rotary evaporation of solvent was subjected to HPLC with 15% ethyl acetate in hexanes as eluting solvent. Data for spatol benzyl ether (+)-**54** (3.6 mg, 62.2%) thus obtained: $[\alpha]^{22}_D$ + 8° (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.22 (2 H, d, *J* = 8.2 Hz), 6.83 (2 H, d, *J* = 8.2 Hz), 5.09 (1 H, s), 5.02 (1 H, s), 4.48 (1 H, d, *J* = 11.8 Hz), 4.29 (1 H, d, *J* = 11.8 Hz), 3.77 (3 H, s), 3.43 (1 H, d, *J* = 4.4 Hz), 3.38 (1 H, d, *J* = 3 Hz), 2.93 (1 H, m), 2.87 (1 H, dd, *J* = 7.8, 4.4 Hz), 2.52 (1 H, d, *J* = 7.8 Hz), 2.11-1.61 (10 H), 1.41 (3 H, s), 1.30 (3 H, s), 1.01 (3 H, s), 0.89 (3 H, d, *J* = 6.4 Hz).

(+)-**Spatol** (**3**). To a magnetically stirred solution of spatol benzyl ether (+)-**54** (3.6 mg, 0.0081 mmol) in methylene chloride (1.5 mL) and water (84 μL) was added DDQ (6.0 mg) at 0 °C, and stirring was continued at the same temperature. After 1 h, TLC analysis showed no unreacted starting material. Solvents were rotary evaporated, and the residue was passed through a short column of silica gel with 30% ethyl acetate in hexanes as eluant. The residue obtained after rotary evaporation was purified by HPLC with 24% ethyl acetate in hexanes as eluant to deliver (+)-**3** (2.1 mg, 81%): $[\alpha]^{22}_D$ +44.2° (*c* 0.66, $CHCl_3$) (reported[2] $[\alpha]_D$ +45.6° (*c* 1.56, $CHCl_3$)): ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (1 H, dd, *J* = 3.0, 1.5 Hz), 5.03 (1 H, s), 3.74 (1 H, d, *J* = 4.4 Hz), 3.44 (1 H, d, *J* = 3.8 Hz), 3.03 (1 H, ddd, *J* = 14.5, 5.5, 5.5 Hz), 2.87 (1 H, dd, *J* = 7.9, 4.3 Hz), 2.49 (1 H, d, *J* = 7.9 Hz), 2.28 (1 H, ddd, *J* = 13.2, 13.2, 4.3 Hz), 2.12-2.05 (2 H), 1.97 (1 H, t, *J* = 6.8 Hz), 1.89-1.80 (2 H), 1.78-1.65 (2 H), 1.47-1.18 (3 H), 1.41 (3 H, s), 1.29 (3 H, s), 0.99 (3 H, s), 0.91 (3 H, d, *J* = 6.7 Hz); ^{13}C NMR (100.607 MHz, $CDCl_3$, for APT spectra a (+) indicates 0 or 2 attached protons and a (-) indicates 1 or 3 attached protons) δ 141.5 (+), 111.0 (+), 79.96 (-), 58.42 (+), 58.12 (+), 57.06 (-), 55.14 (-), 47.21 (+), 43.79 (-), 43.40 (-), 43.25 (-), 37.82 (-), 36.87 (+), 36.56 (-), 35.18 (+), 27.87 (+), 24.23 (-), 19.26 (-), 14.47 (-), 12.97 (-).

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Registry No. (±)-**1**, 89196-20-3; **2**, 132199-63-4; **3**, 76520-52-0; **5**, 930-30-3; (±)-**6**, 89165-79-7; (±)-**7**, 89165-80-0; (+)-**7**, 127182-28-9; (±)-**8**, 89177-59-3; **9**, 132101-35-0; (+)-**11**, 127182-29-0; (+)-**12**, 132101-36-1; (+)-**13**, 132199-64-5; (+)-**14**, 132199-65-6; **19**, 132101-37-2; **19** alcohol, 26639-84-9; (±)-**20**, 132199-66-7; **21**, 132101-38-3; (±)-**22**, 132101-39-4; (±)-**23**, 132101-40-7; (±)-**24e**, 132101-41-8; (±)-**24t**, 132199-69-0; (±)-**25e**, 132101-42-9; (±)-**25t**, 132199-70-3; (±)-**26e**, 132101-43-0; (±)-**26t**, 132199-71-4; (±)-**27**, 132101-44-1; (±)-**28**, 132101-45-2; (±)-**29**, 132101-46-3; (±)-*trans,erythro*-**31**, 132101-47-4; (±)-*cis,erythro*-**31**, 132199-72-5; (±)-**32**, 132101-48-5; (±)-**33**, 132101-49-6; (±)-**34**, 132101-50-9; (±)-**35**, 132101-51-0; (±)-**36**, 132101-52-1; (±)-**37e**, 132101-53-2; (±)-**37t**, 132101-65-6; (±)-**38e**, 132101-54-3; (±)-**38t**, 132199-73-6; **39**, 132101-55-4; **40t**, 132199-75-8; **40e**, 132101-56-5; **41t**, 132199-74-7; **41e**, 132101-57-6; **42**, 132101-58-7; **42** (tosylate precursor), 132101-66-7; (+)-**43**, 132101-59-8; (-)-**44**, 132101-60-1; (-)-**45**, 132101-61-2; (+)-**46**, 127156-24-5; (-)-**47a**, 132199-67-8; (-)-**47b**, 127135-70-0; (-)-**48a**, 127135-76-6; (-)-**49b**, 127135-71-1; *threo*-**50a**, 132199-68-9; *threo*-**50b**, 127182-31-4; *erythro*-**50b**, 127135-72-2; *threo*-**50b** TES ether, 127182-32-5; *erythro*-**50b** TES ether, 127135-73-3; **51**, 132101-62-3; (-)-**52**, 127135-75-5; (-)-**53**, 127304-32-9; (+)-**54**, 127182-33-6; $HC{\equiv}C(CH_3)_2OH$, 115-19-5; $HC{\equiv}C(CH_3)_2OTES$, 17963-41-6; (±)-$HC{\equiv}C(CH_3)_2OTHP$, 132101-64-5; $HC{\equiv}CSiMe_3$, 1066-54-2; $(CH_3)_2CHC(CHO){=}CH_2$, 4417-80-5; diethyl cyclopentylmalonate, 18928-91-1; monoethyl (±)-cyclopentylmalonate, 132101-63-4; ethyl 2-cyclopentylacrylate, 81143-91-1.

Synthesis and Chemistry of Dynemicin A Models

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Abstract: The synthesis of the model systems **10** and **22** of dynemicin A (**2**) containing the nitrogen, enediyne, and epoxide functionalities has been achieved. These models are shown to undergo acid-induced triggering to give the corresponding Bergman-cyclized products in the presence of suitable H atom donors. Removal of the N protecting group from **22** gave the unstable free amine **30**, which was shown to cause double-stranded-DNA cleavage, presumably in a manner similar to that of dynemicin A (**2**) itself. Some interesting chemistry related to dicobalt complexes of the enediynes is also presented.

Introduction

A number of years ago, a new series of highly active antibiotics, the esperamicins[1] and calicheamicins,[2] was isolated. These antibiotics, containing a unique 1,5-diyn-3-ene bridging ring, displayed extremely potent antitumor activity with IC_{50} values in the nanogram per milliliter range against a number of murine and human cell lines.[3] The autitumor activity of these compounds has been ascribed to DNA damage resulting from H atom abstraction from the sugar phosphate backbone by a benzenoid diradical. This benzenoid diradical is generated by Bergman cyclization[4] of the enediyne bridge upon triggering by conformational changes brought about by bioreductive cleavage of the trisulfide moiety and 1,4-addition of the resulting thiol. The potency of these molecules has spawned considerable interest in the synthetic community, with the synthesis of a number of model

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‡ Recipient of a Verband der Chemischen Industrie Doctoral Fellowship, 1989-1990.

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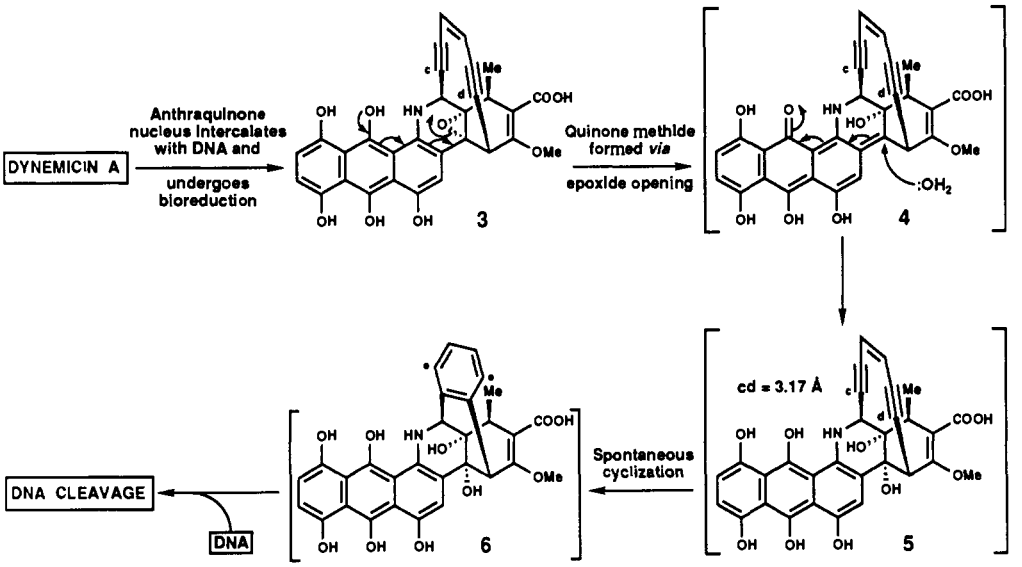
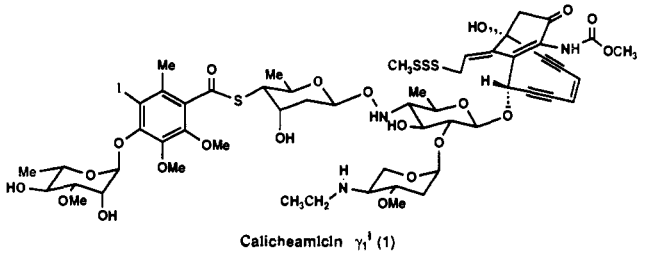
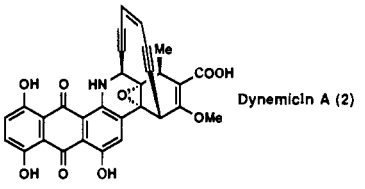
Scheme I. Proposed Mechanism of Action of Dynemicin A



systems of the bicyclic core[5] and total syntheses of the calicheamicin aglycone[6] and calicheamicin γ_1^I (**1**) carbohydrate fragments.[7]



