with saturated ammonium chloride, the aqueous solution was extracted three times with ether. The combined ethereal extracts were washed with brine, dried over magnesium sulfate, and filtered. After solvent removal *in vacuo* the product was purified by column chromatography over silica gel eluting with 25% ethyl acetate:hexane to give 13.8 mg (87%) of the dimethyl ether: R_f 0.54 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 7.40 (d overlapping, J = 7.5 Hz, 1H), 7.2 (m, 2H), 6.26 (bs, 1H), 5.57 (dd, J = 9.4, 1.8 Hz, 1H), 5.42 (dd, J = 9.4, 1.6 Hz, 1H), 3.76 (s, 3H), 3.71 (m, 1H), 3.60 (dd, J = 9.6, 5.2 Hz, 1H), 3.55 (dd, J = 9.6, 5.3 Hz, 1H), 3.50 (m, 2H), 3.40 (m overlapping, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.33 (m, 1H), 2.18 (m, 1H), 1.95 (d, J = 0.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 136.6, 134.0, 129.0, 128.5, 128.2, 126.2, 126.1, 125.6, 125.3, 121.3, 104.9, 96.8, 88.1, 81.2, 74.4, 72.6, 59.0, 58.7, 53.2, 46.7, 40.3, 40.0, 39.2, 33.2, 15.1; IR (neat) 2984, 2926, 2829, 2249, 2200, 1705, 1581, 1493, 1441, 1373, 1323, 1296, 1248, 1192, 1105, 1049, 856, 912, 760, 731, 648 cm^{-1}; MS (EI) *m/e* calcd for $C_{26}H_{27}NO_4$ 417.1940, found 417.1959; 417 ([M]$^+$); yellow oil.

(6*R,6a*S**,7*R**,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(methoxymethyl)-6a,7-epoxy-7-methyl-6,10-[3]hexene-[1,5]-diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (12).** The bis-methyl ether **27** (13.8 mg, 0.033 mmol, 1 equiv) was dissolved in 3.2 mL of a 1:1 mixture of methylene chloride and pH 7 phosphate buffer. *m*-Chloroperbenzoic acid (11.4 mg, 0.066 mmol, 2 equiv) was added, and the biphasic reaction was stirred vigorously for 3 h. The reaction was diluted with ether and saturated sodium thiosulfate. The ether layer was washed three times with saturated sodium bicarbonate and once with brine. After drying over magnesium sulfate, the suspension was filtered, and the solvent was removed *in vacuo*. The product was purified by column chromatography over silica gel eluting with 20% ethyl acetate/hexane to give 7 mg (50%) of the epoxy-ether: R_f 0.55 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (bs, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.23 (m overlapping, 1H), 7.17 (m, 1H), 5.68 (dd, J = 9.5, 1.8 Hz, 1H), 5.56 (dd, J = 9.5, 1.9 Hz, 1H), 5.33 (bs, 1H), 3.81 (s, 3H), 3.70 (bs, 1H), 3.67−3.57 (m overlapping, 2H), 3.43 (t, J = 9.9 Hz, 1H), 3.34 (s, 3H), 3.30 (m overlapping, 2H), 3.28 (s, 3H), 2.63 (m, 1H), 2.04 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 136.6, 130.8, 128.2, 125.8, 125.4, 125.0, 121.9, 104.0, 93.3, 89.9, 83.8, 74.5, 74.3, 71.4, 62.9, 58.8, 58.5, 53.4, 50.7, 39.6, 38.9, 37.1, 27.7, 19.3; IR (neat) 2984, 2926, 2893, 2812, 1711, 1495, 1441, 1375, 1329, 1288, 1252, 1194, 1109, 1060, 1022, 956, 912, 760, 729, 696 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{26}H_{27}NO_5Na$ 456.1787, found 456.1795; 456 ([M + Na]$^+$); yellow oil.

