Molecular Design and Chemical Synthesis of Potent Enediynes. 2. Dynemicin Model Systems Equipped with C-3 Triggering Devices and Evidence for Quinone Methide Formation in the Mechanism of Action of Dynemicin A

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Abstract: Continuing the theme of the preceding article, this paper describes the synthesis and chemical properties of designed enediynes related to dynemicin A. These model systems are equipped with triggering devices at C-3 of the aromatic nucleus. The design of these compounds (**1** and **2**) was based on the hypothesis that a C-3 phenolic group generated in situ would be capable of promoting epoxide opening and subsequent Bergman cycloaromatization according to the dynemicin A cascade. Compound **1** carrying a *tert*-butyl ester group at C-3 was synthesized from quinoline derivative **28** via the sequence **28** → **36** → **45** → **46** → **47** → **48** → **44** → **49** → **50** → **1**. Compound **2** carrying the photoremovable (2-nitrobenzyl)oxy group at C-3 was constructed from quinoline **29** by a similar sequence. Exposure of **1** and **49** to aqueous LiOH in EtOH led to Bergman cycloaromatization products **58** and **57**, respectively. Compounds **2** and **62** bearing the 2-nitrobenzyl group at C-3 were photolytically converted to free phenolic systems **63** and **64**, respectively. Reaction of **63** and **64** with the nucleophiles EtOH, EtSH, or $^{n}PrNH_2$ under anaerobic conditions in basic buffer solutions led to aromatized products **66–70**. Exposure of **63** and **75**, on the other hand, with EtOH under aerobic conditions in basic buffer solutions furnished the novel quinone methide epoxide systems **71** and **76–77**, respectively. The chemistry of compounds **63** and **64** combined with their DNA-cleaving capabilities provides support for the quinone methide mechanism of action of dynemicin A.

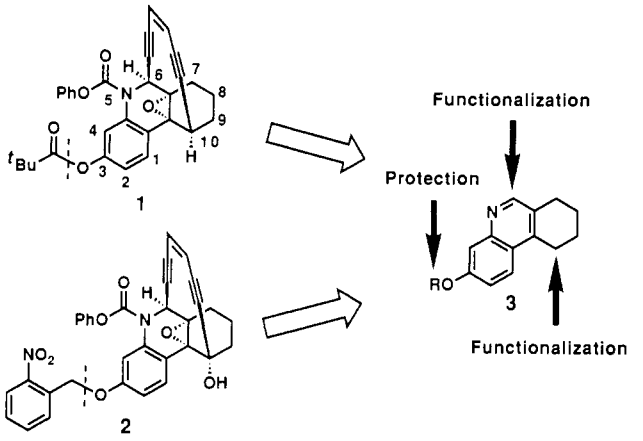
Introduction

In the preceding paper in this issue,[1] we discussed the molecular design and synthesis of a series of dynemicin A related enediynes with substitutions and devices at the nitrogen, C-2, and C-10 positions. In this article, we describe the synthesis and chemistry of a separate set of designed enediynes equipped with base-sensitive and photosensitive triggering devices at C-3. Molecular design considerations for compounds such as **1** carrying an ester functionality as a triggering device at C-3 (Scheme I) have been discussed in the preceding paper in this issue.[1] Compound **2** carrying the photoremovable *o*-nitrobenzyl protecting group at C-3 was also considered to be a potentially triggerable molecule for DNA-cleaving action as well as cytotoxic activity.

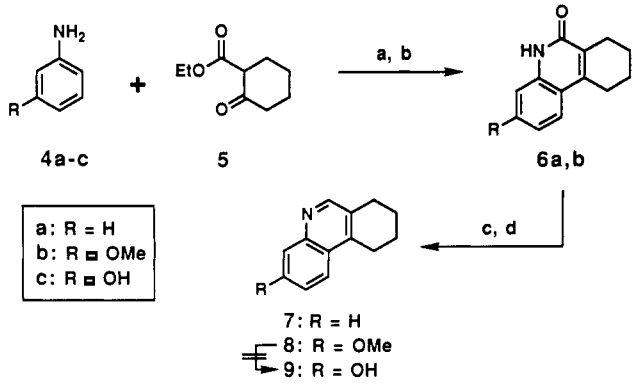
Results and Discussion

Synthesis of Enediynes 1 and 2. Due to the sensitivity of the epoxy functionality toward C-3 substituents, the synthetic strategy for the construction of compounds **1** and **2** (Scheme I) had to be substantially modified from the one used in the previous paper in this issue.[1] Difficulties were encountered even at the beginning of the sequence in our attempts to prepare the requisite quinoline derivative **9** according to Scheme II. Thus, whereas condensation of aniline **4a** with keto ester **5** at 200 °C followed by ring closure and reduction/oxidation leads to compound **7**[2] (Scheme II), the corresponding sequence starting with 3-aminophenol (**4c**) failed at the first step. On the other hand, the alternative sequence to **9** via formation of **8** (ca. 20% overall, Scheme II) followed by demethylation (**8** → **9**, Scheme II) failed at the latter step. To circumvent these problems, a new method based on the chemistry of acylthiazolidine derivatives[3,4] was devised as shown in Scheme III. Reaction of carboxylic acid **10** with 2-mercaptothiazoline (**11**) under the influence of DCC/DMAP gave derivative **12** in 96% yield. Exclusive amide bond formation occurred upon refluxing **12** with 3-aminophenol in THF, leading smoothly to **13** (87%).[3] The generality of the method was demonstrated by the successful condensation of **12** under the same conditions with

Scheme I. Designed Enediynes Equipped with Triggering Devices at C-3



Scheme II[a]



[a] Reagents and conditions: (a) 200 °C; (b) H_2SO_4 (concentrated), Δ; (c) $LiAlH_4$, THF, reflux; (d) O_2, silica gel, PhH, 25 °C.

4-aminophenol, leading to **15** (86%), or 5-aminosalicylic acid, giving **17** (87%). Derivatives **14** (72%), **16** (78%), and **18** (77%)

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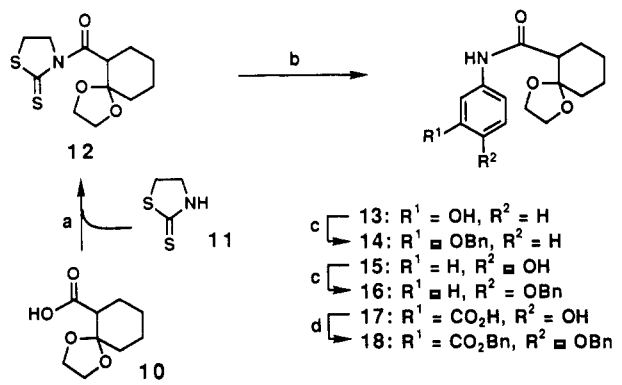
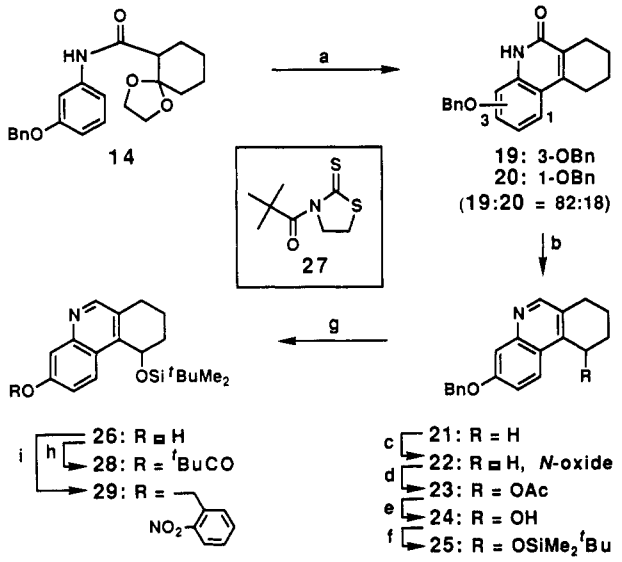
Scheme III[a]



[a] Reagents and conditions: (a) 1.0 equiv of **11**, 1.2 equiv of DCC, 0.1 equiv of DMAP, CH_2Cl_2, 25 °C, 14 h, **10** → **12**, 96%; (b) 1.0 equiv of 3-aminophenol, THF, reflux, 96 h, **12** → **13**, 87%, or 1.0 equiv of 4-aminophenol, THF, reflux, 15 h, **12** → **15**, 86%, or 1.0 equiv of 5-aminosalicylic acid, THF, reflux, 7 days, **12** → **17**, 87%; (c) 1.05 equiv of NaH, 1.0 equiv of $PhCH_2Br$, 0.1 equiv of $^nBu_4NI$, THF, 25 °C, 1 h, **13** → **14**, 72%, or **15** → **16**, 78%; (d) 3.0 equiv of NaH, 3.0 equiv of $PhCH_2Br$, 0.2 equiv of $^nBu_4NI$, THF, reflux, 3 h, **17** → **18**, 77%.

Scheme IV[a]

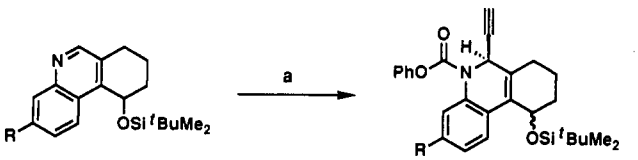


[a] Reagents and conditions: (a) 37% HCl/THF (1:2.7), reflux, 3 h, **14** → **19** + **20**, 100%; (b) 1.0 equiv of Dibal, 2.0 equiv of $LiAlH_4$, THF, reflux, 3 h; O_2, SiO_2, 25 °C, 24 h, **19** + **20** → **21**, 53% based on the ratio of **19** (the 1-substituted isomer was not isolated); (c) 1.0 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 30 min, **21** → **22**, 88%; (d) Ac_2O, 25 °C, 14 h, **22** → **23**, 80%; (e) 0.2 equiv of K_2CO_3, MeOH, 25 °C, 3 h, **23** → **24**, 98%; (f) 1.2 equiv of $^tBuMe_2SiOTf$, 1.4 equiv of 2,6-lutidine, CH_2Cl_2, 25 °C, 30 min, **24** → **25**, 98%; (g) H_2, 10% Pd/C, EtOH, 25 °C, 4 h, **25** → **26**, 89%; (h) 1.05 equiv of NaH, 1.0 equiv of **27**, THF, 25 °C, 5 min, **26** → **28**, 99%; (i) 1.05 equiv of NaH, 1.05 equiv of 2-nitrobenzyl bromide, 0.1 equiv of $^nBu_4NI$, THF, 25 °C, 1 h, **26** → **29**, 90%.

were easily accessible from **13**, **15**, and **17**, respectively, by standard chemistry (Scheme III).