Calicheamicin γ_1^I (1)



Dynemicin A (2)

More recently, a novel violet-colored antibiotic was discovered in the fermentation broth of *Micromonospora chersina*.[8] The antibiotic dynemicin A (**2**) exhibits very potent antibacterial activity against Gram-positive bacteria and antitumor activity with IC_{50} values of ~4–5 ng/mL against a number of human cell lines and prolongs the life span of mice inoculated with P388 leukemia and B16 melanoma. Unlike the esperamicin antibiotics, dynemicin A (**2**) displays significant in vivo antibacterial activity and low toxicity. Structural studies[9] revealed that dynemicin A (**2**), like the esperamicins/calicheamicins, belongs to the class of antibiotics containing a 1,5-diyn-3-ene bridging ring; however, dynemicin A (**2**) is unique in combining the enediyne unit with the anthraquinone chromophore of the anthracycline antibiotics.[10]

A mechanism for the antitumor activity of dynemicin A (**2**) has been proposed[11,12] that combines elements of the mechanisms of action of the esperamicin/calicheamicin, neocarzinostatin, and anthracycline classes of antibiotics and that is supported by the observation that DNA strand cleavage by dynemicin A (**2**) is enhanced by the presence of reducing agents such as NADPH and thiols.[11] In this mechanism (Scheme I), the anthraquinone nucleus intercalates with the DNA and undergoes bioreduction to give the 9,10-anthraquinol **3**. This rearranges via epoxide opening to give the quinone methide **4**, which is trapped by a nucleophile (e.g., H_2O or Cl^-) to give a cis-opened epoxide such as **5**. The strategically located nitrogen atom may also facilitate epoxide opening, either directly by electron donation or indirectly by acting as a base to deprotonate the adjacent acidic phenol in **3**. Opening of the epoxide moiety causes a dramatic conformational change in the molecule such that the distance between the termini of the 1,5-diyn-3-ene system (cd distance) is reduced from 3.54 Å in dynemicin A (**2**) to 3.17 Å [MMX-derived distance][13,14] in the *cis*-diol **5**. The resulting increase in strain energy of the enediyne system facilitates Bergman cyclization to give the benzenoid diradical **6**, which abstracts H atoms from the sugar phosphate backbone of the DNA, hence causing DNA cleavage. The proposed mechanism of action of dynemicin A (**2**) thus involves opening of the epoxide as the trigger for Bergman cyclization of the enediyne and the DNA cleavage/antitumor activity (cf. neocarzinostatin).[15]

The elegance and synthetic challenge of the dynemicin A structure, combined with its potent antitumor activity, prompted us to explore the synthesis and properties of models for dynemicin

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

(14) Although the strain energy of the 1,5-diyn-3-ene system is the main factor that determines the ease of cyclization in these systems, this distance often provides a useful guide (see ref 5a). Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986–4987. Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367–5369 and references cited therein.

(15) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331–334. Meyers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493–4496. Meyers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212–7214. Meyers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146–1147.

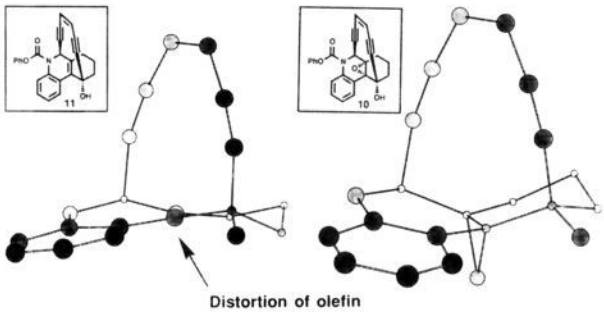
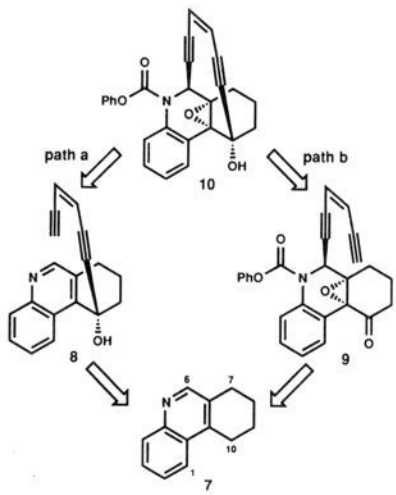


Figure 1. MMX-minimized structures of compounds **10** and **11**. Hydrogen atoms and carbamate omitted for clarity.

Scheme II. Possible Retrosynthetic Disconnections for Model System **10**



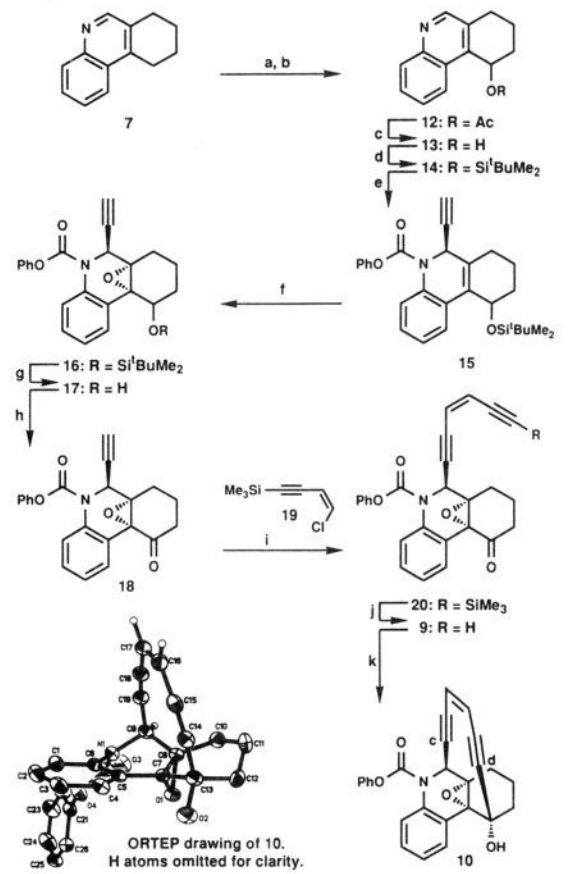
A (**2**) with a view to synthesizing dynemicin A (**2**) itself and to shed further light upon the mechanism of action of this fascinating molecule. In a recent communication, we disclosed the first syntheses of model systems containing the nitrogen, epoxide, and enediyne moieties of the natural product, together with the acid-induced Bergman cyclization of one of these models.[16] In this paper, we describe in more detail the syntheses of several dynemicin A models and the interesting chemistry associated with these molecules.

Results and Discussion

Retrosynthetic Analysis and Synthesis of Dynemicin A Models. A search of the literature revealed that 7,8,9,10-tetrahydrophenanthridine (**7**) is readily prepared on a large scale in a few steps,[17] and the electronic properties of this molecule suggested that it should be possible to selectively functionalize at the C6 and C10 positions (Scheme II). Thus, two possible approaches for the synthesis of a dynemicin A model presented themselves, namely, introduction of the enediyne at C10 followed by ring closure at C6 (path a), or vice versa (path b). Examination of molecular models and MMX calculations (Figure 1)[13] indicated that path a would require ring closure of **8** to form a highly strained intermediate (**11**) in which the olefin was severely distorted. By contrast, path b would allow the prior introduction of the epoxide so that ring closure of **9** would give the much less strained **10**. Therefore, synthetic efforts were directed along path b.

Scheme III summarizes the construction of the dynemicin A model **10** starting from 7,8,9,10-tetrahydrophenanthridine (**7**).

Scheme III. Synthesis of a Dynemicin A Model[a]



[a] Reagents and conditions: (a) 1.2 equiv of *m*CPBA, CH_2Cl_2, 25 °C, 1 h, 78%; (b) Ac_2O, reflux, 20 h, 87%; (c) K_2CO_3 (catalytic), MeOH, 25 °C, 1 h, 100%; (d) 1.2 equiv of *t*-$BuMe_2SiOTf$, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 92%; (e) 1.2 equiv of ethynylmagnesium bromide, 1.2 equiv of PhOCOCl, THF, −78 → +25 °C, 1 h, 97%; (f) 2.0 equiv of *m*CPBA, CH_2Cl_2, 25 °C, 2 h, 85%; (g) 1.2 equiv of TBAF, THF, 42 °C, 3 h, 100%; (h) 1.7 equiv of pyridinium chlorochromate (PCC), CH_2Cl_2, 4-Å molecular sieves, 25 °C, 1 h, 80%; (i) 1.5 equiv of **19**, 1.5 equiv of *n*-$BuNH_2$, 0.25 equiv of PPh_3, 0.07 equiv of $Pd(OAc)_2$, 0.2 equiv of CuI, PhH, 25 °C, 2 h, 86%; (j) 4.0 equiv of $AgNO_3$, 7.0 equiv of KCN, H_2O, EtOH, THF, 25 °C, 10 min, 78%; (k) 1.0 equiv of LDA, toluene, −78 °C, 1 h, 80% based on 25% recovery of **9**.

Thus, treatment of **7**[17] with *m*-chloroperoxybenzoic acid (*m*CPBA) in dichloromethane gave the corresponding *N*-oxide, which underwent regiospecific rearrangement[18] upon heating in acetic anhydride to give the acetoxy derivative **12** (68% overall yield). This was converted to the corresponding silyl ether **14** in 92% overall yield by standard methods via hydroxy compound **13**. Addition of phenyl chloroformate[19] to a mixture of compound **14** and ethynylmagnesium bromide at −78 °C led to the formation of compound **15** in 97% yield as a 3:1 mixture of isomers. Treatment of **15** with *m*CPBA gave epoxide **16** (85%) as a 3:1 mixture of isomers, and this was converted to ketone **18** via alcohol **17** by desilylation followed by oxidation (80% overall). Ketone **18** was obtained as a single isomer, indicating that epoxidation had taken place exclusively from the opposite face to the acetylene. Coupling **18** with vinyl chloride **19** via Pd(0)–Cu(I) catalysis followed by $AgNO_3$/KCN treatment resulted in the formation of the requisite precursor **9** via coupling product **20** (67% overall yield). Finally, treatment of **9** with lithium diisopropylamide (LDA) in toluene at −78 °C gave the targeted dynemicin A model **10** in 59% yield together with 25% recovered **9** (presumably due to enolization of the ketone).