(6*R,7a*S**,7*R**,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(acetoxymethyl)-6a,7-epoxy-7-methyl-6,10-[3]hexene-[1,5]-diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (11).** The *trans*-diol epoxide **10** (16.4 mg, 0.04 mmol, 1 equiv) was dissolved in 2 mL of methylene chloride. Triethylamine (22 μL, 0.16 mmol, 4 equiv) and acetic anhydride (11 μL, 0.12 mmol, 3 equiv) were added. A few crystals of (*N,N*-dimethylamino)pyrindine were added. The reaction was stirred at ambient temperature for 30 min and quenched with saturated ammonium chloride. The product was extracted into ether, and the ethereal solution washed with brine. The aqueous layer was back extracted with ether. The combined ethereal solution was dried over magnesium sulfate. Filtration and solvent removal *in vacuo* provided the crude product. Purification by column chromatography (silica gel, 20% ethyl acetate/hexane) gave 12.8 mg (68%) of the desired bis-acetate: R_f 0.44 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (bs, 1H), 7.24 (m overlapping, 2H), 7.18 (m, 1H), 5.68 (dd, J = 9.5, 1.7 Hz, 1H), 5.59 (dd, J = 9.5, 1.9 Hz, 1H), 5.34 (bs, 1H), 4.40 (dd, J = 11.1, 5.1 Hz, 1H), 4.30 (dd, J = 11.1, 9.3 Hz, 1H), 4.11 (s, 1H), 4.09 (s, 1H), 3.81 (s, 3H), 3.60 (bd, J = 4.2 Hz, 1H), 3.34 (d, J = 4.2 Hz, 1H), 2.59 (ddd, J = 12.1, 5.1, 3.0 Hz, 1H), 2.27 (dd, J = 9.0, 5.7 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 170.7, 170.4, 136.6, 130.2, 126.8, 125.4, 125.3, 125.2, 125.1, 122.5, 101.8, 93.2, 90.0, 84.6, 71.4, 66.0, 65.7, 62.4, 53.5, 50.6, 39.1, 38.9, 36.7, 28.1, 21.0, 20.9, 19.5; IR (neat) 2957, 2256, 2206, 1740, 1495, 1441, 1375, 1288, 1232, 1039, 912, 729 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{28}H_{27}NO_7Na$ 512.1685, found 512.1699; 512 ([M + Na]$^+$), 490 ([M + H]$^+$); colorless oil.

(6*R,6a*S**,7*R**,8*S**,9*S**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(acetoxymethyl)-6a,7-epoxy-7-methyl-6,10-[3]hexene-[1,5]-diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (15).** The *cis*-diol epoxide **14** (19.8 mg, 0.049 mmol, 1 equiv) was dissolved in 2.5 mL of methylene chloride. Triethylamine (27 μL, 0.196 mmol, 4 equiv), acetic anhydride (14 μL, 0.147 mmol, 3 equiv), and a few crystals of (*N,N*-dimethylamino)pyridine were added sequentially. The reaction was stirred at ambient temperature for 20 min and then poured into a separatory funnel containing ether and saturated ammonium chloride. The aqueous layer was extracted twice with ether. The combined ethereal solutions were washed once with brine, dried over magnesium sulfate, and filtered. After solvent removal at reduced pressure, the product was purified by column chromatography (20−30% ethyl acetate:hexane) to give 16.6 mg (69%) of the desired product: R_f 0.66 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (bs, 1H), 7.24 (m overlapping, 2H), 7.17 (m, 1H), 5.66 (dd, J = 9.6, 1.7 Hz, 1H), 5.60 (dd, J = 9.6, 1.9 Hz, 1H), 5.35 (bs, 1H), 4.48 (dd, J = 12.6, 3.2 Hz, 1H), 4.37 (dd, J = 11.2, 5.4 Hz, 1H), 4.23 (dd, J = 12.3, 6.2 Hz, 1H), 4.20 (m overlapping, 1H), 3.81 (s,

3H), 3.45 (m, 1H), 3.24 (d, J = 4.4 Hz, 1H), 2.53 (td, J = 6.1, 3.3 Hz, 1H), 2.39 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.4, 154.0, 136.5, 130.0, 129.0, 125.6, 125.3, 124.8, 124.7, 122.9, 100.6, 93.0, 90.2, 85.4, 71.4, 64.8, 64.7, 62.6, 53.5, 50.7, 46.5, 40.8, 37.6, 29.1, 21.0, 20.9, 19.8; IR (neat) 2957, 2257, 2202, 1740, 1495, 1442, 1375, 1329, 1298, 1232, 1194, 1165, 1126, 1099, 1080, 1033, 1003, 914, 761, 731, 648 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{28}H_{27}NO_7Na$ 512.1685, found 512.1690; 512 ([M + Na]$^+$), 490 ([M + H]$^+$); colorless oil/white amorphous solid.