Next, the requisite tricyclic systems **28** and **29** were constructed from **14** as shown in Scheme IV. Refluxing **14** with aqueous HCl in THF led quantitatively to a mixture of **19** and **20** (ca. 82:18).

Scheme V. Electronic Effect on the Addition of Ethynylmagnesium Bromide to Quinoline Derivatives in the Presence of Phenyl Chloroformate

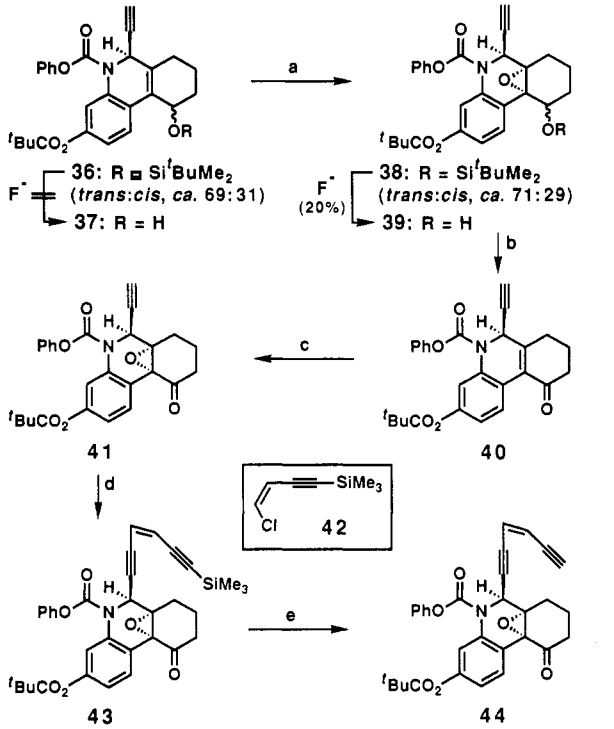


(a) 1.5 equiv of ethynylmagnesium bromide, 1.5 equiv of PhOCOCl, THF, −78 → 0 °C, 15 min, 90–99%

entry	R	quinoline	adduct	ratio (trans:cis)	yield (%)
1	H	**30**	**32**	3.5 (78:22)	95[b]
2	MeO	**31**	**33**	5.3 (84:16)	99
3	BnO	**25**	**34**	3.8 (79:21)	90
4	NBnO[a]	**29**	**35**	3.8 (72:21)	98
5	$^tBuCO_2$	**28**	**36**	2.2 (69:31)	95

[a] NBnO = 2-nitrobenzyloxy. [b] See ref 5.

Scheme VI[a]



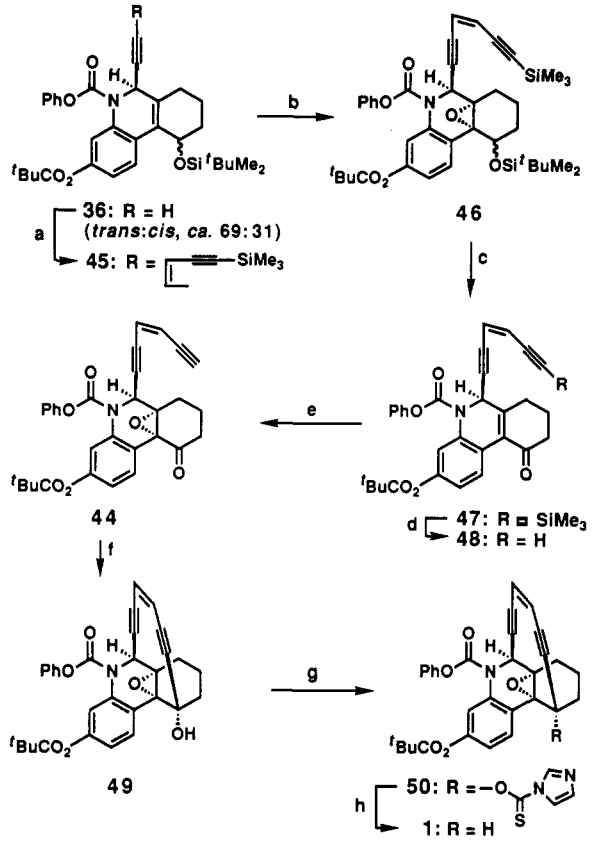
[a] Reagents and conditions: (a) 2.0 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 3 h, **36** → **38**, 99%; (b) 5.0 equiv of $BF_3{\cdot}OEt_2$, wet $CHCl_3$, 25 °C, 1.5 h; SiO_2, $CHCl_3$, 25 °C, 12 h, **38** → **40**, 73%; (c) 1.2 equiv of *m*-CPBA, CH_2Cl_2/saturated aqueous $NaHCO_3$ (1:1), 25 °C, 10 min, **40** → **41**, 67%; (d) 1.5 equiv of **42**, 0.05 equiv of $Pd(PPh_3)_4$, 1.5 equiv of Et_2NH, 0.2 equiv of CuI, PhH, 25 °C, 1 h, **41** → **43**, 32%; (e) 4.0 equiv of $AgNO_3$, H_2O/EtOH/THF (1:1:1), 25 °C, 1 h; 7.0 equiv of KCN, 25 °C, 10 min, **43** → **44**, 66%.

Reduction of the mixture **19**/**20** followed by air oxidation led to a 54% yield of the desired **21**. Conversion of **21** to its *N*-oxide (**22**) with *m*-CPBA (88% yield) followed by exposure to acetic anhydride gave the acetate **23** (80%), which was deprotected by K_2CO_3 in methanol and silylated, furnishing **25** (98%) via **24** (98%). Finally, hydrogenolysis of the benzyl group from **25** led to the phenolic compound **26** (89%), which served as an excellent precursor to both **28** (99%) and **29** (90%) (Scheme IV). Noteworthy is the utilization of the acylthiazolidine **27** in the formation of **28** which, in this instance, gives yields superior to those from other standard methods (e.g., ^tBuCOCl/pyr).

Introduction of the first ethynyl group into the quinoline ring was carried[5-7] out as shown in Scheme V. The effect of sub-

(1) Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendeborn, S. V.; Dai, W.-M.; Chada, R. *J. Am. Chem. Soc.*, preceding article in this issue.
(2) Masamune, T.; Takasugi, M.; Suginome, H.; Yokogama, M. *J. Org. Chem.* **1964**, *29*, 681.
(3) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fijita, E. *Chem. Pharm. Bull. Jpn.* **1984**, *32*, 2687.
(4) Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, *45*, 1–36.

Scheme VII[a]

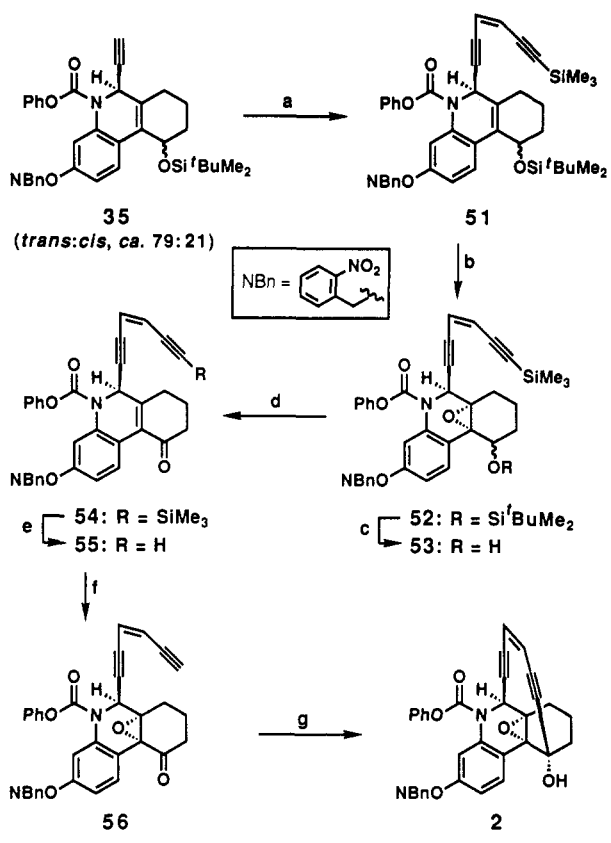


[a] Reagents and conditions: (a) 1.5 equiv of **42**, 0.05 equiv of Pd-$(PPh_3)_4$, 1.5 equiv of $^nPrNH_2$, 0.2 equiv of CuI, PhH, 25 °C, 6–8 h, **36** → **45**, 67%; (b) 1.0 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 1 h, **45** → **46**, 71%; (c) 5.0 equiv of BF_3·OEt_2, wet $CHCl_3$, 25 °C, 10 min; 48% HBr/THF (1:10), 25 °C, 1 h, **46** → **47** (34%) + **48** (18%); (d) 4.0 equiv of $AgNO_3$, H_2O/EtOH/THF (1:1:1), 25 °C, 1 h; 7.0 equiv of KCN, 25 °C, 10 min, **47** → **48**, 90%; (e) 1.2 equiv of *m*-CPBA, CH_2Cl_2/saturated aqueous $NaHCO_3$ (5:1), 25 °C, 10 min, **48** → **44**, 45%; (f) 1.0 equiv of LDA, PhMe, −78 °C, 20 min, **44** → **49**, 80%; (g) 3.0 equiv of thiocarbonyldiimidazole, 0.5 equiv of DMAP, CH_2Cl_2, 25 °C, 22 h, **49** → **50**, 58% (33% of **49** recovered); (h) 2.0 equiv of $^nBu_3SnH$, AIBN (catalytic), PhMe, 80 °C, 1 h, **50** → **1**, 69% (9% of **49** isolated due to hydrolysis of **50**).

stitution at C-3 was studied using compounds **25** and **28–31**. Thus, treatment of the quinoline substrates with ethynylmagnesium bromide and phenyl chloroformate in THF at −78 → 0 °C afforded the corresponding acetylenic carbamate compounds **32–36** (Scheme V) in 90–99% yield. The ratios of trans:cis shown in Scheme V were determined by ^1H NMR spectroscopy and suggested only small electronic effects in this reaction (it was assumed that the major product was the trans isomer obtained by attack from the opposite side of the silyloxy group).