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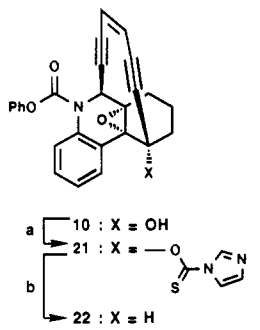
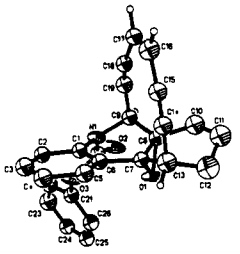
(19) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292–298.

Scheme IV[a]





ORTEP drawing of 22.
H atoms omitted for clarity.

[a] Reagents and conditions: (a) 3 equiv of thiocarbonyldiimidazole, 0.5 equiv of DMAP, CH_2Cl_2, 25 °C, 48 h, 95%; (b) 2 equiv of *n*-Bu_3SnH, AIBN (catalytic), toluene, 80 °C, 2 h, 86%.

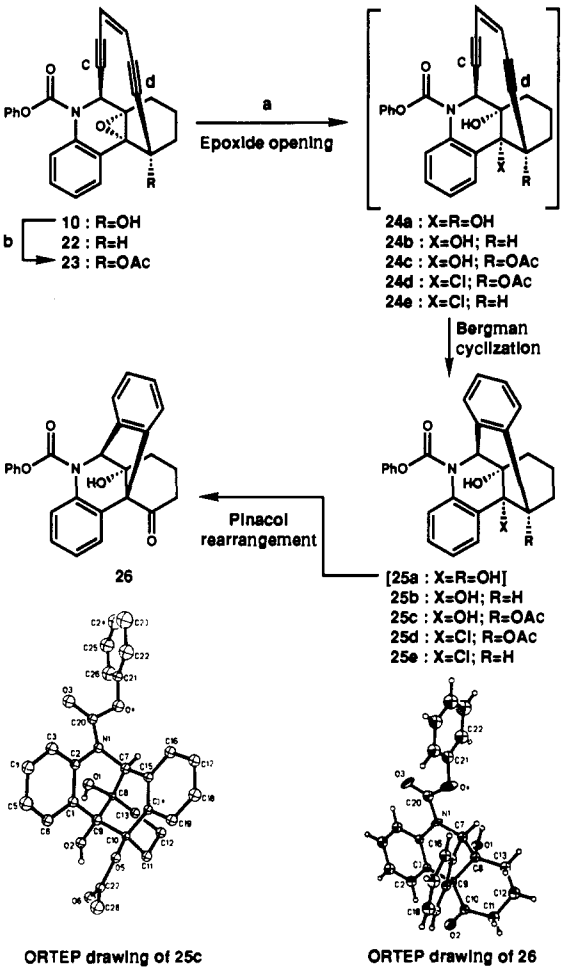
Compound **10** crystallized from ether in colorless prisms mp 228–230 °C dec. X-ray crystallographic analysis confirmed its structure (see ORTEP drawing, Scheme III) and revealed some interesting structural features. The acetylenic moieties are bent from linearity with the following angles: C14, 162.1°; C15, 170.5°; C18, 171.5°; and C19, 162.8°. The distance between carbons C14 and C19 (cd distance) was found to be 3.63 Å, a value that agrees well with the calculated one for the MMX-minimized structure of **10** (3.63 Å)[13] and that of the experimentally derived distance in dynemicin A (**2**) (3.54 Å).[9]

In order to obtain a closer model to dynemicin A (**2**), the tertiary hydroxyl group in **10** was removed to form compound **22** as shown in Scheme IV. Thus, exposure of **10** to thiocarbonyldiimidazole in the presence of 4-(dimethylamino)pyridine (DMAP) resulted in the formation of **21** in 95% yield. This compound (**21**) led to the desired compound **22** in 86% yield upon treatment with *n*-Bu_3SnH–AIBN (catalytic) (AIBN = 2,2′-azobis(isobutyronitrile)) in toluene at 80 °C. X-ray analysis of compound **22** (see ORTEP drawing, Scheme IV) revealed the following angles at the acetylenic carbons: C14, 163.7°; C15, 170.1°; C18, 170.2°; C19, 162.0°. The distance between carbons C14 and C19 (cd distance) was found to be 3.59 Å by both X-ray and MMX calculations.[13]

Triggering of the Dynemicin A Models. The observed sensitivity of dynemicin A (**2**) toward acid-induced epoxide opening and hence triggering of Bergman cyclization[11] prompted us to examine the triggering of our model systems. Scheme V outlines a cascade of novel transformations of model systems **10**, **22**, and **23**. Compound **10** was converted to product **26** in 92% yield upon treatment with *p*-toluenesulfonic acid in benzene/1,4-cyclohexadiene (3:1, 0.05 M) at 25 °C for 24 h. Thus, protonation and epoxide opening of **10** results in simultaneous pinacol-type rearrangement and Bergman cyclization, possibly via intermediates **24a** and **25a** or via direct pinacol rearrangement of the carbonium ion initially formed by epoxide opening. The structure of **26** was supported by its spectroscopic data and was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Scheme V). Furthermore, it was found that TMSOTf in the presence of Et_3SiH[20] induces the same transformation (**10** → **26**, Scheme V) at −78 °C in less than 5 min (68% yield), suggesting a very low energy of activation for the cyclization process. The dramatic shortening of the cd distance in going from epoxide **10** (cd = 3.63 Å, X-ray and MMX) to triol **24a** (cd = 3.19 Å, MMX)[13,14] is noteworthy. In an attempt to prevent the pinacol rearrangement of triol **25a**, the acetate derivative **23** was prepared from **10** (Ac_2O, pyridine, DMAP, 100%) and subjected to the epoxide-opening and cyclization reaction conditions as described above. Indeed, the acetate diol **25c** was obtained (85% yield) as the final product of this cascade by starting with **23** with use of *p*-toluenesulfonic acid as the initiator. Similarly, the deoxygenated compound **22** gave the

(20) For a study that uses Et_3SiH and a number of other hydrogen donors to trap C-centered radicals, see: Newcomb, M.; Park, S. V. *J. Am. Chem. Soc.* **1986**, *108*, 4132–4134. Product **26** derived from this reaction was contaminated with ca. 5% of an, as yet, unidentified product (detected by ^1H NMR spectroscopy).

Scheme V[a]

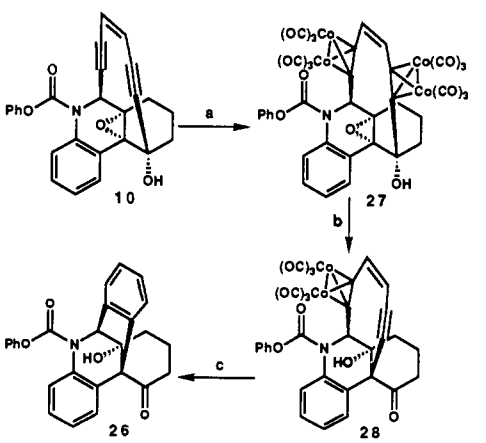


ORTEP drawing of 25c

ORTEP drawing of 26

[a] Chemistry of dynemicin models. Reagents and conditions: (a) (i) 1 equiv of $TsOH·H_2O$, 0.05 M in benzene/1,4-cyclohexadiene (3:1), 25 °C, 24 h, 83–92% (X = OH; R = OH, OAc, or H), (ii) 1 equiv of TMSOTf, 4 equiv of Et_3SiH, CH_2Cl_2, −78 °C, 5 min, 68% (X = OH; R = OH), or (iii) HCl(g), 40 equiv of 1,4-cyclohexadiene, CH_2Cl_2, 25 °C, 1 min, 79–80% (X = Cl; R = OAc or H); (b) excess Ac_2O, DMAP (catalytic), pyridine, 25 °C, 2 h, 100%.

Scheme VI[a]



[a] Reagents and conditions: (a) 2.2 equiv of $Co_2(CO)_8$, CH_2Cl_2, 25 °C, 10 min, 98%; (b) 3 equiv of TFA, CH_2Cl_2, 0 °C, 30 min, 81%; (c) 5 equiv of $Me_3N^+O^-$, CH_2Cl_2, 25 °C, 1 h, 83%.

cyclized product **25b**. The use of anhydrous HCl in CH_2Cl_2 in the presence of 1,4-cyclohexadiene also resulted in triggering of the cyclization cascade leading from **23** to **25d** (80% yield) and **22** to **25e** (79% yield), presumably via the intermediacy of **24d** (cd = 3.14 Å, MMX)[13,14] and **24e**. These cyclizations are

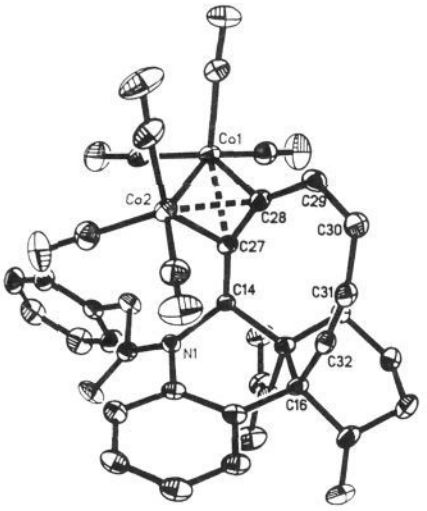
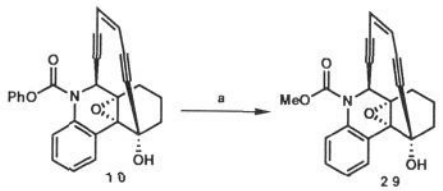


Figure 2. ORTEP drawing of the acetate derivative of cobalt complex **28**. Hydrogen atoms omitted for clarity.