(6*R,6a*S**,7*R**,8*S**,9*S**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-8,9-bis(hydroxymethyl)-6a,7-epoxy-7-methyl-6,10-[3]hexene-[1,5]-diynophenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (16).** Methyl trifluoromethanesulfonate (19 μL, 0.165 mmol, 15 equiv) was added to a solution of *cis*-diol epoxide **14** (4.4 mg, 0.11 mmol, 1 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (67.8 mg, 0.33 mmol, 30 equiv) in 200 μL of methylene chloride. The reaction was stirred at ambient temperature for 2 h. After quenching with saturated aqueous ammonium chloride, the product was extracted into ethyl acetate. The organic phase was washed once with ammonium chloride and once with brine. After drying over magnesium sulfate, filtration, and concentrating *in vacuo*, the crude product was purified by chromatography over silica gel eluting first with 10% ethyl acetate/hexane until the pyridine has been removed and then with 35% ethyl acetate/hexane to obtain the product (1.5 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (bs, 1H), 7.28−7.20 (m overlapping, 2H), 7.14 (td, J = 7.6, 1.4 Hz, 1H), 5.64 (dd, J = 9.5, 1.7 Hz, 1H), 5.59 (dd, J = 9.5, 1.8 Hz, 1H), 5.34 (bs, 1H), 3.81 (s, 3H), 3.59−3.45 (m overlapping, 5H), 3.39 (s, 3H), 3.26 (s, 3H), 3.22 (d, J = 4.5 Hz, 1H), 2.39 (td, J = 6.1, 2.3 Hz, 1H), 2.30 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 136.5, 130.5, 126.5, 125.8, 125.2, 124.8, 124.7, 122.5, 102.3, 93.4, 89.9, 84.4, 73.8, 71.4, 71.2, 65.3, 59.0, 58.1, 53.4, 50.8, 46.6, 41.8, 38.5, 29.2, 19.4; IR (neat) 2986, 2922, 2912, 2250, 2200, 1711, 1495, 1441, 1375, 1327, 1288, 1252, 1196, 1163, 1103, 1057, 1024, 955, 914, 860, 764, 729 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{26}H_{27}NO_5Na$ 456.1787, found 456.1803; 456 ([M + Na]$^+$), 434 ([M + H]$^+$); colorless oil.

(6*R,7a*S**,10a*S**,11*S**,11a*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-11a-hydroxy-7-methyl-10-oxo-6,11-[3]hexene-[1,5]diynofuro[3,4-*j*]-phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (36).** The *cis*-lactone **28** (131 mg, 0.34 mmol, 1 equiv) was dissolved in 17 mL of acetonitrile. A solution of ceric ammonium nitrate (559.2 mg, 1.02 mmol, 3 equiv) in 5.1 mL of water was added followed by 1.7 mL of acetic acid. The solution was stirred for 13 h at ambient temperature and then poured into a separatory funnel containing saturated ammonium chloride. The product was extracted into ether, and the ethereal solution was washed twice with saturated ammonium chloride, three times with saturated sodium bicarbonate, and once with brine. The combined aqueous layers were extracted twice with ether. After drying over magnesium sulfate, the ethereal solution was filtered, and the solvent was removed on a rotary evaporator. The crude product was filtered through a short plug of silica gel (2:1 methylene chloride/ethyl acetate) to give 98.5 mg of the desired product (74% yield): mp 225 °C dec; R_f 0.15 (1:1 methylene chloride:ether); ^{1}H NMR (400 MHz, $CDCl_3$ 333 K) δ 7.55 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.24 (m overlapping, 1H), 6.39 (s, 1H), 5.59 (d, J = 9.4 Hz, 1H), 5.48 (d, J = 9.6 Hz, 1H), 4.54 (t, J = 8.9 Hz, 1H), 4.08 (d, J = 10.0 Hz, 1H), 4.04 (d, J = 6.9 Hz, 1H), 3.81 (s, 3H), 3.63 (dd, J = 9.8, 5.9 Hz, 1H), 3.39 (q apparent, J = 9.9 Hz, 1H), 1.99 (bs, 1H), 1.87 (s, 3H); MS (FAB+NaI) *m/e* calcd for $C_{24}H_{19}NO_5Na$ 424.1161, found 424.1136; 424 ([M + Na]$^+$), 348 ([M + Na − OH]$^+$).