Our initial attempts to construct the requisite cyclization precursor **44** are shown in Scheme VI. Thus, whereas epoxidation of **36** (ca. 69:31 mixture of isomers by ^1H NMR) proceeded to afford epoxide **38**, desilylation of the latter compound to afford **39** proceeded only in 20% yield under the best of circumstances. An attempted maneuver to reverse the sequence failed at the desilylation stage ($^nBu_4NF$, **36** → **37**). However, reaction of **38** with BF_3·Et_2O followed by didehydration by silica gel led to the enone **40** (73%), presumably via the initially formed triol (desilylation,[8] epoxide opening by BF_3·Et_2O and H_2O). Epoxidation

Scheme VIII[a]



[a] Reagents and conditions: (a) 1.5 equiv of **42**, 0.05 equiv of Pd-$(PPh_3)_4$, 1.5 equiv of $^nPrNH_2$, 0.2 equiv of CuI, PhH, 25 °C, 5 h, **35** → **51**, 87%; (b) 1.0 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 1 h, **51** → **52**; (c) 3.0 equiv of BF_3·OEt_2, wet $CHCl_3$, 25 °C, 10 min, **52** → **53**, 81% (two steps from **51**); (d) 48% HBr/THF (1:10), 25 °C, 2 h, **53** → **54**, 82%; (e) 4.0 equiv of $AgNO_3$, H_2O/EtOH/THF (1:1:1), 25 °C, 1 h, 7.0 equiv of KCN, 25 °C, 10 min, **54** → **55**, 83%; (f) 2.0 equiv of *m*-CPBA, CH_2Cl_2/saturated aqueous $NaHCO_3$ (1:1), 25 °C, 1 h, **55** → **56**, 59%; (g) 1.0 equiv of LDA, PhMe, −78 °C, 20 min, **56** → **2**, 52% (18% of **56** recovered).

of **40** with *m*-CPBA under basic conditions furnished **41** in 67% yield. The palladium(0)–copper(I)-catalyzed coupling reaction between terminal acetylene **41** and vinyl chloride **42** proceeded only in modest yield (32%) to give **43**, from which the trimethylsilyl group was removed by standard chemistry. Due to the low yield of the coupling reaction in this sequence, a second strategy was developed.

Scheme VII presents an alternative approach to **44** starting from compound **36**. Thus, coupling of **36** with vinyl chloride **42** under the standard conditions gave **45** in 67% yield. Epoxidation of **45** with *m*-CPBA led to **46** in 71% yield. Reaction of **46** with BF_3·Et_2O[8] followed by exposure to 48% aqueous HBr in THF gave enones **47** (34%) and **48** (18%). Removal of the trimethylsilyl group from **47** under standard conditions (Scheme VII) led to **48** (90%), which was subjected to epoxidation using *m*-CPBA under basic conditions to afford epoxide **44** in 45% yield. Cyclization of **44** under the standard LDA conditions[5-7] gave **49** in 80% yield. Deoxygenation of **49** proceeded as previously described[5,6] for similar compounds via thiocarbonylimidazole **50** (58% yield, plus 33% recovered starting material) to afford the targeted compound **1** (69%, plus 9% recovered **49**). Interestingly, enediyne **49** formed a 1:1 crystalline complex (mp 183–84 °C dec, from ethyl ether) with ethyl ether as shown by ^1H NMR, elemental analysis, and X-ray crystallographic analysis. Figure 1 shows an ORTEP drawing of compound **49** together with some structural parameters.

(5) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3107.
(6) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416.
(7) Nicolaou, K. C.; Dai, W.-M.; Wendeborn, S. V.; Smith, A. L.; Torisawa, Y.; Maligres, P.; Hwang, C.-K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1032.

(8) BF_3·Et_2O in $CHCl_3$ was reported for desilylation, see: Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295.

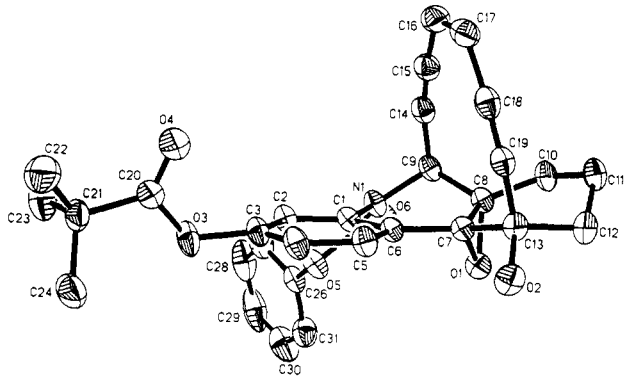
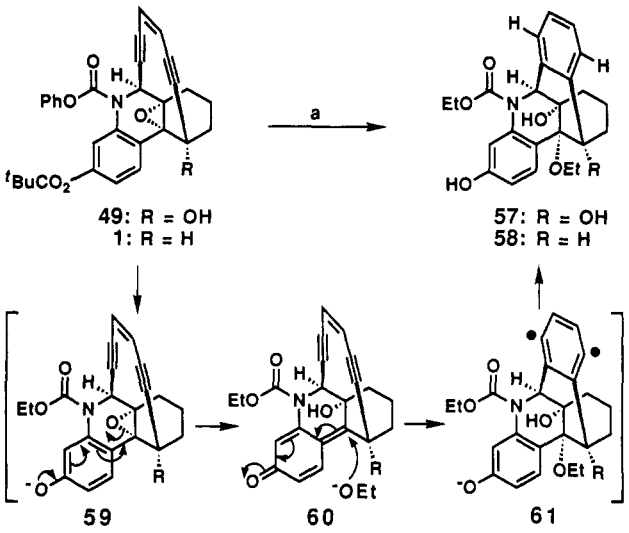


Figure 1. ORTEP drawing of dynemicin A mimic **49**. Hydrogen atoms are omitted for clarity. cd distance ($r_{C14-C19}$) = 3.637 Å. Angles: $C_9-C_{14}-C_{15}$ = 162.6°; $C_{14}-C_{15}-C_{16}$ = 172.5°; $C_{17}-C_{18}-C_{19}$ = 170.3°; $C_{13}-C_{19}-C_{18}$ = 161.3°.

Scheme IX. Base-Induced Bergman Cycloaromatization of Enediynes **49** and **1**[a]

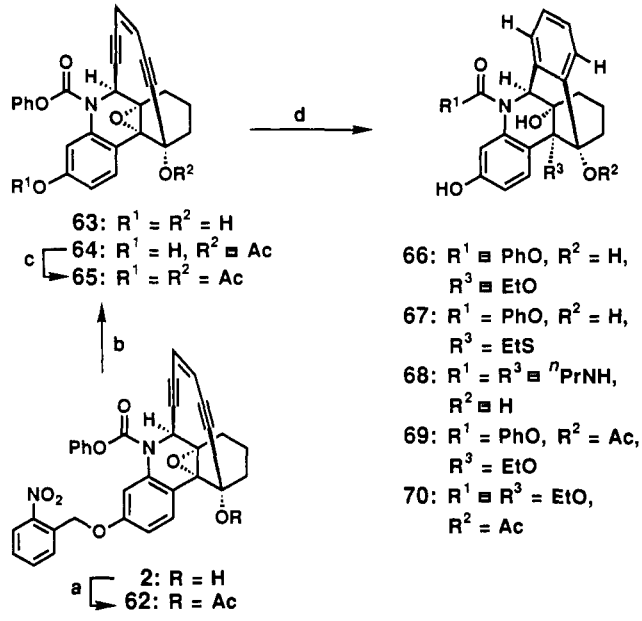


[a] Reagents and conditions: (a) 4.0 equiv of LiOH, $EtOH/H_2O$ (3:1), 25 °C, 4–6 h, **49** → **57**, 56%, or **1** → **58**, 42%.

The *o*-nitrobenzyl derivative **2** was synthesized as summarized in Scheme VIII. This sequence, resembling that used for the synthesis of **49** (Scheme VII), proceeded in good overall yield (see Scheme VIII). Although quite stable for isolation and characterization purposes, enediyne **2** proved rather labile as compared to the ester **49**. Attempted deoxygenation via the thiocarbonylimidazole was not successful due to extensive decomposition at the first stage of the two-step sequence.

Triggering of the Bergman Cycloaromatization of Enediynes 1 and 2. Evidence for Quinone Methide Formation in the Mechanism of Action of Dynemicin A. With enediynes **1** and **49** in hand, we then proceeded to test the hypothesis of triggering the Bergman cycloaromatization[9] under basic conditions. Treatment of **49** or **1** with LiOH in aqueous ethanol produced compound **57** or **58** in 56% or 42% yield, respectively (Scheme IX). To account for these observations, the cascade **49**, **1** → **59** → **60** → **61** → **57** or **58**, shown in Scheme IX, was postulated. Thus, cleavage of the pivaloyl ester with concomitant carbamate exchange leads to phenoxide **59**, which undergoes rearrangement to quinone methide **60** as depicted. Rapid nucleophilic attack on **60** at the indicated sp^2 carbon converts it to an sp^3 center, an event that apparently allows the Bergman reaction[9] to proceed spontaneously, forming

Scheme X. Photodeprotection and Base-Induced Bergman Cycloaromatization of Enediynes **2** and **62–64**[a]



[a] Reagents and conditions: (a) Ac_2O/pyr, DMAP (catalytic), 25 °C, 2 h, **2** → **62**, 77%; (b) *hν*, THF/H_2O (10:1), argon, 0 °C, 40 min, **2** → **63**, high yield based on TLC and ^1H NMR, or **62** → **64**, 83%; (c) Ac_2O/pyr, 25 °C, 30 min, **64** → **65**, 92%; (d) EtOH/THF/phosphate buffer (pH 8.0) (1:1:1), argon, 25 °C, 1.5 h, **63** → **66**, 31% (two steps from **2**), or EtSH/THF/phosphate buffer (pH 8.0) (1:1:1), argon, 25 °C, 1.5 h, **63** → **67**, 34% (two steps from **2**), or $^nPrNH_2$/THF/phosphate buffer (pH 8.0) (1:1:1), argon, 25 °C, 1.5 h, **63** → **68**, 46% (two steps from **2**), or EtOH/THF/phosphate buffer (pH 8.0) (1:1:1), argon, 25 °C, 10 h, **64** → **69** + **70**, 20%.

diradical **61**. Trapping of **61** by hydrogen abstraction from ethanol finally leads to **57** or **58**.