Scheme VII[a]



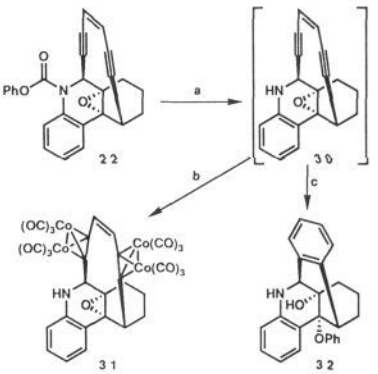
[a] Reagents and conditions: (a) 3 equiv of NaOMe, MeOH, 60 °C, 2 h, 80%.

analogous to those observed for dynemicin A (**2**) itself.[11]

An alternative mode of triggering the cyclization of **10** based upon cobalt complexation of the acetylenes was devised (Scheme VI).[21] This pathway was designed so as to prevent the acetylenes from spontaneously cyclizing upon epoxide opening and thus allow isolation of the postulated *cis*-diol intermediate **24a** in the form of its corresponding cobalt complex. Thus, reaction of **10** with $Co_2(CO)_8$ (2.2 equiv) resulted in the formation of the bis(dicobalt) complex **27** in 98% yield. Treatment of **27** with trifluoroacetic acid in CH_2Cl_2 (0 °C) followed by aqueous workup surprisingly led to the isolation of compound **28** (81% yield) in which epoxide opening had apparently been accompanied by pinacol-type rearrangement and loss of one of the dicobalt complexes. This structure was supported by its spectroscopic data and confirmed by X-ray crystallographic analysis of its acetate (Figure 2). Like Magnus' earlier work,[5d] this rearrangement provides a stable nine-membered ring containing the 1,5-diyn-3-ene unit, albeit in a protected form. Oxidative removal of the dicobalt complex from **28** with the use of trimethylamine *N*-oxide in CH_2Cl_2 in the presence, or absence, of Et_3SiH at 25 °C resulted in the spontaneous Bergman cyclization of the liberated nine-membered enediyne to give the aromatized product **26**. The same experiment carried out in CD_2Cl_2 resulted in the incorporation of two deuterium atoms in **26**, confirming dichloromethane as an effective hydrogen atom donor in these aromatization studies.[2b]

Deprotection of the Dynemicin A Models and DNA-Cleavage Studies. With the synthesis of N-protected models of dynemicin A completed, we naturally turned our attention to the deprotection of these molecules to give the free amine. In the absence of acid and with the nitrogen protected as a carbamate, we were somewhat surprised by the robustness of our model systems **10** and **22**. Thus, treatment of **10** with 3 equiv of sodium methoxide in dry methanol at 25 °C resulted in a very sluggish reaction; heating the reaction mixture to 60 °C for 2 h completed the reaction to give an 80% yield of the transesterified compound **29** (Scheme VII). However, attempted hydrolysis of either **10** or **29** by treatment with hydroxide under a variety of conditions led to the gradual decomposition of the material. Similarly, other standard procedures for carbamate cleavage resulted in decomposition of both **10** and **29**.[22]

Scheme VIII[a]



[a] Reagents and conditions: (a) 2.5 equiv of $LiAlH_4$, THF, 0 °C, 30 min; (b) 2.2 equiv of $Co_2(CO)_8$, CH_2Cl_2, 0 °C, 1 h, 25%; (c) EtOH, 25 °C, 5 h, 28%.

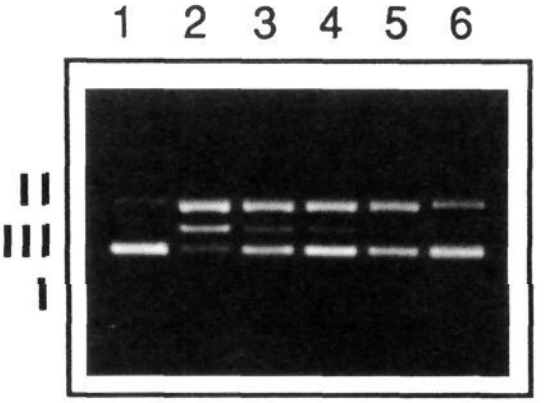


Figure 3. ΦX174 form I DNA (50 μM/base pair) incubated for 12 h at 37 °C with compound **30** (in 20% THF in phosphate buffers, pH 7.4, 50 mM) and analyzed by gel electrophoresis (1% agarose, ethidium bromide stain): lane 1, control; lanes 2–6, 5000, 2000, 1000, 500, and 100 μM of **30**, respectively. Key: I, form I DNA; II, form II DNA, III, form III DNA.

Treatment of **22** with 2.5 equiv of $LiAlH_4$ in THF at 0 °C for 30 min, quenching with a minimum amount of aqueous sodium bicarbonate solution, filtration, and storage at −78 °C gave a solution that was demonstrated to contain a significant quantity of the free amine **30** (Scheme VIII) by fast atom bombardment (FAB+) mass spectral analysis (98% intensity).[23] However, attempted purification of **30** gave a complex mixture of products as shown by ^1H NMR spectroscopy. It was found, though, that the crude amine **30** from the $LiAlH_4$ reduction could be stabilized as its bis(dicobalt) complex **31**, isolated in 25% overall yield, and characterized. Storage of the amine **30** at 25 °C resulted in the rapid formation of the aromatized product **32**, which was isolated in 28% yield.

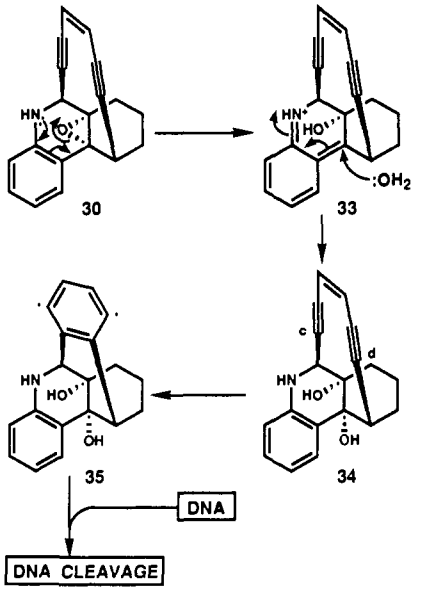
None of the N-protected model systems displayed any DNA-cleavage activity when incubated with ΦX174 DNA as determined by agarose gel electrophoresis. By contrast, the freshly prepared crude solution of amine **30** made by $LiAlH_4$ reduction of **22** as described above was found to cause significant DNA cleavage when incubated with ΦX174 DNA (see Figure 3, concentrations

(21) For similar stabilization of enediynes via cobalt complexation, see: Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626–1628, ref 5d.

(22) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1981.

(23) Treatment of carbamates with $LiAlH_4$ generally gives *N*-methylamines; in this case, the NH compound **30** was obtained due to the stabilization of the *N*-phenyl moiety of the tetrahydroquinoline system.

Scheme IX[a]



[a] Proposed DNA-cleavage mode of action of dynemicin A model **30**.

of **30** calculated assuming quantitative conversion of **22**). Furthermore, these results clearly indicate that, like dynemicin A (**2**) itself,[11] compound **30** causes cleavage of double-stranded DNA (giving linear form III DNA). This is in contrast to other DNA-cleaving agents possessing an alkylating mode of action that have been produced within these laboratories and that display single-stranded cleavage (giving relaxed form II DNA).[24] DNA cleavage by compound **30** was found to be pH-independent over the range 5–8.5. The DNA-cleavage activity of the THF solution of **30** stored at −78 °C was not found to significantly decrease over a period of 7 days, but storage at 25 °C resulted in the rapid loss of DNA-cleavage activity, thus reflecting the low stability of **30**.

These results suggest a DNA-cleavage mode of action of dynemicin A model **30** as outlined in Scheme IX. Opening of the epoxide moiety of **30** is initiated by the lone pair of the nitrogen (which is unavailable due to delocalization in the case of the carbamates) to give the *o*-quinone methide-type intermediate **33**. Nucleophilic trapping of **33** gives the cis-opened epoxide **34** (cd = 3.15 Å, MMX),[13,14] which undergoes the Bergman cyclization to give the benzenoid diradical **35** and which in turn abstracts H atoms from the sugar phosphate backbone of DNA, resulting in DNA cleavage. It is also expected that the introduction of oxygen or nitrogen at strategic positions on the aromatic moiety of dynemicin A models may serve as a suitable trigger for epoxide opening and thus radical generation.

Conclusion

The synthesis of the model systems **10** and **22** of dynemicin A (**2**) containing the nitrogen, enediyne, and epoxide functionalities has been achieved. These models have been shown to undergo acid-induced triggering to give the corresponding Bergman-cyclized products in the presence of suitable H atom donors, supporting epoxide opening as a triggering mechanism for the mode of action of dynemicin A (**2**). Removal of the N protecting group from **22** gave the unstable free amine **30**, which was shown to cause double-stranded-DNA cleavage, presumably in a manner similar to that of dynemicin A (**2**) itself. The synthesis of these models paves the way for the total synthesis of dynemicin A (**2**) itself and suggests the potential of these and related systems as novel DNA-cleaving molecules and anticancer agents.

Experimental Section

General Techniques. NMR spectra were recorded on a Bruker AMX-500 instrument. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under electron impact (EI) or fast atom bombardment (FAB) conditions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

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

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated.

7,8,9,10-Tetrahydrophenanthridine *N*-Oxide (7a). A solution of **7** (27.5 g, 150 mmol) in dichloromethane (500 mL) was treated at 25 °C with *m*CPBA (56.58 g of a 55% sample, 180 mmol) and stirred for 1 h. The solution was poured into saturated sodium bicarbonate solution (500 mL) and extracted. The aqueous layer was extracted with further dichloromethane (2 × 500 mL), the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 25% methanol in ethyl acetate) to give the *N*-oxide **7a** (23.35 g, 78%): off-white crystalline solid; mp 131–132 °C (from ethyl acetate); R_f = 0.34 (25% methanol in ethyl acetate); IR ($CDCl_3$) ν_{max} 2950, 1580, 1390, 1300, 1210, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, J = 8.3 Hz, 1 H, H4), 8.31 (s, 1 H, H6), 7.91 (d, J = 8.3 Hz, 1 H, H1), 7.68 (t, J = 8.3 Hz, 1 H, H2 or H3), 7.61 (t, J = 8.3 Hz, 1 H, H2 or H3), 3.02 (t, J = 6.3 Hz, 2 H, H10), 2.79 (t, J = 6.3 Hz, 2 H, H7), 1.98–1.84 (m, 4 H); MS (FAB+) *m/e* (rel intens) 200 (M + H, 100), 184 (12); HRMS for $C_{13}H_{14}NO$ (M + H), calcd 200.1075, found 200.1055.