(6*R,7*R**,7a*R**,10a*S**,11*S**-(±)-7a,8,10,10a,11,11a-Hexahydro-6a,11a-didehydro-7-methyl-10-oxo-6,11-[3]hexene-[1,5]diynofuro-[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (37).** The benzylic alcohol **36** (28.0 mg, 0.07 mmol, 1 equiv) was azeotroped with xylenes and then dissolved in 28 mL of methylene chloride. The solution was cooled to −78 °C, and methyl aluminum dichloride (1 M in hexane, 210 μL, 0.21 mmol, 3 equiv) was added dropwise. The reaction turns green initially, but fades to faint yellow. The reaction was stirred at −78 °C for 5 min, at −35 °C for 15 min, and then was recooled to −78 °C. A solution of (mesitylsulfonyl)hydrazine (15.5 mg, 0.073 mmol, 1.04 equiv) in 1 mL of methylene chloride was added *via* cannula. After addition was complete, the reaction was stirred at −78 °C for 5 min and then at 0 °C for 2.5 h. The reaction was quenched with pH 7 phosphate buffer. The aqueous solution was extracted with ethyl acetate, and the organic solution was washed with sodium potassium tartrate and brine, after which it was dried over magnesium sulfate. The drying agent was remove by filtration, and the solvent was removed at reduced pressure. The crude product was purified by HPLC eluting with 1:2 hexane/ethyl acetate to give 13.1 mg (49%) of the desired product: R_f 0.61 (1:1 CH_2Cl_2:Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (bd, J = 7.3 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.25 (m overlapping, 1H), 7.16 (m, 1H), 5.93 (s, 1H), 5.72 (dd, J = 9.3, 1.4 Hz, 1H), 5.65 (dd, J = 9.3, 1.4 Hz, 1H), 4.49 (d, J = 8.5 Hz, 1H), 4.45 (dd, J = 9.4, 4.8 Hz, 1H), 4.38 (dd, J = 9.4, 6.9 Hz, 1H), 3.84 (s, 3H), 3.20 (t, J = 9.1 Hz, 1H), 2.95 (m, 2H), 1.26 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 153.7, 133.6, 132.9, 127.6, 126.4, 125.7, 124.8, 124.5, 124.0, 122.9, 122.8, 101.2, 94.3, 92.3, 91.1, 69.5, 53.5, 51.2, 39.8, 37.1, 32.8, 28.7, 12.8; IR (neat) 2175, 1772, 1709, 1489, 1439, 1377, 1329, 1282, 1252, 1228, 1217, 1196, 1176, 1155, 1134, 1091, 1059, 1037, 989, 979, 756 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{19}NO_4Na$ 408.1212, found 408.1231; 408 ([M + Na]$^+$), 386 ([M + H]$^+$); colorless oil.