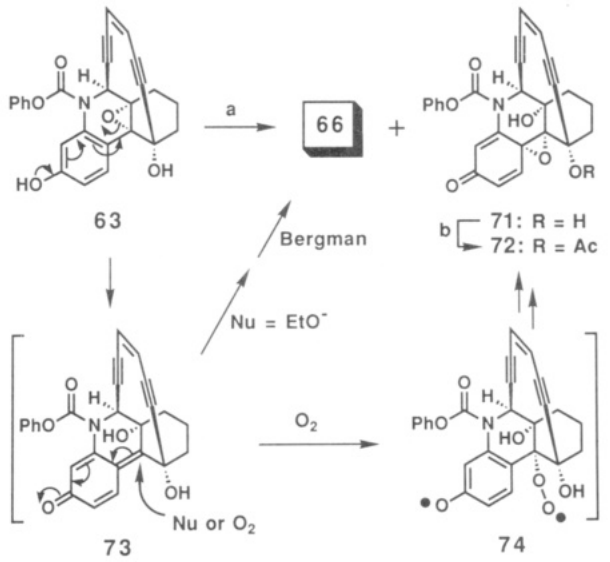
A similar reaction cascade is postulated to explain the conversion of **63** and **64** to the cycloaromatized products **66–70** (Scheme X). The free phenolic compounds **63** and **64** were generated from **2** and **62**, respectively, by photolysis under neutral conditions (THF/H_2O) at 0 °C. Compound **63** was found to be rather unstable and was observed only by ^1H NMR and TLC (high yield), whereas **64** was quite stable and isolable under neutral conditions (83%). The diacetate **65** was prepared from **64** by standard chemistry (92%) and also proved quite stable under neutral conditions. Exposure of compound **63** to the nucleophiles EtOH, EtSH, or $^nPrNH_2$ in THF, pH 8.0, phosphate buffer solution under anaerobic conditions provided the corresponding cycloaromatized products **66–68** in 31–46% yield (Scheme X). Similar treatment of **64** with EtOH resulted in the formation of **69** and **70** (20% total yield).

When the above base-induced reaction with **63** was carried out in the presence of oxygen, the novel epoxy quinone methide **71** (Scheme XI) was obtained in 9% yield along with product **66** (33%). The structure of **71** was tentatively assigned on the basis of its ^1H and ^{13}C NMR, mass, and IR spectra. The corresponding acetate **72** (Scheme XI) also exhibited supportive spectroscopic properties for the proposed structure. The formation of compound **71** may be envisioned to proceed via incorporation of molecular oxygen[10] into quinone methide intermediate **73** followed by rearrangement of the resulting phenoxy radical **74** and epoxide formation, as postulated in Scheme XI. A similar result was observed when compound **75** was exposed to air under basic conditions to afford epoxy quinone methides **76** and **77** in much improved yields (Scheme XII). The rather acid-sensitive enediyne compound **78** was synthesized according to our initially reported sequences[5,6] to provide another possibility for a triggering device working under acidic conditions. Thus, treatment of **78** with 1.0

(9) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (c) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (d) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091.

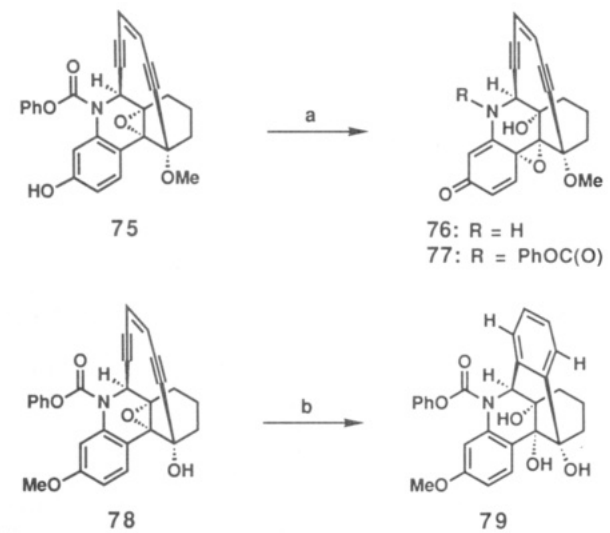
(10) Gandiano, G.; Koch, T. H. *J. Am. Chem. Soc.* **1990**, *112*, 9423.

Scheme XI. Trapping of Quinone Methide Intermediate by Molecular Oxygen[a]



[a] Reagents and conditions: (a) EtOH/THF/phosphate buffer (pH 8.0) (1:1:1), air, 25 °C, 1.5 h, **63** → **66** (33%) + **71** (9%); (b) Ac_2O/pyr, DMAP (catalytic), 25 °C, 1 h, **71** → **72**, 84%.

Scheme XII[a]

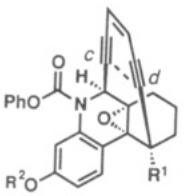
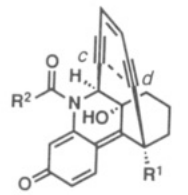
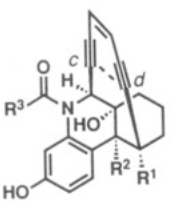


[a] Reagents and conditions: (a) THF/pH 9.0 buffer (boric acid/potassium chloride/sodium hydroxide) (1:1), air, 25 °C, 48 h, **75** → **76** (35%) + **77** (25%); (b) 1.0 equiv of $TsOH \cdot H_2O$, PhH/1,4-cyclohexadiene (1:1), 25 °C, 1.5 h, **78** → **79**, 32%.

equiv of $TsOH \cdot H_2O$ in benzene/1,4-cyclohexadiene (1:1) at 25 °C for 1.5 h furnished, as expected, the corresponding Bergman cycloaromatization product **79** in 32% yield. Interestingly, the triol system in this case is stable to the reaction conditions and does not undergo further pinacol rearrangement[5,6] (Scheme XII).

Calculations of cd Distances. Although it was recognized that the distance between the remote acetylenic carbons (cd)[11-13] in these enediynes was not the only deciding factor determining their stability toward Bergman cycloaromatization, it was of interest

Table I. cd Distances of the Intermediates in the Dynemicin A Mimics Cascade[a]

	compd	R^1	R^2	R^3	cd distance (Å)
	**1**	H	^{t}BuCO		3.64
	80	H	H		3.63
	49	OH	^{t}BuCO		3.65 (3.64)[b]
	2	OH	NBn		3.66
	63	OH	H		3.66
	65	OAc	OAc		3.65
	62	OAc	NBn		3.66
	64	OAc	H		3.62
	**60a**	H	OEt		3.52
	60b	OH	OEt		3.54
	81	OH	OPh		3.53
	82	OH	NH^{n}Pr		3.52
	83	OAc	OEt		3.51
	84	OAc	OPh		3.50
	**85**	H	OEt	OEt	3.15
	86	OH	OEt	OEt	3.16
	87	OH	OEt	OPh	3.10
	88	OH	SEt	OPh	3.11
	89	OH	NH^{n}Pr	NH^{n}Pr	3.10
	90	OAc	OEt	OEt	3.14
	91	OAc	OEt	OPh	3.15

[a] Obtained by MMX calculations (ref 14). [b] Obtained from X-ray analysis.

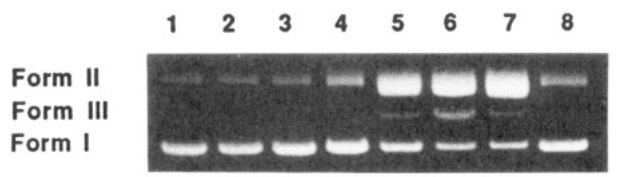


Figure 2. Supercoiled DNA interaction with synthesized model compounds. ΦX174 DNA (50 μM/bp) was incubated for 36 h at 37 °C with the indicated enediynes (5.0 mM) in buffer (50 mM Tris-HCl, pH 8.5) and analyzed by electrophoresis (1% agarose gel, ethidium bromide stain): lane 1, DNA control; lane 2, **49** + DNA; lane 3, **1** + DNA; lane 4, **2** + DNA; lane 5, **63** + DNA; lane 6, **71** + DNA; lane 7, **64** + DNA; lane 8, **65** + DNA. Key: Form I, supercoiled DNA; Form II, nickel DNA; Form III, linear DNA.

to calculate this distance for the three types of compounds listed in Table I. Molecular mechanics (MMX) calculations[14] led to the cd distances 3.62–3.66 Å for the epoxide series of enediynes, which correlates well with their relatively high stability. In the case of **49**, the calculated value (3.65 Å) agrees remarkably well with the experimental value (3.64 Å) derived from the X-ray crystallographic analysis (see Figure 1). Calculations on the *p*-quinone methide series (**60a,b**, **81–84**) also revealed a consistent cd distance of 3.50–3.54 Å (Table I), suggesting stability toward cycloaromatization for these compounds; these systems, however, do suffer from a different type of reactivity. Finally, for the epoxide-opened products **85–91**, much shorter cd distances (3.10–3.16 Å, Table I) were revealed by calculations. These results are in line with the spontaneous Bergman cyclization of these enediynes at ambient temperatures. It should be pointed out, however, that the cd distance–Bergman reactivity correlation applies only within a given series of similar enediynes and that the ultimate determinant is the GS–TS differential in energy.[11-13]

DNA Cleavage and Cytotoxicity Studies. Compounds **63** and **64** exhibited significant DNA-cleaving action against ΦX174 supercoiled DNA as expected from their chemistry (Figure 2).

(11) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. Nicolaou, K. C.; Zuccarello, G.; Riemer, C.; Estevez, V. A.; Dai, W.-M. *J. Am. Chem. Soc.*, in press.
(12) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986. Magnus, P.; Cater, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Banta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.
(13) Langley, D. R.; Doyle, T. W.; Beveridge, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 4395.

(14) A 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).

Compound **71** also exhibited DNA-cleaving capability (Figure 2), although its triggering mechanism is not clear at present. As expected from their chemical profiles, compounds **49**, **1**, **2**, and **65** were found to be inert toward supercoiled DNA (Figure 2).

The extensive cytotoxicity studies performed with the synthesized compounds will be reported elsewhere.[15] It is important to mention here, however, that both the parent warhead compound **64** and the ester-protected precursor **1** exhibited powerful cytotoxicity against various tumor cell lines, particularly leukemia molt-4 cells (IC_{50} ca. 1.0×10^{-11} M for compound **1**). These results suggest a mechanistic pathway for the activation of **1** via ester hydrolysis–Bergman cycloaromatization as postulated in the design of these systems.[1] The *o*-nitrobenzyl protected compound **2** showed considerably less potency than **1**, presumably due to the following combination of deactivating effects: (a) the oxygen substituent at C-10 and (b) the weakness of the cell's chemical machinery to generate the free phenol from this structure.