10-Acetoxy-7,8,9,10-tetrahydrophenanthridine (12). A solution of 7,8,9,10-tetrahydrophenanthridine *N*-oxide (**7a**) (23.35 g, 117 mmol) in acetic anhydride (400 mL) was heated to 100 °C for 20 h, evaporated to dryness, dissolved in dichloromethane (500 mL), and washed with saturated sodium bicarbonate solution (200 mL). The aqueous layer was extracted with dichloromethane (2 × 200 mL), the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, ether) to give the acetate **12** (24.55 g, 87%): white crystalline solid; mp 128–129 °C (from ether); R_f = 0.33 (ether); IR ($CDCl_3$) ν_{max} 2970, 1728, 1241 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1 H, H6), 8.08 (d, J = 9.5 Hz, 1 H, H4), 7.76 (d, J = 9.5 Hz, 1 H, H1), 7.63 (t, J = 7.2 Hz, 1 H, H2 or H3), 7.52 (t, J = 7.2 Hz, 1 H, H2 or H3), 6.57 (br s, 1 H, C*H*OAc), 3.02 (br d, J = 17.5 Hz, 1 H, H7) 2.88–2.80 (m, 1 H, H7), 2.27 (br d, J = 13.8 Hz, 1 H, H9), 2.05 (s, 3 H, OAc), 2.01–1.88 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 152.3, 147.5, 137.8, 131.8, 130.1, 127.9, 127.0, 126.8, 122.2, 64.5, 29.1, 27.8, 21.7, 18.4; MS (FAB+) *m/e* (rel intens) 242 (M + H, 100), 182 (23); HRMS for $C_{15}H_{16}NO_2$ (M + H), calcd 242.1181, found 242.1181. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.59; H, 6.31; N, 5.82.

10-Hydroxy-7,8,9,10-tetrahydrophenanthridine (13). A solution of **12** (24.55 g, 102 mmol) in methanol (400 mL) was treated with potassium carbonate (2.0 g, catalytic) and stirred at 25 °C for 1 h. The solution was concentrated to ca. 100 mL, poured into saturated sodium bicarbonate solution (500 mL), and extracted with dichloromethane (1 × 500 mL, 2 × 250 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, ethyl acetate) to give alcohol **13** (20.36 g, 100%): white crystalline solid; mp 176–177 °C (from ether); IR ($CDCl_3$) ν_{max} 3600, 2950, 1510 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1 H, H6), 8.20 (d, J = 9.1 Hz, 1 H, H4), 8.00 (d, J = 9.1 Hz, 1 H, H1), 7.61 (t, J = 6.8 Hz, 1 H, H2 or H3), 7.55 (t, J = 6.8 Hz, 1 H, H2 or H3), 5.39 (br s, 1 H, C*H*OH), 2.89 (br d, J = 16.1 Hz, 1 H, H7), 2.80–2.72 (m, 1 H, H7), 2.80–2.60 (br s, 1 H, OH), 2.24 (br d, J = 12.5 Hz, 1 H, H8 or H9), 2.07–1.88 (m, 3 H); MS (FAB+) *m/e* (rel intens) 200 (M + H), 100), 154 (41), 136 (37), 109 (24); HRMS for $C_{13}H_{14}NO$ (M + H), calcd 200.1075, found 200.1085.

10-[(*tert*-Butyldimethylsilyl)oxy]-7,8,9,10-tetrahydrophenanthridine (14). A stirred solution of **13** (20.36 g, 102 mmol) in dry dichloromethane (300 mL) was cooled to 0 °C and treated with 2,6-lutidine (17.9 mL, 150 mmol) and *tert*-butyldimethylsilyl triflate (23.5 mL, 120 mmol). After 1 h at 0 °C, methanol (10 mL) was added, stirring was continued

(24) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247–7248. Nicolaou, K. C.; Skokotas, G.; Maligres, P.; Zuccarello, G.; Schweiger, E. J.; Toshima, K.; Wendeborn, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1272–1275. Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825–7826. Nicolaou, K. C.; Skokotas, G.; Furuya, S.; Suemune, H.; Nicolaou, D. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1064–1067.

for 5 min, and the reaction mixture was poured into saturated sodium bicarbonate solution (500 mL) and extracted. The aqueous layer was extracted with further dichloromethane (2 × 250 mL), the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 50% ether in petroleum ether) to give silyl ether **14** (29.40 g, 92%): colorless oil; R_f = 0.50 (70% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 2970, 2930, 2860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1 H, H6), 8.08 (d, J = 4.7 Hz, 1 H, H1 or H4), 8.05 (d, J = 4.7 Hz, 1 H, H1 or H4), 7.62 (t, J = 4.7 Hz, 1 H, H2 or H3), 7.53 (t, J = 4.7 Hz, 1 H, H2 or H3), 5.45 (t, J = 2.8 Hz, 1 H, H10), 3.00 (dd, J = 5.5, 16.6 Hz, 1 H, C*H*(Ar)), 2.81 (m, 1 H, C*H*(Ar)), 2.23–2.10 (m, 2 H, CH_2), 1.88–1.78 (m, 2 H, CH_2), 0.84 (s, 9 H, *t*-Bu), 0.22 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 147.0, 141.2, 129.8, 129.3, 127.9, 126.9, 126.1, 123.6, 63.2, 31.8, 27.0, 25.8, 18.2, 16.4, −3.6, −4.5; MS (FAB+) m/e (rel intens) 314 (M + H, 100), 256 (7), 182 (11); HRMS for $C_{19}H_{28}NOSi$ (M + H), calcd 314.1940, found 314.1951.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6-ethynyl-5,6,7,8,9,10-hexahydrophenanthridine (15).** A solution of quinoline **14** (32.33 g, 103 mmol) in dry THF (500 mL) was cooled to −78 °C and treated with ethynylmagnesium bromide (250 mL of a 0.5 M solution in THF, 125 mmol). The solution was briefly warmed to 0 °C and cooled to −78 °C again, and phenyl chloroformate (15.7 mL, 125 mmol) was added. The reaction mixture was allowed to slowly warm to 25 °C over 1 h, quenched with saturated ammonium chloride solution (50 mL), poured into saturated sodium bicarbonate solution (1 L), and extracted. The aqueous layer was extracted with dichloromethane (2 × 300 mL), the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 10% ether in petroleum ether) to give the carbamate **15** (45.71 g, 97%): colorless oil (ca. 3:1 mixture of isomers as judged by NMR); R_f = 0.85 (30% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3300, 2952, 2858, 2250, 1715, 1473, 1204 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 1 H, H4), 7.40–7.12 (m, 8 H), 5.68 and 5.61 (2 s, 1 H, H6), 5.00 and 4.69 (2 br s, 1 H, H10), 2.50–1.50 (m, 7 H), 0.80 and 0.92 (2 s, 9 H, *t*-Bu), 0.28, 0.19, 0.10, and 0.09 (singlets, 6 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) 151.1, 136.3, 132.9, 129.8, 129.3, 127.2, 126.0, 125.4, 125.1, 124.2, 124.1, 123.9, 122.0, 80.2, 72.3, 65.0 and 64.2, 48.7 and 48.2, 32.3 and 31.4, 28.0, 26.1, 18.4 and 16.3, −4.1 and −4.8; MS m/e (rel intens) 459 (M^+, 10), 402 (100), 366 (10), 308 (24), 206 (26), 151 (27), 75 (29); HRMS for $C_{28}H_{33}O_3NSi$ (M^+), calcd 459.2230, found 459.2233.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6a,10a-epoxy-6-ethynyl-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (16).** A solution of **15** (45.71 g, 99.6 mmol) in dichloromethane (300 mL) was treated with *m*CPBA (62.5 g of a 55% sample, 200 mmol) and stirred at 25 °C for 2 h. The reaction mixture was poured into saturated sodium bicarbonate solution (500 mL) and extracted, and the aqueous layer was extracted with further dichloromethane (2 × 300 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 10% ether in petroleum ether) to give epoxide **16** (40.02 g, 85%): white foam (ca. 3:1 mixture of isomers as judged by NMR); R_f = 0.73 (30% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3307, 2953, 2250, 1721, 1494, 1384, 1322, 1250, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.1 Hz, 1 H, H4), 7.50–7.10 (m, 8 H), 5.58 (br s, 1 H, H6), 4.82 (dd, J = 10.0, 5.7 Hz, 1 H, H10), 2.34 (dd, J = 14.8, 5.6 Hz, 1 H), 2.09 (br s, 1 H), 1.95–1.85 (m, 2 H), 1.78–1.62 (m, 2 H), 1.40–1.30 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 and 151.1, 135.5, 129.2, 129.2, 129.1, 128.3, 128.1, 127.9, 127.1, 125.5, 121.6, 78.5, 73.8, 72.8, 69.9, 60.4, 48.0, 31.0 and 29.6, 26.0 and 25.8, 24.0 and 26.5, 18.2 and 20.3, −0.28, −0.28, −0.37; MS m/e (rel intens) 475 (M^+, 2), 419 (100), 325 (28), 268 (10), 222 (14), 151 (18), 73 (42); HRMS for $C_{28}H_{33}O_4NSi$ (M^+), calcd 475.2179, found 475.2175.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-ethynyl-10-hydroxy-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (17).** A solution of epoxide **16** (40.02 g, 84.3 mmol) in THF (400 mL) was treated with tetrabutylammonium fluoride ((TBA)F) (100 mL of a 1.0 M solution in THF, 100 mmol) and heated to 42 °C for 3 h. The solution was evaporated in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give alcohol **17** (30.43 g, 100%): white crystalline solid (ca. 3:1 mixture of isomers as judged by NMR); mp 78–79 °C (from ether); R_f = 0.31 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3580, 3306, 2951, 2250, 1720, 1595, 1494, 1382, 1322, 1206 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 and 7.88 (d, J = 8.0 Hz, 1 H, H4), 7.50–7.08 (m, 8 H), 5.62 and 5.59 (d, J = 1.0 Hz, 1 H, H6), 4.89 and 4.70 (m, 1 H, H10), 2.47–1.35 (m, 8 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9, 135.5, 129.3, 128.7, 128.6, 128.4, 127.7, 127.3, 126.1, 125.8, 121.5, 78.7 and 78.2, 74.8 and 70.8, 73.2, 66.6, 65.9 and 64.4, 60.9 and 58.2, 47.8, 30.3 and 27.0, 24.1 and 19.0, 15.2 and 13.8; MS m/e (rel intens) 361 (M^+, 65), 224 (100), 196 (24), 180 (29), 167 (30), 94 (40), 77 (45); HRMS for $C_{22}H_{19}NO_4$ (M^+), calcd 361.1314, found 361.1317.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-ethynyl-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (18).** Alcohol **17** (30.43 g, 84.3 mmol) was dissolved in dichloromethane (600 mL) and treated with activated, powdered 4-Å molecular sieves (30 g) and pyridinium chlorochromate (31.7 g, 147 mmol). The suspension was stirred for 1 h at 25 °C, diluted with ether (600 mL), filtered through Celite, and concentrated in vacuo, and the residue was purified by flash chromatography (silica, 30% ether in petroleum ether) to give ketone **18** (24.1 g, 80%): white foam; R_f = 0.51 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3306, 2259, 1721, 1491, 1321, 1206 cm^{-1}; ^1H NMR (500 MHZ, $CDCl_3$) δ 8.50 (d, J = 7.8 Hz, 1 H, H4), 7.53–7.10 (m, 8 H, aromatic), 5.73 (d, J = 2.4 Hz, 1 H, H6), 2.76 (dt, J = 15.2, 4.9 Hz, 1 H, H9), 2.60 (ddd, J = 15.2, 10.4, 6.1 Hz, 1 H, H9), 2.37–2.28 (m, 2 H, H7), 2.21 (br s, 1 H, C≡CH), 2.04–1.90 (m, 2 H, H8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 153.9, 151.0, 135.8, 129.9, 129.3, 129.0, 127.6, 126.1, 125.9, 123.0, 121.5, 77.7, 74.9, 74.2, 57.4, 47.3, 38.9, 23.8, 18.3; MS m/e (rel intens) 359 (M^+, 100), 266 (52), 222 (65), 194 (54), 180 (51), 146 (45), 69 (80); HRMS for $C_{22}H_{17}NO_4$ (M^+), calcd 359.1158, found 359.1154. Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.27; H, 4.79; N, 3.91.