(6*R,6a*S**,7*R**,7a*R**,10a*S**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-6a,11a-epoxy-7-methyl-10-oxo-6,11-[3]hexene-[1,5]diynofuro-[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (38).** The enediyne **37** (4.4 mg, 0.011 mmol, 1 equiv) was dissolved in 660 μL of methylene chloride. Phosphate buffer (pH 7, 660 μL) was added followed by mCPBA (1.9 mg, 0.011 mmol, 1 equiv). The reaction was stirred at ambient temperature for 24 h after which it was quenched with saturated sodium thiosulfate. The aqueous solution was extracted with ethyl acetate, washed twice with sodium thiosulfate, twice with sodium bicarbonate, and once with brine. The organic solution was dried over magnesium sulfate and filtered and the solvent removed *in vacuo*. The product was purified by preparative thin layer chromatography (2.5 mm, 4:1 methylene chloride:ether) to give the desired epoxide in 79% yield (3.5 mg): R_f 0.64 (1:1 CH_2Cl_2:Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.9 Hz, 1H), 7.34−7.20 (m overlapping, 3H), 5.73 (dd, J = 9.8, 1.4 Hz, 1H), 5.65 (dd, J = 9.9, 1.5 Hz, 1H), 5.62 (bs, 1H), 4.57 (t apparent, J = 8.9 Hz, 1H), 4.33 (t apparent, J = 8.7 Hz, 1H), 4.24 (d, J = 5.8 Hz, 1H), 3.77 (s, 3H), 3.10 (m overlapping, 2H), 2.98 (dd, J = 9.5, 6.5 Hz, 1H), 1.39 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 177.3, 136.2, 128.6, 127.7, 126.8, 126.5, 125.5, 124.4, 123.7, 98.8, 95.0, 91.3, 90.5, 72.1, 69.8, 62.9, 53.7, 47.8, 38.8, 33.2, 31.3, 28.7, 14.7; IR (neat) 2924, 2855, 1772, 1709, 1495, 1441, 1371, 1323, 1282, 1248, 1176, 1151, 1039, 1022, 993, 960, 914, 806, 731, 648 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{19}NO_5Na$ 424.1161, found 424.1178; 424 ([M + Na]$^+$), 402 ([M + H]$^+$).

(6*R,6a*S**,7*R**,7a*R**,10a*S**,11*S**)-(±)-7a,8,10,10a,11,11a-Hexahydro-11a-chloro-6a-hydroxy-7-methyl-10-oxo-6,11-[3]hexene-[1,5]-diynofuro[3,4-*j*]phenanthridine-5(6*H*)-carboxylic Acid Methyl Ester (39).** A 0.25 M solution of HCl in methylene chloride was prepared by the addition of 20 μL of methanol (0.5 mmol) to a 0.25 M solution of acetyl chloride (35.6 μL, 0.5 mmol) in methylene chloride. The enediyne **38** (1 mg, 0.025 mmol, 1 equiv) was dissolved in 600 μL of methylene chloride. The hydrochloric acid stock solution (80 μL) was added, and the reaction was stirred for 2 h. The solvent was removed *in vacuo*, and the crude product was purified by preparative thin layer chromatography (2.5 mm, eluting with 4:1 methylene chloride/ether) to give the product in quantitative yield: R_f 0.54 (4:1 methylene chloride:ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.7, 1.9 Hz, 1H), 7.38 (d, J = 7.0 Hz, 1H), 7.30 (bs, 1H), 7.26 (m overlapping, 1H), 7.16−7.04 (m overlapping, 3H), 6.98 (d, J = 7.6 Hz, 1H), 5.97 (bs, 1H), 3.89 (s, 3H), 3.87 (m overlapping, 1H), 3.80 (t, J = 9.0 Hz, 1H), 3.58 (dd, J = 9.0, 5.2 Hz, 1H), 2.98 (m, 1H), 2.78 (m, 1H), 2.64 (dd, J = 12.1, 8.8 Hz, 1H), 1.55 (bs, 1H, OH), 1.19 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 155.5, 134.5, 133.9, 133.8, 130.0, 129.6, 129.4, 129.3, 129.1, 128.8, 128.2, 124.8, 123.8, 77.6, 70.2, 69.8, 57.9, 53.6, 52.8, 43.6, 37.3, 35.7, 10.6; IR (neat) 3460, 1769, 1701, 1491, 1439, 1375, 1332, 1280, 1230, 1215, 1190, 1169, 1140, 1043, 1018, 910, 763, 731, 659, 609 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{22}NO_5Na$ 462.1084, found 462.1096; 462 ([M + Na]$^+$), 439 ([M]$^+$).

General Procedure for Thermolysis. In base washed glassware the enediyne (2−10 mg) was dissolved in toluene to a final concentration of 0.008 M. The solution was degassed using two cycles of freeze-pump-thaw, and then 1,4-cyclohexadiene (62 equiv) was added. The reaction was heated to the appropriate temperature (all studies were at 80 °C except where noted in the text) for the time indicated in the text (a typical experiment ran for 12 h).