Conclusion

A series of designed enediynes related to dynemicin A and equipped with base-sensitive and photosensitive triggering devices at C-3 were synthesized. The chemistry of these systems, particularly reactions leading to their conversion to the phenolic species, was studied. As anticipated at the design stage,[1] such phenolic species are quite activated, showing propensity toward epoxide opening, leading to *p*-quinone methides which can be intercepted with a variety of nucleophiles. The derived cis products undergo spontaneous Bergman cycloaromatization at ambient temperatures. An interesting reaction of the postulated *p*-quinone methide intermediates with molecular oxygen leading to novel epoxide structures was detected. These results strengthen the notion of the intermediacy of quinone methide species in the mechanism of action of dynemicin A.[7,16]

The described chemistry together with the results reported in the preceding paper[1] supports the viability of the scenarios outlined in Scheme III (preceding article in this issue)[1] as triggering mechanisms for the dynemicin A cascade by demonstrating that a lone pair of electrons on a heteroatom (N or O) strategically positioned on the aromatic ring in relation to the oxirane ring serves to initiate the Bergman cycloaromatization. Reactive species may be generated within the cell from suitable stable precursors or, as shown above, be released in vitro under mild laboratory conditions. The reported observations also allow for the possibility of dynemicin A undergoing bioreduction prior to intercalation and for nucleophilic interaction of DNA with quinone methide species derived from dynemicin A. Thus, the proposal[16a] that dynemicin A may be interacting with DNA by a dual mechanism (radical and nucleophilic) appears attractive in view of the chemistry of **63** and the previously reported preference of dynemicin A to cleave at A and G bases.[16a]

The foundation is now laid for further design, synthesis, and development of more sophisticated enediynes.[17,18] Targeting such systems may provide powerful and selective agents for DNA cleavage and chemotherapy.

Experimental Section

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

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

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

3-Methoxy-7,8,9,10-tetrahydrophenanthridone (6b). Prepared from 3-methoxyaniline (**4b**) and ethyl 2-oxocyclohexanecarboxylate (**5**) in 31% yield by following the reported procedure.[2] **6b**: powder, mp 256–258 °C; R_f = 0.35 (silica, 3.2% methanol in dichloromethane); IR (KBr) ν_{max} 3150, 3069, 2938, 2859, 2831, 1652, 1622, 1614, 1567, 1515, 1218, 1119, 1036, 915, 800 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.55 (s, 1 H, N*H*), 7.57 (d, J = 9.6 Hz, 1 H, H1), 6.80–6.74 (m, 2 H, H2 and H4), 3.77 (s, 3 H, OCH_3), 2.76 (t, J = 5.6 Hz, 2 H, H7 or H10), 2.40 (t, J = 6.1 Hz, 2 H, H7 or H10), 1.80–1.65 (m, 4 H, H8 and H9); HRMS for $C_{14}H_{16}NO_2$ (M + H) calcd 230.1181, found 230.1160.

3-Methoxy-7,8,9,10-tetrahydrophenanthridine (8). To a suspension of **6b** (2.00 g, 8.72 mmol) in dry THF (50 mL) was added DIBAL dropwise (1 M in CH_2Cl_2, 9.0 mL, 9.0 mmol) to generate a homogeneous solution. $LiAlH_4$ (1.75 g, 46.0 mmol) was added followed by reflux for 2 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4, diluted with ethyl ether (300 mL), dried over anhydrous Na_2SO_4, and filtered through Celite. The solvent was removed in vacuo to give mainly the corresponding secondary amine. Oxidative aromatization was carried out by stirring a solution of the crude amine in benzene (50 mL) containing silica gel (2.0 g) under oxygen atmosphere at room temperature for 24 h. Silica gel was filtered off and washed with ethyl ether (100 mL). The combined filtrate was concentrated and purified by flash column chromatography (silica gel, 20% ethyl ether in benzene) to afford crystalline **8** (1.2 g, 65%): mp 53–54.7 °C (from ethyl ether/petroleum ether); R_f = 0.50 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2941, 1623, 1507, 1421, 1344, 1230, 1161, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1 H, H6), 7.79 (d, J = 9.2 Hz, 1 H, H1), 7.39 (d, J = 2.7 Hz, 1 H, H4), 7.17 (dd, J = 9.0, 2.7 Hz, 1 H, H2), 3.93 (s, 3 H, OCH_3), 3.06 (t, J = 6.0 Hz, 2 H, H7 or H10), 2.85 (t, J = 6.2 Hz, 2 H, H7 or H10), 1.95–1.85 (m, 4 H, H8 and H9); HRMS for $C_{14}H_{16}NO$ (M + H) calcd 214.1232, found 214.1240.

1,4-Dioxaspiro[4.5]decane-6-carboxylic Acid (10). A mixture of ethyl 2-oxocyclohexanecarboxylate (**5**, 100.0 mL, 97%, 0.606 mol), ethylene glycol (33.8 mL, 0.606 mol), and *p*-toluenesulfonic acid monohydrate (11.53 g, 60.6 mmol) in dry benzene (800 mL) was refluxed under argon for 5 h with azeotropic removal of water. The reaction mixture was diluted with ethyl ether (500 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a crude product (135.0 g). An analytical sample was prepared by preparative TLC (silica gel plate, 9% ethyl ether in petroleum ether): colorless oil; R_f = 0.16 (silica, 9% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2943, 1728, 1448, 1377, 1253, 1234, 1214, 1185, 1157, 1087, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.01–3.84 (m, 4 H, OCH_2CH_2O), 2.67 (dd, J = 8.2, 5.7 Hz, 1 H, COC*H*CH_2), 1.99–1.81 (m, 3 H, CH_2CH_2), 1.74–1.58 (m, 3 H, CH_2CH_2), 1.53–1.42 (m, 1 H, CH_2), 1.39–1.26 (m, 1 H, CH_2), 1.27 (t, J = 7.1 Hz, 3 H, OCH_2CH_3); MS (FAB^+) m/e (relative intensity) 215 (M + H, 35), 169 (100), 125 (18); HRMS for $C_{11}H_{19}O_4$ (M + H) calcd 215.1283, found 215.1283.

To a solution of the crude ester obtained above (135.0 g) in MeOH (300 mL) was added aqueous NaOH (48.48 g, 1.212 mol in 400 mL of water), and the mixture was then heated under reflux for 15 h. After cooling to room temperature, the mixture was extracted with ethyl ether (300 mL), and the aqueous layer was separated, acidified carefully (under ice cooling) with dilute aqueous $NaHSO_4$ (167.4 g) to pH 2.0, extracted with ethyl ether (1 L × 3), and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give crystalline carboxylic acid **10** (87.5 g, 78% from **5**): colorless prisms, mp 137–139 °C (from ethyl ether); IR ($CHCl_3$) ν_{max} 3508, 3221 (br), 3026, 3017, 2946, 2900, 2868, 1757, 1710, 1381, 1141, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.5–8.0 (br s, 1 H, COO*H*), 4.05 (m, 4 H, OCH_2CH_2O), 2.71 (dd, J = 9.2, 4.9 Hz, 1 H, COC*H*CH_2), 2.04–1.83 (m, 3 H, CH_2CH_2), 1.76–1.56 (m, 3 H, CH_2CH_2), 1.56–1.42 (m, 1 H, CH_2), 1.42–1.27 (m, 1 H, CH_2); MS (FAB^+) m/e (relative intensity) 187 (M + H, 51), 169 (100), 125 (26), 107 (13); HRMS for $C_9H_{15}O_4$ (M + H) calcd 187.0970, found 187.0970. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.21; H, 7.75.

(15) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172.

(16) (a) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3831. (b) Sugiura, Y.; Arakawa, T.; Uesugi, M.; Shiraki, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, *30*, 2989. (c) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *31*, 1521. (d) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, *112*, 4040.

(17) Review: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

(18) Review: Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235.

3-[1,4-Dioxaspiro[4.5]decane-6-carbonyl]-1,3-thiazolidine-2-thione (12). To a solution of carboxylic acid **10** (27.0 g, 0.145 mol) and 2-mercaptothiazoline (**11**, 17.29 g, 0.145 mol) in dry CH_2Cl_2 (500 mL) cooled in an ice–water bath were added DCC (35.9 g, 0.174 mol) and DMAP (1.83 g, 15.0 mmol) followed by stirring at room temperature for 14 h. The precipitate was filtered off through Celite and the filtrate was concentrated in vacuo to give a residue. Flash column chromatography of the residue (silica gel, ethyl ether/petroleum ether/benzene, 1:2:4) afforded oily yellow-colored imide **12** (40.2 g, 96%): R_f = 0.56 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2945, 1708, 1647, 1367, 1281, 1228, 1160, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (t, J = 7.5 Hz, 1 H, $COCHCH_2$), 4.64–4.39 (m, 2 H, NCH_2CH_2S), 4.05–3.84 (m, 4 H, OCH_2CH_2O), 3.42–3.16 (m, 2 H, NCH_2CH_2S), 2.10–1.30 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 288 (M + H, 74), 225 (5), 169 (100), 125 (13); HRMS for $C_{12}H_{18}NO_3S_2$ (M + H) calcd 288.0728, found 288.0750.

Amide Bond Formation of Imide 12 with Aminophenols. *N*-(3-Hydroxyphenyl)-1,4-dioxaspiro[4.5]decane-6-carboxamide (13). Representative Procedure. A solution of imide **12** (40.0 g, 0.139 mol) and 3-aminophenol (15.19 g, 0.139 mol) in THF (500 mL) was refluxed for 96 h. The solvent was removed in vacuo to give a solid residue, which was recrystallized from acetone/ethyl ether to afford 30.2 g of **13**. The mother liquor was concentrated and purified repeatedly by flash column chromatography (silica gel, 20% ethyl ether in benzene) to give 3.3 g of **13**. 2-Mercaptothiazoline (**11**, 15.2 g, 92%) was recovered. Combined weight of **13** was 33.5 g (87%). **13**: white crystalline solid, mp 181–183 °C (from acetone/ethyl ether); R_f = 0.16 (silica, 20% ethyl ether in benzene); IR (KBr) ν_{max} 3381, 3178 (br), 2943, 1651, 1617, 1604, 1550, 1448, 1282, 1237, 1158, 1151, 1141, 1091, 1036, 877, 755, 690 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.73 (br s, 1 H, N*H*), 8.28 (s, 1 H, ArO*H*, exchangeable by D_2O), 7.35 (dd, J = 2.1, 2.1 Hz, 1 H, aromatic), 7.08 (dd, J = 8.0, 7.9 Hz, 1 H, aromatic), 6.99 (ddd, J = 8.0, 1.9, 1.2 Hz, 1 H, aromatic), 6.52 (ddd, J = 7.8, 2.4, 1.1 Hz, 1 H, aromatic), 4.02–3.84 (m, 4 H, OCH_2CH_2O), 2.62 (dd, J = 9.7, 5.2 Hz, 1 H, $COCHCH_2$), 1.99–1.24 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 278 (M + H, 100), 216 (3), 169 (19); HRMS for $C_{15}H_{20}NO_4$ (M + H) calcd 278.1392, found 278.1401. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.87; H, 6.97; N, 5.01.