***N*-[(Phenyloxy)carbonyl]-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (20).** Palladium(II) acetate (364 mg, 1.63 mmol) and triphenylphosphine (1.58 g, 6.02 mmol) in dry, degassed benzene (200 mL) were heated under argon at 60 °C for 1 h. The resulting dark red solution was cooled to 25 °C, and the (*Z*)-chloroeyne **19** (5.50 g, 34.8 mmol) in dry, degassed benzene (50 mL) was added, followed by *n*-butylamine (3.64 mL, 36.8 mmol). The solution was stirred for 15 min at 25 °C and cooled to 0 °C, and the acetylene **18** (8.51 g, 23.7 mmol) in dry, degassed benzene (120 mL) was added, followed by copper(I) iodide (973 mg, 5.11 mmol). The solution was stirred for 2 h at 25 °C, poured into saturated sodium bicarbonate solution (400 mL), and extracted. The aqueous layer was extracted with dichloromethane (2 × 200 mL), the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 20% ether in petroleum ether) to give the enediyne **20** (9.83 g, 86%): colorless gum; R_f = 0.51 (30% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 2962, 1720, 1492, 1378, 1322, 1252, 1206, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.5 Hz, 1 H, H4), 7.52–7.09 (m, 8 H, aromatic), 5.99 (d, J = 1.6 Hz, 1 H, H6), 5.82 (d, J = 11.2 Hz, 1 H, olefinic), 5.66 (dd, J = 11.2, 1.6 Hz, 1 H, olefinic), 2.76 (dt, J = 15.3, 4.7 Hz, 1 H, H9), 2.71 (ddd, J = 15.3, 10.8, 6.1 Hz, 1 H, H9), 2.39–2.30 (m, 2 H, H7), 2.07–1.89 (m, 2 H, H8), 0.25 (s, 9 H, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 150.9, 135.8, 129.9, 129.2, 128.9, 128.4, 127.7, 126.0, 125.8, 122.9, 121.4, 120.8, 118.9, 103.6, 101.5, 90.4, 83.0, 74.9, 57.5, 48.3, 38.9, 23.9, 18.2, 0.00; MS m/e (rel intens) 481 (M^+, 11), 360 (100), 146 (10); HRMS for $C_{29}H_{27}O_4NSi$ (M^+), calcd 481.1709, found 481.1705.

***N*-[(Phenyloxy)carbonyl]-6-(3(*Z*)-hexene-1,5-diynyl)-6a,10a-epoxy-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (9).** Silver nitrate (13.8 g, 81.6 mmol) was added to a solution of the silylacetylene **20** (9.83 g, 20.4 mmol) in 200 mL of a H_2O–EtOH–THF mixture (1:1:1) at 25 °C, and the mixture was stirred until TLC analysis (30% ether in petroleum ether) indicated consumption of **20** (approximately 5 min). Potassium cyanide (10.7 g, 143 mmol) was then added and the mixture stirred for 10 min, poured into saturated sodium bicarbonate solution (200 mL), and extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 30% ether in petroleum ether) to give the enediyne **9** (6.51 g, 78%): colorless gum; R_f = 0.38 (30% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3304, 2940, 2260, 2240, 1720, 1492, 1378, 1321, 1206 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, J = 7.8, 1.4 Hz, 1 H, H4), 7.53–7.09 (m, 8 H, aromatic), 5.93 (d, J = 1.2 Hz, 1 H, H6), 5.78 and 5.79 (AB quartet, J = 10.1 Hz, 2 H, olefinic), 3.16 (d, J = 1.2 Hz, 1 H, C≡CH), 2.79–2.66 (m, 2 H, H9), 2.38–2.29 (m, 2 H, H7), 2.04–1.89 (m, 2 H, H8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 150.9, 135.9, 130.0, 129.3, 129.3, 128.8, 127.6, 125.9, 125.8, 123.0, 121.4, 120.4, 120.2, 90.6, 85.1, 82.8, 80.1, 75.1, 57.4, 48.1, 38.9, 23.9, 18.3; MS m/e (rel intens) 409 (M^+, 2), 262 (15), 212 (18), 162 (59), 58 (100); HRMS for $C_{26}H_{19}NO_4$ (M^+), calcd 409.1314, found 409.1308.

Compound 10. A solution of enediyne **9** (6.51 g, 15.9 mmol) in dry toluene (400 mL) was cooled to −78 °C and treated with lithium diisopropylamide (10.6 mL of a 1.5 M solution in cyclohexane, 15.9 mmol). After the solution was stirred for 1 h at −78 °C, the reaction was quenched with saturated ammonium chloride solution (10 mL) and the solution allowed to warm to room temperature, poured into saturated sodium bicarbonate solution (400 mL), and extracted. The aqueous layer was extracted with dichloromethane (2 × 200 mL), and the combined

organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 30 → 50% ether in petroleum ether) to give recovered **9** (1.61 g, 25%) followed by the 10-membered enediyne **10** (3.86 g, 59%): white crystalline solid; mp 228–230 °C dec (from ether); R_f = 0.42 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3420, 2205, 2192, 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, J = 8.1, 1.3 Hz, 1 H, aromatic), 7.47–7.10 (m, 8 H, aromatic), 5.83 (d, J = 10.1 Hz, 1 H, olefinic), 5.67 (dd, J = 10.1, 1.6 Hz, 1 H, olefinic), 5.53 (d, J = 1.6 Hz, 1 H, C*H*N), 2.35–1.71 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 135.8, 131.3, 129.3, 128.0, 127.8, 126.3, 125.8, 125.3, 124.0, 122.2, 121.6, 121.6, 100.4, 94.3, 93.9, 88.8, 74.1, 73.2, 64.4, 50.5, 35.4, 23.2; 19.1; MS m/e (rel intens) 409 (M^+, 26), 368 (18), 236 (11), 162 (13), 131 (100); HRMS for $C_{26}H_{19}NO_4$ (M^+), calcd 409.1314, found 409.1314. Anal. Calcd for $C_{26}H_{19}NO_4 \cdot H_2O$: C, 73.06; H, 4.95; N, 3.28. Found: C, 73.44; H, 5.04; N, 3.26.

Compound 21. Thiocarbonyldiimidazole (180 mg, 0.99 mmol) was added to a solution of the alcohol **10** (137 mg, 0.335 mmol) and DMAP (25 mg, 0.18 mmol) in dichloromethane (2 mL) at 25 °C. After 48 h, the solution was concentrated in vacuo and the residue purified by flash chromatography (silica, 80% ether in petroleum ether) to give thionoimidazolide **21** (160 mg, 95%): white crystalline solid; mp 178–179 °C dec (from ether/dichloromethane); R_f = 0.62 (70% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3042, 2912, 2195, 1710, 1500, 1495, 1212, 1105 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1 H, NC*H*=N) 7.71–7.05 (m, 11 H, aromatic), 5.93 (d, J = 10.3 Hz, 1 H, olefinic), 5.73 (dd, J = 10.3, 1.6 Hz, 1 H, olefinic), 5.60 (d, J = 1.6 Hz, 1 H, NC*H*C≡C), 3.08 (d, J = 11.1 Hz, 1 H, CH_2), 2.46–1.70 (m, 5 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 153.4, 151.0, 137.0, 135.9, 130.9, 129.4, 129.3, 128.2, 127.0, 126.4, 125.8, 125.4, 123.9, 123.2, 121.3, 117.7, 100.6, 94.3, 93.9, 88.9, 85.4, 74.5, 65.9, 63.2, 50.3, 28.0, 22.7, 18.4; MS (FAB+) m/e (rel intens) 653 (M + Cs, 21), 419 (19), 379 (15), 286 (100), 154 (30); HRMS for $C_{30}H_{21}N_3O_4SCs$ (M + Cs), calcd 653.0385, found 653.0360. Anal. Calcd for $C_{30}H_{21}N_3O_4S$: C, 69.35; H, 4.07; N, 8.09; S, 6.17. Found: C, 69.01; H, 4.17; N, 7.91; S, 6.19.