(6*R,6a*S**,9*R**,10*S**)-(±)-5,6,6a,10a,9,10-Hexahydro-6a-hydroxy-8,9-bis(hydroxymethyl)-7-methyl-6,10-[1′,2′]benzenophenanthridine-5(6*H*)-carboxylic acid methyl ester (33):** R_f 0.07 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (bs, 1H), 7.31 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.21−6.94 (m overlapping, 6H), 5.63 (bs, 1H), 4.20 (d, *J* = 12.3 Hz, 1H), 4.04 (d, *J* = 6.1 Hz, 2H), 3.90 (s, 3H), 3.72 (d, *J* = 12.3 Hz, 1H), 3.26 (bs, 1H), 3.21 (bs, 1H), 2.55 (bs, 1H, (OH)), 2.42 (bs, 1H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 156, 138.1, 135.3, 135.0, 134.6, 132.4, 129.6, 129.4, 128.4, 128.3, 126.9, 126.7, 124.2, 123.5, 69.5, 66.4, 62.6, 57.0, 53.4, 50.4, 49.7, 41.3, 11.9; IR (neat) 3393, 3017, 2955, 2926, 1686, 1493, 1441, 1377, 1319, 1375, 1232, 1194, 1138, 1116, 1059, 1037, 758, 704, 667, 634 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{24}H_{25}NO_5Na$ 430.1630, found 430.1621; 430 ($[M + Na]^+$), 407 ($[M]^+$), 390 ($[M + H - H_2O]^+$); white solid.

6*R,6a*S**,7*R**,8*S**,9*R**,10*S**-(±)-5,6,8,9,10,10a-Hexahydro-6a,7-epoxy-9-carbomethoxy-8-(hydroxymethyl)-7-methyl-6,10-[1′,2′]benzenophenanthridine-5(6*H*)-carboxylic acid methyl ester (31):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.17−7.12 (m, 3H), 7.09−7.04 (m, 2H), 6.98−6.95 (m, 1H), 5.60 (bs, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 3.76 (m, 1H), 3.68 (m, 1H), 3.41 (d, *J* = 2.5 Hz, 1H), 3.16 (s, 1H), 2.62 (d, *J* = 6.7 Hz, 1H), 2.44 (m, 1H), 1.43 (bt, *J* = 5.4 Hz, 1H (OH)), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 175.5, 140.0, 136.4, 135.7, 129.3, 129.0, 128.4, 127.8, 127.2, 127.1, 123.9, 122.9, 62.1, 61.0, 59.3, 54.1, 53.4, 52.8, 52.5, 50.4, 45.1, 37.8, 13.1; IR (neat) 3502, 2955, 1716, 1493, 1439, 1379, 1323, 1294, 1278, 1224, 1192, 1163, 1138, 1099, 1057, 1037, 1022, 978, 856, 758, 731 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{25}H_{25}NO_6Na$ 458.1580, found 458.1567; 458 ($[M + Na]^+$), 435 ($[M]^+$).

(6*R,6a*S**,7*R**,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-6a,7-epoxy-8,9-bis(acetoxymethyl)-7-methyl-6,10-[1′,2′]benzenophenathridine-5(6*H*)-carboxylic acid methyl ester (34):** R_f 0.44 (50:50 hexane: ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.30 (m, 1H), 7.16−7.11 (m overlapping, 2H), 7.10−7.06 (m overlapping, 2H), 7.00−6.95 (m overlapping, 2H), 5.61 (bs, 1H), 4.41 (dd, *J* = 11.4, 3.3 Hz, 1H), 4.36 (dd, *J* = 11.7, 4.3 Hz, 1H), 4.28 (dd, *J* = 11.4, 6.5 Hz, 1H), 4.00 (dd, *J* = 11.6, 9.0 Hz, 1H), 3.89 (s, 3H), 3.31 (d, *J* = 2.3 Hz, 1H), 2.94 (bs, 1H), 2.20 (s, 3H), 2.19−2.07 (m overlapping, 1H), 2.05 (s, 3H), 2.03−1.97 (m, 1H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 170.9, 170.7, 140.7, 136.3, 135.8, 129.2, 129.0, 128.9, 128.2, 128.0, 127.0, 124.0, 123.1, 66.4, 62.8, 61.6, 60.2, 54.4, 53.4, 53.2, 44.5, 40.7, 37.8, 21.0, 20.9, 13.2; IR (neat) 2955, 1741, 1703, 1493, 1439, 1379, 1323, 1294, 1228, 1194, 1138, 1118, 1039, 1024, 976, 954, 912, 858, 761, 733 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{28}H_{29}NO_7Na$ 514.1842, found 514.1851; 514 ($[M + Na]^+$), 491 ($[M]^+$); colorless oil.