***N*-[3-(Benzyloxy)phenyl]-1,4-dioxaspiro[4.5]decane-6-carboxamide (14).** To a solution of **13** (20.0 g, 72.12 mmol) in dry THF (300 mL) cooled at 0 °C was added NaH (60%, 3.03 g, 75.72 mmol) followed by stirring at 0 °C for 10 min. Benzyl bromide (8.58 mL, 72.14 mmol) and tetra-*n*-butylammonium iodide (2.66 g, 7.20 mmol) were added, and the resultant mixture was stirred at room temperature for 1 h. Water was added to the reaction mixture which was extracted with ethyl acetate (500 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a residue. Flash column chromatography of the residue (silica gel, ethyl ether/petroleum ether/benzene, 1:2:4) afforded amide **14** (19.0 g, 72%): white crystalline solid, mp 88–89.5 °C (from EtOAc/petroleum ether); R_f = 0.52 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3355 (br), 3014, 2945, 1684, 1600, 1539, 1492, 1441, 1287, 1157, 1082, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1 H, N*H*), 7.47–7.31 (m, 6 H, aromatic), 7.19 (dd, J = 8.0, 8.0 Hz, 1 H, aromatic), 6.97 (ddd, J = 7.4, 1.1, 0.8 Hz, 1 H, aromatic), 6.70 (ddd, J = 8.2, 2.7, 0.7 Hz, 1 H, aromatic), 5.06 (s, 2 H, benzylic), 4.05–3.86 (m, 4 H, OCH_2CH_2O), 2.65 (dd, J = 11.5, 4.3 Hz, 1 H, $COCHCH_2$), 2.08–1.22 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 368 (M + H, 100), 306 (9), 199 (6), 169 (37); HRMS for $C_{22}H_{26}NO_4$ (M + H) calcd 368.1862, found 368.1850. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.80; H, 6.76; N, 3.87.

***N*-(4-Hydroxyphenyl)-1,4-dioxaspiro[4.5]decane-6-carboxamide (15).** Compound **15** was prepared from 4-aminophenol and **12** in a manner similar to that described for **13** in 86% yield. **15**: white crystalline solid, mp 173–174.4 °C (from acetone/petroleum ether); R_f = 0.10 (silica, 20% ethyl ether in benzene); IR (KBr) ν_{max} 3243 (br), 2947, 1655, 1601, 1552, 1513, 1441, 1270, 1223, 1080, 923, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 8.77 (d, J = 8.9 Hz, 1 H, aromatic), 8.43 (br s, 1 H, N*H*), 7.33 (d, J = 6.4 Hz, 1 H, aromatic), 6.80–6.40 (m, 2 H, aromatic), 3.96 (br s, 4 H, OCH_2CH_2O), 3.19 (br s, 1 H, ArO*H*), 2.59 (br s, 1 H, $COCHCH_2$), 2.00–1.20 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 278 (M + H, 100), 169 (17), 109 (24); HRMS for $C_{15}H_{20}NO_4$ (M + H) calcd 278.1392, found 278.1399. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.99; H, 6.98; N, 5.00.

***N*-[4-(Benzyloxy)phenyl]-1,4-dioxaspiro[4.5]decane-6-carboxamide (16).** Compound **16** was prepared from **15** in a manner similar to that described for **14** in 78% yield. **16**: colorless, fine needles, mp 134–135.5 °C (from EtOAc/petroleum ether); R_f = 0.49 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3356, 2943, 1676, 1598, 1528, 1510, 1083, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (br s, 1 H, N*H*), 7.45–7.30 (m, 8 H, aromatic), 6.92 (m, 1 H, aromatic), 5.03 (s, 2 H, benzylic), 4.04–3.90 (m, 4 H, OCH_2CH_2O), 2.64 (dd, J = 11.3, 4.3 Hz, 1 H, $COCHCH_2$), 2.10–1.25 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 368 (M + H, 100), 169 (38), 125 (8), 108 (6); HRMS for $C_{22}H_{26}NO_4$ (M + H) calcd 368.1862, found 368.1863. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.90; H, 6.83; N, 3.81.

***N*-(3-Hydroxy-4-carboxyphenyl)-1,4-dioxaspiro[4.5]decane-6-carboxamide (17).** Compound **17** was prepared from 5-aminosalicylic acid and **12** in a manner similar to that described for **13** in 87% yield, except for a modified workup procedure. The reaction mixture was first filtered through Celite to remove the solid materials, and the filtrate was treated with saturated aqueous $NaHCO_3$ and extracted with ethyl ether. The aqueous layer was then acidified with 5% HCl and extracted with ethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give the product **17**: white crystalline solid, mp 183–186 °C (from ethyl ether); IR ($CHCl_3$) ν_{max} 3403, 3348, 3073, 2945, 1678, 1619, 1543, 1528, 1491, 1446, 1291, 1083, 1036, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1 H, N*H*), 8.07 (d, J = 3.2 Hz, 1 H, aromatic), 7.90 (br s, 1 H, ArO*H*), 7.55 (dd, J = 10.7, 3.2 Hz, 1 H, aromatic), 6.94 (d, J = 10.7 Hz, 1 H, aromatic), 7.50–6.50 (br s, 1 H, COO*H*), 4.15–3.95 (m, 4 H, OCH_2CH_2O), 2.73 (dd, J = 13.4, 5.2 Hz, 1 H, $COCHCH_2$), 2.10–1.20 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 322 (M + H, 100), 268 (9), 169 (27), 120 (26), 107 (14); HRMS for $C_{16}H_{20}NO_6$ (M + H) calcd 322.1291, found 322.1290.

***N*-[3-(Benzyloxy)-4-(benzyloxycarbonyl)phenyl]-1,4-dioxaspiro[4.5]decane-6-carboxamide (18).** Compound **18** was prepared from **17** in a manner similar to that described for **14** in 77% yield. **18**: colorless, fine needles, mp 96–98 °C (from EtOAc/petroleum ether); R_f = 0.44 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3350, 2944, 1721, 1679, 1534, 1500, 1454, 1298, 1083, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (br s, 1 H, N*H*), 7.90 (dd, J = 9.1, 2.9 Hz, 1 H, aromatic), 7.71 (d, J = 2.9 Hz, 1 H, aromatic), 7.43–7.28 (m, 10 H, aromatic), 6.97 (d, J = 9.1 Hz, 1 H, aromatic), 4.03–3.85 (m, 4 H, OCH_2CH_2O), 2.63 (dd, J = 11.0, 4.4 Hz, 1 H, $COCHCH_2$), 2.04–1.25 (m, 8 H, 4 × CH_2); MS (FAB^+) m/e (relative intensity) 502 (M + H, 100), 394 (10), 242 (7), 181 (7), 169 (95), 125 (16); HRMS for $C_{30}H_{32}NO_6$ (M + H) calcd 502.2230, found 502.2250. Anal. Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.90; H, 6.42; N, 3.01.

3-(Benzyloxy)-7,8,9,10-tetrahydrophenanthridone (19) and 1-(Benzyloxy)-7,8,9,10-tetrahydrophenanthridone (20). A solution of amide **14** (29.0 g, 78.92 mmol) in THF (230 mL) and 37% HCl (84 mL) was heated under reflux for 3 h. After the mixture was cooled to room temperature, the white precipitate was collected by filtration and dried over P_2O_5 under vacuum to give a 82:18 mixture of **19** and **20** (24.1 g, 100%). **19** + **20**: white powder, mp 288–290 °C dec (from THF/H_2O); R_f = 0.40 (**19**) and 0.36 (**20**) (silica, 3.2% methanol in dichloromethane); IR (KBr) ν_{max} 3400, 2930, 1648, 1602, 1590, 1530, 1254, 1197, 1182 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.60 (br s, 1 H, N*H*), 7.55 (d, J = 8.9 Hz, 0.82 H, H1), 7.51–7.29 (m, 5 H, aromatic), 7.26 (t, J = 8.2 Hz, 0.18 H, H3), 6.92 (d, J = 8.2 Hz, 0.18 H, H2 or H4), 6.90 (d, J = 2.3 Hz, 0.82 H, H4), 6.83 (dd, J = 8.9, 2.3 Hz, 0.82 H, H2), 6.75 (d, J = 8.2 Hz, 0.18 H, H2 or H4), 5.17 (s, 0.36 H, benzylic), 5.12 (s, 1.64 H, benzylic), 3.14 (br s, 0.36 H, H7 or H10), 2.78 (t, J = 5.8 Hz, 1.64 H, H7 or H10), 2.53 (t, J = 1.6 Hz, 0.36 H, H7 or H10), 2.46 (t, J = 5.9 Hz, 1.64 H, H7 or H10), 1.86–1.50 (m, 4 H, H8 and H9); MS (FAB^+) m/e (relative intensity) 306 (M + H, 100), 215 (10); HRMS for $C_{20}H_{20}NO_2$ (M + H) calcd 306.1494, found 306.1500.