Compound 22. A solution of thionoimidazolide **21** (144.5 mg, 0.278 mmol) in toluene (5 mL) was treated with n-Bu_3SnH (150 μL, 0.56 mmol) and AIBN (10 mg, catalytic) and stirred at 80 °C for 2 h. The solution was concentrated in vacuo and the residue purified by flash chromatography (silica, 5 → 30% ether in petroleum ether) to give the deoxygenated compound **22** (94.3 mg, 86%): white crystalline solid; mp 248–250 °C dec (from ether); R_f = 0.62 (30% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 2945, 2872, 2232, 2205, 1712, 1465, 1325, 1185 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 7.5 Hz, 1 H, aromatic), 7.6–7.14 (m, 8 H, aromatic), 5.84 (dd, J = 10.5, 1.6 Hz, 1 H, olefinic), 5.72 (dd, J = 10.5, 1.6 Hz, 1 H, olefinic), 5.57 (d, J = 1.6 Hz, 1 H, NC*H*C≡C), 3.85 (d, J = 1.6 Hz, 1 H, C≡CC*H*C), 2.49 (m, 1 H, CH_2), 2.30 (m, 1 H, CH_2), 2.12–1.60 (m, 4 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 135.5, 129.4, 129.4, 128.2, 127.3, 125.8, 125.8, 125.4, 125.0, 122.0, 122.0, 121.5, 101.8, 94.9, 91.4, 88.8, 70.5, 61.1, 50.0, 29.8, 22.9, 22.5, 15.5; MS m/e (rel intens) 393 (M^+, 20), 294 (9), 262 (15), 212 (11), 149 (42); HRMS for $C_{26}H_{19}O_3N$ (M^+), calcd 393.1365, found 393.1332.

Compound 23. A solution of enediyne **10** (100.1 mg, 0.224 mmol) in pyridine (2 mL) was treated with acetic anhydride (0.50 mL, 5.31 mmol) and DMAP (10 mg, catalytic) at 25 °C. After 2 h, the reaction mixture was poured into saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane (3 × 25 mL), the combined organic layers were dried (Na_2SO_4) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 30% ether in petroleum ether) to give acetate **23** (110.7 mg, 100%): white crystalline solid; mp 212–214 °C dec (from ether); R_f = 0.55 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3075, 2950, 2215, 1742, 1720, 1500, 1216, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.1 Hz, 1 H, aromatic), 7.50–7.09 (m, 8 H, aromatic), 5.83 (d, J = 10.1 Hz, 1 H, olefinic), 5.65 (d, J = 10.1 Hz, 1 H, olefinic), 5.53 (s, 1 H, NC*H*(C)C), 2.51–1.70 (m, 6 H, CH_2), 2.18 (s, 3 H, OAc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 150.8, 130.0, 129.3, 128.4, 128.1, 128.0, 127.2, 126.8, 125.7, 125.2, 124.3, 122.9, 121.5, 97.9, 96.5, 93.7, 88.9, 78.0, 73.5, 62.6, 50.3, 29.8, 22.7, 21.8, 18.8; MS (FAB+) m/e 452 (M + H, 52), 410 (37), 392 (100), 316 (32), 272 (43), 242 (30), 154 (77), 136 (70); HRMS for $C_{28}H_{28}NO_5$ (M + H), calcd 452.1498, found 452.1469.

Compound 25b. A solution of enediyne **22** (30 mg, 0.076 mmol) and 1,4-cyclohexadiene (0.5 mL) in benzene (1.5 mL) was treated with p-toluenesulfonic acid (18 mg, 0.09 mmol) and stirred at 25 °C for 24 h. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give diol **25b** (26 mg, 85%): colorless gum; R_f = 0.35 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3310, 3082, 2925, 1705, 1592, 1395, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (br d, J = 4.4 Hz, 1 H, aromatic), 7.47 (br d, J = 7.8 Hz, 1 H, aromatic), 7.40–7.09 (m, 10 H, aromatic), 6.81 (d, J = 8.1 Hz, 1 H, aromatic), 5.78 (s, 1 H, N-benzylic), 4.00 (br s, 2 H, O*H*), 3.24 (s, 1 H, benzylic), 2.42–0.72 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 138.2, 134.7, 129.4, 129.4, 129.3, 128.8, 128.4, 128.3, 127.1, 126.9, 125.7, 125.0, 124.4, 121.8, 121.8, 121.5, 83.0, 66.2, 65.1, 51.2, 33.5, 27.1, 18.7; MS (FAB+) m/e (rel intens) 546 (M + Cs, 15), 379 (31), 312 (30), 286 (100); HRMS for $C_{26}H_{23}O_4NCs$ (M + Cs), calcd 546.0681, found 546.0691.

Compound 25c. A solution of enediyne **23** (93.0 mg, 0.206 mmol) and 1,4-cyclohexadiene (1.0 mL) in benzene (3.0 mL) was treated with p-toluenesulfonic acid (39 mg, 0.23 mmol) and stirred at 60 °C for 2 h. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give diol **25c** (80.2 mg, 83%): white crystalline solid; mp 198–200 °C (from ether); R_f = 0.22 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3360, 3072, 2950, 1738, 1715, 1500, 1192 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.8 Hz, 1 H, aromatic), 7.40–7.01 (m, 12 H, aromatic), 6.83 (br s, 1 H, O*H*), 5.59 (s, 1 H, NC*H*(C)C), 3.17 (m, 1 H, CH_2), 2.28 (m, 1 H, CH_2), 2.26 (s, 3 H, OAc), 1.80–1.40 (m, 3 H, CH_2), 0.72 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 150.8, 137.7, 134.8, 133.5, 129.7, 129.3, 129.2, 129.0, 128.8, 128.5, 128.2, 127.8, 127.7, 125.5, 124.8, 123.4, 121.8, 93.8, 75.1, 70.6, 61.4, 32.5, 31.4, 22.6, 19.8; MS m/e (rel intens) 471 (M^+, 19), 245 (100), 162 (100), 94 (42); HRMS for $C_{28}H_{25}O_6N$ (M^+), calcd 471.1682, found 471.1683. Anal. Calcd for $C_{28}H_{25}O_6N$: C, 71.33; H, 5.34; N, 2.97. Found: C, 71.36; H, 5.54; N, 2.84.

Compound 25d. Dry HCl gas was bubbled through a solution of acetate **23** (32 mg, 0.071 mmol) and 1,4-cyclohexadiene (40 mg, 0.32 mmol) in dichloromethane (4 mL) at 25 °C for 1 min. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give chloride **25d** (25 mg, 80%): colorless gum; R_f = 0.21 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3500, 2945, 1710, 1492, 1400, 1225, 789 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 1 H, aromatic), 7.45–6.96 (m, 12 H, aromatic), 5.85 (s, 1 H, benzylic), 2.56 (br s, 1 H, O*H*), 2.37 (br s, 1 H, O*H*), 2.34–1.42 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 134.7, 132.6, 130.4, 129.4, 129.3, 128.6, 128.5, 128.2, 128.2, 128.1, 127.5, 125.7, 124.5, 124.2, 124.0, 121.7, 81.2, 80.4, 70.2, 62.7, 35.4, 33.7, 18.8; MS (FAB+) m/e (rel intens) 580 (M + Cs, 100), 419 (42), 286 (100), 154 (37); HRMS for $C_{26}H_{22}O_4NClCs$ (M + Cs), calcd 580.0291, found 580.0286.

Compound 25e. Dry HCl gas was bubbled through a solution of enediyne **22** (28 mg, 0.071 mmol) and 1,4-cyclohexadiene (40 mg, 0.32 mmol) in dichloromethane (4 mL) at 25 °C for 1 min. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give chloride **25e** (24.3 mg, 79%): pale yellow solid; mp 114–116 °C (from ether); R_f = 0.62 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3500, 3065, 2932, 1712, 1495, 1382, 1200 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71–6.73 (m, 13 H, aromatic), 5.87 (s, 1 H, N-benzylic), 3.62 (s, 1 H, benzylic), 2.52 (br s, 1 H, O*H*), 2.50–1.60 (m, 6 H, CH_2); MS m/e (rel intens) 564 (M + Cs, 5), 419 (100), 379 (58); HRMS for $C_{26}H_{22}O_3NClCs$ (M + Cs), calcd 564.0343, found 564.0351.

Compound 26. Method i. A solution of enediyne **10** (57.8 mg, 0.141 mmol) and 1,4-cyclohexadiene (0.5 mL) in benzene (1.5 mL) was treated with p-toluenesulfonic acid (29.6 mg, 0.155 mmol) and stirred at 25 °C for 24 h. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give ketone **26** (53.7 mg, 92%).

Method ii. Trimethylsilyl triflate (15 μL, 0.08 mmol) was added to a solution of enediyne **10** (32 mg, 0.078 mmol) and triethylsilane (40 mg, 0.32 mmol) in dichloromethane (2 mL) at −78 °C. After 5 min, the mixture was quenched at −78 °C with saturated ammonium chloride solution (1 mL), diluted with ether (10 mL), washed with water (2 × 3 mL) and brine (3 mL), and dried ($MgSO_4$). The organic solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 50% ether in petroleum ether) to give ketone **26** (22 mg, 68%).

Method iii. Dry HCl gas was bubbled through a solution of enediyne **10** (32 mg, 0.078 mmol) and 1,4-cyclohexadiene (40 mg, 0.32 mmol) in dichloromethane (4 mL) at 25 °C for 30 s. The solvent was removed in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give ketone **26** (25 mg, 78%): white crystalline solid; mp 191–193 °C (from dichloromethane/ether); R_f = 0.63 (70% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3480, 3080, 2935, 1712, 1490, 1264, 1192 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33 (dd, J = 7.9, 1.3 Hz, 1 H, aromatic), 8.09 (d, J = 7.5 Hz, 1 H, aromatic), 7.54–7.02 (m, 11 H, aromatic), 5.65 (s, 1 H, benzylic), 2.75 (br s, 1 H, O*H*), 2.69–1.80 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 153.0, 150.9, 148.2, 137.1, 134.2, 129.8, 129.5, 128.5, 128.2, 127.8, 127.1, 126.1, 126.0, 124.3, 122.8, 121.8, 121.3, 82.5, 65.0, 64.1, 40.0, 30.2, 23.5; MS m/e (rel

intens) 411 (M^+, 100), 318 (58), 274 (49), 246 (12), 217 (55), 94 (29); HRMS for $C_{26}H_{21}O_4N$ (M^+), calcd 411.1471, found 411.1468. Anal. Calcd for $C_{26}H_{21}O_4N$: C, 75.90; H, 5.14; N, 3.40. Found: C, 75.66; H, 5.45; N, 3.14.