(6*R,6a*S**,7*R**,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-6a,7-epoxy-8,9-bis(methoxymethyl)-7-methyl-6,10-[1′,2′]benzenophenathridine-5(6*H*)-carboxylic acid methyl ester (35):** R_f 0.40 (50:50 hexane: ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.12−6.94 (m overlapping, 6H), 5.58 (bs, 1H), 3.88 (s, 3H), 3.63 (dd, *J* = 9.8, 3.3 Hz, 1H), 3.52 (dd overlapping, *J* = 9.3, 2.9 Hz, 1H), 3.50 (d overlapping, *J* = 9.5 Hz, 1H), 3.45 (s, 3H), 3.40 (d, *J* = 8.0 Hz, 1H), 3.39 (bm overlapping, 1H), 3.30 (s, 3H), 2.95 (bs, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 141.9, 136.4, 135.9, 135.8, 129.2, 128.9, 128.8, 128.4, 126.7, 126.5, 123.7, 122.8, 75.2, 71.4, 61.8, 61.1, 59.3, 58.6, 54.4, 53.4, 45.4, 41.3, 37.9, 13.1; IR (neat) 2924, 1711, 1493, 1377, 1323, 1294, 1277, 1223, 1192, 1155, 1118, 1074, 1057, 1037, 1022, 954, 858, 758, 733 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{26}H_{29}NO_5Na$ 458.1946, found 458.1965; 458 ($[M + Na]^+$), 435 ($[M]^+$); white solid.

(6*R,6a*S**,7*R**,8*S**,9*R**,10*S**)-(±)-5,6,8,9,10,10a-Hexahydro-6a,7-epoxy-8-(acetoxymethyl)-9-carbomethoxy-7-methyl-6,10-[1′,2′]benzenophenathridine-5(6*H*)-carboxylic acid methyl ester (32):** R_f 0.38 (50:50 hexane:ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (bs, 1H), 7.30 (m 1H), 7.16 (m overlapping, 2H), 7.11 (m overlapping, 1H), 7.06 (m overlapping, 2H), 6.97 (ddd, *J* = 8.6, 7.4, 1.1 Hz, 1H), 5.61 (bs, 1H), 4.13−4.04 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.42 (d, *J* = 2.6 Hz, 1H), 3.16 (bs, 1H), 2.66−2.56 (m, 2H), 2.03 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, partial) δ 174.7, 170.5, 139.7, 136.4, 135.7, 129.4, 129.3, 129.1, 128.4, 127.6, 127.4, 127.2, 124.0, 123.0, 63.2, 61.0, 58.9, 54.0, 53.5, 52.9, 52.5, 50.4, 41.8, 37.7, 20.8, 13.1; IR (neat) 2955, 1736, 1493, 1437, 1379, 1323, 1294, 1278, 1226, 1192, 1167, 1136, 1057, 1037, 1022, 978, 912, 856, 761, 731 cm^{-1}; MS (FAB + NaI) *m/e* calcd for $C_{27}H_{27}NO_7Na$ 500.1685, found 500.1675; 500 ($[M + Na]^+$), 477 ($[M]^+$); white solid.

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Supplementary Material Available: Crystal data, atomic coordinates, bond lengths, bond angles, and anisotropic displacement coefficients for the X-ray structure of compound **5**, ^{1}H and ^{13}C NMR spectra of compounds **7**−**22**, **24**−**29**, **31**−**35**, and **37**−**39**, and ^{1}H NMR spectra of compounds **30** and **36** (41 pages); observed and calculated structure factors for the X-ray structure of **5** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.