3-(Benzyloxy)-7,8,9,10-tetrahydrophenanthridine (21). To a suspension of a mixture of **19** and **20** (ca. 82:18, 24.1 g, 78.92 mmol) in dry THF (300 mL) was added DIBAL dropwise (1 M in CH_2Cl_2, 78.9 mL, 78.9 mmol) to generate a homogeneous solution. $LiAlH_4$ (6.0 g, 0.158 mol) was added followed by reflux for 3 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4, diluted with ethyl ether (800 mL), dried over anhydrous Na_2SO_4, and filtered through Celite. The solvent was removed in vacuo to give mainly the corresponding secondary amine. Oxidative aromatization was carried out by stirring a solution of the amine in benzene (500 mL) containing silica gel (20.0 g) under an oxygen atmosphere at room temperature for 24 h. Silica gel was filtered off and washed with ethyl ether (300 mL). The combined filtrate was concentrated and purified by flash column chromatography (silica gel, 20% ethyl ether in benzene) to furnish crystalline **21** (10.0 g, 53% based on the ratio of **19**). The corresponding 1-benzyloxy isomer was not isolated. **21**: colorless, fine needles, mp 122–124 °C (from ethyl ether); R_f = 0.11 (silica, 10% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2943, 1621, 1506, 1423, 1345, 1299, 1241, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1 H, H6), 7.83 (d, J = 11.0 Hz, 1 H, H1), 7.54–7.29 (m, 6 H, H4 and aromatic), 7.26 (dd, J = 11.0, 3.2 Hz, 1 H, H2), 5.20 (s, 2 H, benzylic), 3.07 (t, J = 7.5 Hz, 2 H, H7 or H10), 2.86

(t, J = 7.0 Hz, 2 H, H7 or H10), 2.03–1.82 (m, 4 H, H8 and H9); MS (FAB^+) m/e (relative intensity) 290 (M + H, 100); HRMS for $C_{20}H_{20}NO$ (M + H) calcd 290.1545, found 290.1540. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.86; H, 6.59; N, 4.66.

3-(Benzyloxy)-7,8,9,10-tetrahydrophenanthridine *N*-Oxide (22). To a solution of **21** (2.12 g, 7.33 mmol) in CH_2Cl_2 (40 mL) cooled in an ice–water bath was added *m*-CPBA (50%, 2.53 g, 7.33 mmol) followed by stirring at 25 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Ethyl ether (50 mL) was added to the residue and the precipitate was collected by filtration to provide *N*-oxide **22** (1.97 g, 88%): pale yellow powder, mp 139–141 °C (from ethyl ether); R_f = 0.40 (silica, 3.2% methanol in dichloromethane); IR ($CHCl_3$) ν_{max} 2947, 1625, 1575, 1509, 1423, 1392, 1280, 1232, 1182, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1 H, H6), 8.22 (d, J = 2.6 Hz, 1 H, H4), 7.87 (d, J = 9.3 Hz, 1 H, H1), 7.53–7.37 (m, 5 H, aromatic), 7.34 (dd, J = 9.3, 2.6 Hz, 1 H, H2), 5.26 (s, 2 H, benzylic), 3.04 (t, J = 6.0 Hz, 2 H, H7 or H10), 2.81 (t, J = 6.0 Hz, 2 H, H7 or H10), 2.02–1.83 (m, 4 H, H8 and H9); MS (FAB^+) m/e (relative intensity) 306 (M + H, 100), 290 (16), 215 (3); HRMS for $C_{20}H_{20}NO_2$ (M + H) calcd 306.1494, found 306.1501.

10-Acetoxy-3-(benzyloxy)-7,8,9,10-tetrahydrophenanthridine (23). A suspension of *N*-oxide **22** (1.879 g, 6.15 mmol) in acetic anhydride (40 mL) was stirred at 25 °C for 14 h. Acetic anhydride was removed in vacuo to give a residue, which was purified by flash column chromatography (silica gel, 33% ethyl ether in benzene) to afford **23** (1.714 g, 80%): white crystalline solid, mp 70–72 °C (from benzene/petroleum ether); R_f = 0.40 (silica, 33% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2952, 1730, 1620, 1508, 1240, 1016 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (s, 1 H, H6), 7.69 (d, J = 9.2 Hz, 1 H, H1), 7.51 (d, J = 2.7 Hz, 1 H, H4), 7.48 (d, J = 6.9 Hz, 2 H, aromatic), 7.43–7.31 (m, 3 H, aromatic), 7.28 (dd, J = 9.2, 2.6 Hz, 1 H, H2), 6.55 (t, J = 3.0 Hz, 1 H, H10), 5.20 (s, 2 H, benzylic), 3.08–2.96 (m, 1 H, H7), 2.88–2.76 (m, 1 H, H7), 2.28–2.20 (m, 1 H, H8 or H9), 2.07 (s, 3 H, $COCH_3$), 2.03–1.85 (m, 3 H, H8 and H9); MS (FAB^+) m/e (relative intensity) 348 (M + H, 100), 288 (12), 258 (3); HRMS for $C_{22}H_{22}NO_3$ (M + H) calcd 348.1600, found 348.1600. Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.04; H, 6.05; N, 3.92.

3-(Benzyloxy)-10-hydroxy-7,8,9,10-tetrahydrophenanthridine (24). To a solution of **23** (1.425 g, 4.10 mmol) in MeOH (25 mL) was added solid K_2CO_3 (120 mg, 0.87 mmol) followed by stirring at 25 °C for 3 h. The solvent was removed in vacuo and the residue was purified by passing it through a short column (silica gel, elution with ethyl ether) to furnish **24** (1.23 g, 98%): white crystalline solid, mp 155–157 °C (from CH_2Cl_2/Et_2O); R_f = 0.12 (silica, 33% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3602, 2948, 1620, 1507, 1455, 1348, 1298, 1242, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1 H, H6), 8.09 (d, J = 9.2 Hz, 1 H, H1), 7.47 (d, J = 6.9 Hz, 2 H, aromatic), 7.42–7.30 (m, 4 H, H4 and aromatic), 7.25 (dd, J = 9.2, 2.9 Hz, 1 H, H2), 5.32 (t, J = 3.5 Hz, 1 H, H10), 5.13 (s, 2 H, benzylic), 2.89–2.65 (m, 2 H, H7), 2.28–2.16 (m, 1 H, H8 or H9), 2.12–1.82 (m, 3 H, H8 and H9); MS (FAB^+) m/e (relative intensity) 306 (M + H, 100), 290 (6); HRMS for $C_{20}H_{20}NO_2$ (M + H) calcd 306.1494, found 306.1495. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.80; H, 6.27; N, 4.50.

3-(Benzyloxy)-10-[(*tert*-butyldimethylsilyl)oxy]-7,8,9,10-tetrahydrophenanthridine (25). To a suspension of **24** (1.10 g, 3.60 mmol) in dry CH_2Cl_2 (10 mL) under ice cooling were added successively 2,6-lutidine (0.59 mL, 5.07 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.99 mL, 4.31 mmol), and the resultant homogeneous solution was then stirred at 25 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, ethyl ether/petroleum ether/benzene, 1:2:2) to give **25** (1.475 g, 98%): colorless, fine needles, mp 123–125 °C (from ethyl ether/petroleum ether); R_f = 0.50 (silica, 33% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2952, 2933, 1621, 1506, 1336, 1295, 1256, 1240, 1174, 1151, 1090, 1025, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1 H, H6), 7.98 (d, J = 9.2 Hz, 1 H, H1), 7.55–7.48 (m, 3 H, H4 and aromatic), 7.46–7.34 (m, 3 H, aromatic), 7.27 (dd, J = 9.2, 2.7 Hz, 1 H, H2), 5.42 (t, J = 2.6 Hz, 1 H, H10), 5.20 (s, 2 H, benzylic), 3.04–2.93 (m, 1 H, H7), 2.87–2.72 (m, 1 H, H7), 2.26–2.05 (m, 2 H, H8 or H9), 1.92–1.76 (m, 2 H, H8 or H9), 0.84 (s, 9 H, $SiC(CH_3)_3$), 0.22 (s, 6 H, $Si(CH_3)_2$); MS (FAB^+) m/e (relative intensity) 420 (M + H, 100), 362 (23), 330 (3), 288 (9); HRMS for $C_{26}H_{34}NO_2Si$ (M + H) calcd 420.2359, found 420.2360.

10-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-7,8,9,10-tetrahydrophenanthridine (26). A solution of **25** (2.00 g, 4.77 mmol) in EtOH (80 mL) was hydrogenated over 10% Pd/C (1.00 g) under a hydrogen atmosphere (ambient pressure) for 4 h. The catalyst was removed by filtration through Celite with elution by 50% Et_3N in THF (1.5 L). The combined filtrate was evaporated in vacuo to provide **26** (1.40 g, 89%): white crystalline solid, mp 248–250 °C dec (from $MeOH/Et_3N$); R_f = 0.48 (silica, 3.2% methanol in dichloromethane); IR (KBr) ν_{max} 3400, 2929, 2857, 1622, 1619, 1611, 1477, 1404, 1249, 1238, 1212, 1088, 1034, 838, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (br s, 1 H, ArO*H*), 8.52 (s, 1 H, H6), 7.91 (d, J = 9.0 Hz, 1 H, H1), 7.20 (d, J = 2.4 Hz, 1 H, H4), 7.14 (dd, J = 9.0, 2.4 Hz, 1 H, H2), 5.43 (s, 1 H, H10), 2.95–2.84 (m, 1 H, H7), 2.79–2.65 (m, 1 H, H7), 2.14–2.04 (m, 1 H, H8 or H9), 2.00–1.87 (m, 1 H, H8 or H9), 1.86–1.65 (m, 2 H, H8 or H9), 0.79 (s, 9 H, $SiC(CH_3)_3$), 0.00 (s, 3 H, $SiCH_3$), –0.02 (s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 330 (M + H, 100), 272 (14), 198 (9); HRMS for $C_{19}H_{28}NO_2Si$ (M + H) calcd 330.1889, found 330.1890. Anal. Calcd for $C_{19}H_{27}NO_2Si$: C, 69.26; H, 8.26; N, 4.25. Found: C, 69.10; H, 8.17; N, 4.16.

3-(Trimethylacetyl)-1,3-thiazolidine-2-thione (27). To a suspension of NaH (60%, 1.06 g, 26.5 mmol) in dry THF (10 mL) cooled at 0 °C was added a solution of 2-mercaptothiazoline (**11**, 3.0 g, 25.17 mmol) in dry THF (20 mL) followed by stirring at 0 °C for 10 min. To the mixture was added trimethylacetyl chloride (3.1 mL, 25.17 mmol), and the resultant mixture was then stirred at 25 °C for 2 h. Water was added to the reaction mixture, followed by extraction with ethyl acetate (100 mL), drying over anhydrous Na_2SO_4, and removal of the solvent in vacuo to give a crude product. Flash column chromatography (silica gel, 17% ethyl ether in petroleum ether) afforded **27** (4.68 g, 91%): pale yellow prisms; mp 99–102 °C (from ethyl ether/petroleum ether); R_f = 0.19 (silica, 17% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2980, 1808, 1738, 1480, 1463, 1396, 1388, 1286, 1251, 1139, 1044, 1003, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21 (t, J = 7.3 Hz, 2 H, NCH_2CH_2S), 3.51 (t, J = 7.3 Hz, 2 H, NCH_2CH_2S), 1.41 (s, 9 H, $C(CH_3)_3$); MS (FAB^+) m/e (relative intensity) 204 (M + H, 100), 120 (27); HRMS for $C_8H_{14}NOS_2$ (M + H) calcd 204.0157, found 204.0500.