Compound 27. A solution of enediyne **10** (124 mg, 0.30 mmol) in dichloromethane (4 mL) was treated with $Co_2(CO)_8$ (260 mg, 0.76 mmol) and stirred at 25 °C for 10 min. The solution was concentrated in vacuo and the residue purified by flash chromatography (silica, 30% ether in petroleum ether) to give the bis(dicobalt) complex **27** (291 mg, 98%): green crystalline solid; mp >300 °C (from ether); R_f = 0.80 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3500, 2950, 2872, 2095, 2070, 2025, 1725, 1492, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.87 (br s, 1 H, aromatic), 7.61–7.02 (m, 8 H, aromatic), 6.47 (br s, 1 H, NC*H*-(C)C), 6.38 (br d, J = 10.7 Hz, 1 H, olefinic), 6.19 (br d, J = 10.7 Hz, 1 H, olefinic), 3.50 (br s, 1 H, O*H*), 2.70–1.71 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 198.6, 197.8, 151.3, 134.9, 132.9, 130.9, 129.4, 128.8, 127.2, 125.8, 125.3, 125.1, 124.8, 123.4, 121.6, 98.5, 88.9, 81.5, 80.1, 78.0, 73.9, 63.1, 59.0, 44.2, 24.9, 17.1; MS (FAB+) m/e (rel intens) 1114 (M + Cs, 11), 1086 (M + Cs-CO, 18), 1058 (M + Cs – 2 CO, 6), 1030 (M + Cs – 3 CO, 19), 1002 (M + Cs – 4 CO, 11), 943 (M + Cs – 4 CO – Co, 10), 918 (11), 890 (24), 862 (34), 813 (100); HRMS for $C_{38}H_{19}O_{16}NCo_4Cs$ (M + Cs), calcd 1113.7086, found 1113.7001.

Compound 28. A solution of the cobalt complex **27** (291 mg, 0.30 mmol) in dichloromethane (4 mL) was treated at 0 °C with trifluoroacetic acid (68.6 μL, 0.89 mmol). After 5 min, the mixture was poured into saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 50% ether in petroleum ether) to give ketone **28** (167.4 mg, 81%): brown crystalline solid; mp >300 °C (from ether); R_f = 0.25 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3408, 2945, 2100, 2065, 2032, 1875, 1735, 1680, 1512, 1217 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 1 H, aromatic), 7.42–7.11 (m, 8 H, aromatic), 7.00 (d, J = 10.2 Hz, 1 H, olefinic), 6.39 (s, 1 H, NC*H*-(C)C), 5.52 (d, J = 10.2 Hz, 1 H, olefinic), 3.35–1.82 (m, 7 H, CH_2, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 198.9, 198.1, 154.3, 150.9, 144.0, 133.2, 132.8, 129.6, 128.3, 128.1, 126.7, 126.0, 125.8, 123.3, 121.8, 108.7, 93.2, 92.5, 82.1, 81.0, 68.5, 56.2, 38.0, 30.2, 21.6; MS (FAB+) m/e (rel intens) 828 (M + Cs, 17), 800 (18), 688 (74), 639 (20), 555 (32), 527 (100); HRMS for $C_{32}H_{19}NO_{10}Co_2Cs$ (M + Cs), calcd 827.8727, found 827.8730. Anal. Calcd for $C_{32}H_{19}NO_{10}Co_2$: C, 55.27; H, 2.75; N, 2.01; Co, 16.97. Found: C, 54.98; H, 2.79; N, 1.86; Co, 15.22.

Compound 26. A solution of cobalt complex **28** (42 mg, 0.060 mmol) in dichloromethane (1 mL) was treated with trimethylamine *N*-oxide (32.7 mg, 0.29 mmol) and stirred at 25 °C for 1 h. The solution was concentrated in vacuo and the residue purified by flash chromatography (silica, 50% ether in petroleum ether) to give aromatized product **26** (17.7 mg, 83%).

Compound 29. A solution of the phenyl carbamate **10** (42 mg, 0.103 mmol) in dry methanol (4 mL) was treated with sodium methoxide (17 mg, 0.31 mmol) and heated at 60 °C for 2 h. The reaction mixture was diluted with dichloromethane (25 mL), washed with sodium bicarbonate solution (25 mL), dried (Na_2SO_4), and evaporated in vacuo, and the residue was purified by flash chromatography (silica, 40% ether in petroleum ether) to give methyl carbamate **29** (28.5 mg, 80%): white crystalline solid; mp 126–127 °C (from ether/petroleum ether); R_f = 0.43 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3600, 3450, 2957, 2257, 2250, 1706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 8.0 Hz, 1 H, aromatic), 7.25–7.10 (m, 3 H, aromatic), 5.81 (d, J = 10.1 Hz, 1 H, olefinic), 5.69 (d, J = 10.1 Hz, 1 H, olefinic), 5.45 (s, 1 H, C*H*N), 3.82 (s, 3 H, OCH_3), 2.79 (s, 1 H, O*H*), 2.27–1.72 (m, 6 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 131.3, 127.8, 127.5, 126.1, 124.9, 123.9, 122.1, 100.7, 94.1, 88.3, 74.2, 73.1, 65.8, 64.2, 53.7, 50.1, 35.2, 23.2, 19.2, 15.2; MS m/e (rel intens) 347 (M^+, 100) 291 (35), 204 (50); HRMS for $C_{21}H_{17}NO_4$ (M^+), calcd 347.1158, found 347.1159. Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.63; H, 5.24; N, 3.79.

Compound 30. Carbamate **22** (39 mg, 0.10 mmol) in THF (3 mL) was treated at 0 °C with $LiAlH_4$ (0.25 mL of a 1.0 M solution in ether, 0.25 mmol). After the solution was stirred for 30 min, the reaction was quenched with saturated sodium bicarbonate solution (1 mL) and the solution diluted with ether (20 mL), washed with 1.0 M aqueous LiOH solution (2 × 5 mL) in order to remove phenol, dried (Na_2SO_4), filtered, and stored under argon at −78 °C until required. MS (FAB+) m/e (rel intens) 290 (97), 278 (75), 274 (M + H, 98), 235 (100); HRMS for $C_{19}H_{16}NO$ (M + H), calcd 274.1232, found 274.1247.

Compound 31. The ethereal solution of **30** produced as above by the $LiAlH_4$ reduction of **22** (39 mg, 0.10 mmol) was concentrated in vacuo at 0 °C, and the residue was dissolved in dichloromethane (5 mL) at 0 °C and treated with $Co_2(CO)_8$ (75 mg, 0.22 mmol). The reaction mixture was stirred for 1 h and concentrated in vacuo, and the residue was purified by flash chromatography (silica, 10% ether in petroleum ether) to give the bis(dicobalt) complex **31** (15.5 mg, 25%): green solid; mp >300 °C (from ether); R_f = 0.80 (30% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 2870, 2080, 2040, 1510 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 7.4 Hz, 1 H, aromatic), 7.04 (t, J = 7.4 Hz, 1 H, aromatic), 6.73 (t, J = 7.4 Hz, 1 H, aromatic), 6.40 (d, J = 7.4 Hz, 1 H, aromatic), 6.31 (d, J = 12.3 Hz, 1 H, olefinic), 6.19 (d, J = 12.3 Hz, 1 H, olefinic), 4.97 (s, 1 H, C*H*N), 4.30 and 4.20 (2 s, 2 H, C*H*CCo, N*H*), 2.60–1.50 (m, 6 H, CH_2); MS (FAB+) m/e (rel intens) 978 (M + Cs, 19), 950 (20), 894 (25), 838 (28), 810 (25), 705 (39), 677 (78), 633 (80), 593 (74), 523 (100); HRMS for $C_{31}H_{15}O_{13}NCo_4Cs$ (M + Cs), calcd 977.6926, found 977.6966.

Compound 32. Carbamate **22** (42 mg, 0.11 mmol) in THF (3 mL) was treated at 0 °C with $LiAlH_4$ (0.25 mL of a 1.0 M solution in ether, 0.25 mmol). After the solution was stirred for 30 min, the reaction was quenched with saturated ammonium chloride solution (1 mL) and the solution diluted with ether (15 mL), washed with water (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was dissolved in ethanol and stirred 5 h. The ethanol was removed in vacuo and the residue purified by flash chromatography (silica, 30% ether in petroleum ether) to give **32** (11 mg, 28%): colorless gum; R_f = 0.45 (50% ether in petroleum ether); IR ($CDCl_3$) ν_{max} 3400, 3350, 2920, 2840, 1500 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (br s, 1 H, N*H*), 7.30 (d, J = 7.1 Hz, 1 H, aromatic), 7.20 (d, J = 7.7 Hz, 1 H, aromatic), 7.17 (t, J = 6.5 Hz, 1 H, aromatic), 7.12 (t, J = 7.1 Hz, 1 H, aromatic), 7.03 (t, J = 7.7 Hz, 2 H, aromatic), 6.97 (t, J = 7.7 Hz, 1 H, aromatic), 6.93 (d, J = 7.7 Hz, 1 H, aromatic), 6.82 (t, J = 7.1 Hz, 1 H, aromatic), 6.77 (d, J = 8.3 Hz, 2 H, aromatic), 6.72 (t, J = 7.1 Hz, 1 H, aromatic), 6.45 (d, J = 7.7 Hz, 1 H, aromatic), 4.42 (br s, 1 H, C*H*N), 3.60 (br s, 1 H, O*H*), 3.52 (s, 1 H, benzylic), 2.61 (t, J = 11.1 Hz, 1 H, CH_2), 2.29 (dt, J = 3.3, 10.2 Hz, 1 H, CH_2), 1.69 (dd, J = 3.3, 10.2 Hz, 1 H, CH_2), 1.50 (dd, J = 8.3, 10.2 Hz, 1 H, CH_2), 1.38 (d, J = 10.2 Hz, 1 H, CH_2), 0.88 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 147.8, 140.7, 138.2, 137.9, 128.4, 128.2, 128.1, 127.9, 127.6, 126.9, 126.4, 120.5, 120.3, 119.6, 116.8, 80.3, 70.4, 64.5, 56.2, 32.3, 27.9, 18.7; MS m/e (rel intens) 276 (M^+ – OPh, 59), 258 (100), 218 (21), 204 (25), 162 (14), 141 (10); HRMS for $C_{19}H_{18}NO$ (M^+ – OPh), calcd 276.1388, found 276.1379.

DNA-Cleavage Assay of Compound 30. The ethereal solution of **30** produced as above by the $LiAlH_4$ reduction of **22** (39 mg, 0.10 mmol) was evaporated in vacuo to dryness and dissolved in THF (4 mL) to give a 25 mM solution of **30**, assuming complete conversion of **22**. Analysis of compound **30** induced damage to supercoiled, covalently closed, circular (form I) ΦX174 DNA was performed by incubation at varying concentrations of **30** (100–5000 μM) in buffered aqueous solution at 37 °C for 12 h, followed by agarose gel electrophoresis to separate the various DNA products—namely, nicked relaxed circular DNA (form II) and linearized DNA (form III). DNA bands were visualized with use of ethidium bromide binding and UV illumination.

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