10-[(*tert*-Butyldimethylsilyl)oxy]-3-(trimethylacetoxy)-7,8,9,10-tetrahydrophenanthridine (28). To a suspension of **26** (1.28 g, 3.88 mmol) in dry THF (50 mL) cooled in an ice–water bath was added NaH (60%, 163 mg, 4.08 mmol) followed by stirring for 10 min. A yellow-colored solution of **27** (0.789 g, 3.88 mmol) in dry THF (10 mL) was added, and the mixture was then stirred at 25 °C for 5 min. The reaction mixture was quenched with water, extracted with ethyl acetate (50 mL), washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a residue. Flash column chromatography (silica gel, 20% ethyl ether in benzene) provided pure **28** (1.59 g, 99%): white crystalline solid, mp 125–126.5 °C (from ethyl ether/petroleum ether); R_f = 0.49 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2957, 2934, 1750, 1261, 1131, 1116, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1 H, H6), 7.98 (d, J = 9.1 Hz, 1 H, H1), 7.67 (d, J = 2.1 Hz, 1 H, H4), 7.21 (dd, J = 9.1, 2.1 Hz, 1 H, H2), 5.33 (t, J = 2.9 Hz, 1 H, H10), 2.90 (br dd, J = 17.2, 3.3 Hz, 1 H, H7), 2.72 (ddd, J = 17.2, 11.2, 5.7 Hz, 1 H, H7), 2.17–1.96 (m, 2 H, H8 or H9), 1.83–1.67 (m, 2 H, H8 or H9), 1.31 (s, 9 H, $COC(CH_3)_3$), 0.74 (s, 9 H, $SiC(CH_3)_3$), 0.12 (s, 6 H, $Si(CH_3)_2$); MS (FAB^+) m/e (relative intensity) 414 (M + H, 100), 357 (9), 330 (12), 283 (5), 198 (10); HRMS for $C_{24}H_{36}NO_3Si$ (M + H) calcd 414.2464, found 414.2484. Anal. Calcd for $C_{24}H_{35}NO_3Si$: C, 69.69; H, 8.53; N, 3.39. Found: C, 69.68; H, 8.44; N, 3.23.

10-[(*tert*-Butyldimethylsilyl)oxy]-3-[(2-nitrobenzyl)oxy]-7,8,9,10-tetrahydrophenanthridine (29). To a suspension of **26** (1.00 g, 3.03 mmol) in dry THF (20 mL) cooled in an ice–water bath was added NaH (60%, 128 mg, 3.19 mmol) followed by stirring for 10 min. To the resultant solution were added 2-nitrobenzyl bromide (0.689 g, 3.19 mmol) and tetra-*n*-butylammonium iodide (0.11 g, 0.3 mmol), and the mixture was then stirred at 25 °C for 1 h. Water was added to the reaction mixture followed by extraction with ethyl acetate (50 mL), washing with brine, drying over anhydrous Na_2SO_4, and concentration in vacuo to give a crude product. Flash column chromatography (silica gel, 20% ethyl ether in benzene) afforded **29** (1.27 g, 90%): colorless crystalline solid, mp 144.5–146 °C (from ethyl ether/petroleum ether); R_f = 0.33 (silica, 20% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2953, 2933, 1623, 1528, 1343, 1090, 1027, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1 H, H6), 8.21 (dd, J = 8.0, 0.9 Hz, 1 H, aromatic), 8.01 (d, J = 9.2 Hz, 1 H, H1), 7.92 (d, J = 7.8 Hz, 1 H, aromatic), 7.68 (dt, J = 7.8, 0.9 Hz, 1 H, aromatic), 7.50 (t, J = 8.0 Hz, 1 H, aromatic), 7.44 (d, J = 2.6 Hz, 1 H, H4), 7.32 (dd, J = 9.2, 2.6 Hz, 1 H, H2), 5.66 (s, 2 H, benzylic), 5.42 (t, J = 3.1 Hz, 1 H, H10), 2.97 (br dd, J = 14.0, 4.0 Hz, 1 H, H7), 2.86–2.72 (m, 1 H, H7), 2.25–2.15 (m, 2 H, H8 or H9), 1.90–1.80 (m, 2 H, H8 or H9), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.22 (s, 6 H, $Si(CH_3)_2$); MS (FAB^+) m/e (relative intensity) 465 (M + Cs, 100), 407 (19), 330 (26), 198 (17), 136 (18); HRMS for $C_{26}H_{32}N_2O_4SiCs$ (M + Cs) calcd 465.2210, found 465.2210. Anal. Calcd for $C_{26}H_{32}N_2O_4Si$: C, 67.21; H, 6.94; N, 6.03. Found: C, 67.31; H, 6.91; N, 5.96.

10-[(*tert*-Butyldimethylsilyl)oxy]-3-methoxy-7,8,9,10-tetrahydrophenanthridine (31). Prepared from **8** by following the procedures described for **25**. **31**: colorless prisms, mp 105–107 °C (from ethyl ether); R_f = 0.53 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 2951, 2933, 2857, 1624, 1508, 1472, 1336, 1257, 1090, 1033, 975, 870, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1 H, H6), 7.95 (d, J = 9.2 Hz, 1 H, H1), 7.41 (d, J = 2.6 Hz, 1 H, H4), 7.19 (dd, J = 9.2, 2.6 Hz, 1 H, H2), 5.41 (t, J = 3.1 Hz, 1 H, H10), 3.94 (s, 3 H, OCH_3), 3.20–2.92 (m, 1 H, H7), 2.86–2.72 (m, 1 H, H7), 2.27–2.03 (m, 2 H, H8 or 9), 1.90–1.75 (m, 2 H, H8 or H9), 0.81 (s, 9 H, $SiC(CH_3)_3$), 0.20 (s, 6 H, $Si(CH_3)_2$); MS (FAB^+) m/e (relative intensity) 344 (M + H, 100), 286 (15), 212 (21); HRMS for $C_{20}H_{30}NO_2Si$ (M + H) calcd 344.2046, found 344.2075. Anal. Calcd for $C_{20}H_{29}NO_2Si$: C, 69.92; H, 8.51; N, 4.08. Found: C, 69.99; H, 8.55; N, 4.22.

Addition of Ethynylmagnesium Bromide to Quinoline Derivatives. *N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6-ethynyl-3-(trimethylacetoxy)-5,6,7,8,9,10-hexahydrophenanthridine (36). Representative Procedure. To a solution of **28** (5.066 g, 12.25 mmol) in dry THF (50 mL) cooled in a dry ice/acetone bath (−78 °C) were added ethynylmagnesium bromide (0.5 M in THF, 36.8 mL, 18.40 mmol) and phenyl chloroformate (2.3 mL, 18.33 mmol). The reaction mixture was then warmed to 0 °C over 15 min, quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate (200 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 33% ethyl ether in benzene) gave **36** (6.68 g, 97%) as a 69:31 mixture of trans and cis isomers (by ^1H NMR). **36**: white foam; R_f = 0.61 (silica, 20% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3306, 2957, 2933, 1746 (shoulder), 1731 (shoulder), 1720, 1500, 1384, 1311, 1201, 1183, 1119, 1025, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.6 Hz, 0.31 H, H1), 7.44–7.34 (m, 3.69 H, aromatic), 7.28–7.17 (m, 3.31 H, aromatic), 6.92 (dd, J = 8.6, 2.3 Hz, 0.69 H, H2), 5.66 (d, J = 2.3 Hz, 0.69 H, H6), 5.61 (d, J = 2.0 Hz, 0.31 H, H6), 4.96 (t, J = 3.0 Hz, 0.69 H, H10), 4.64 (br s, 0.31 H, H10), 2.53–1.64 (m, 7 H, acetylenic, H7, H8 and H9), 1.33 and 1.32 (s, 9 H, $COC(CH_3)_3$), 0.93 (s, 2.79 H, $SiC(CH_3)_3$), 0.82 (s, 6.21 H, $SiC(CH_3)_3$), 0.25 (s, 0.93 H, $SiCH_3$), 0.19 (s, 0.93 H, $SiCH_3$), 0.10 (s, 2.07 H, $SiCH_3$), 0.09 (s, 2.07 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 692 (M + Cs, 68), 534 (11), 502 (52), 428 (29), 222 (12); HRMS for $C_{33}H_{41}NO_5SiCs$ (M + Cs) calcd 692.1808, found 692.1849.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6-ethynyl-3-methoxy-5,6,7,8,9,10-hexahydrophenanthridine (33).** Prepared from **31** in 99% yield as an 84:16 mixture. **33**: white foam; R_f = 0.25 (silica, 9% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3303, 2954, 2931, 1703, 1576, 1432, 1302, 1288, 1259, 1073, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–6.70 (m, 8 H, aromatic), 5.64 (d, J = 2.1 Hz, 0.84 H, H6), 5.59 (br, 0.16 H, H6), 4.94 (br, 0.84 H, H10), 4.64 (br, 0.16 H, H10), 3.81 (s, 3 H, OCH_3), 2.50–1.60 (m, 7 H, acetylenic, H7, H8, and H9), 0.93 (s, 1.44 H, $SiC(CH_3)_3$), 0.82 (s, 7.56 H, $SiC(CH_3)_3$), 0.26 (s, 0.48 H, $SiCH_3$), 0.18 (s, 0.48 H, $SiCH_3$), 0.09 (s, 2.52 H, $SiCH_3$), 0.08 (s, 2.52 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 622 (M + Cs, 23), 464 (34), 432 (82), 358 (52), 236 (27); HRMS for $C_{29}H_{35}NO_4SiCs$ (M + Cs) calcd 622.1390, found 622.1390.

***N*-[(Phenyloxy)carbonyl]-3-(benzyloxy)-10-[(*tert*-butyldimethylsilyl)oxy]-6-ethynyl-5,6,7,8,9,10-hexahydrophenanthridine (34).** Prepared from **25** in 90% yield as a 79:21 mixture. **34**: white foam; R_f = 0.30 (silica, 9% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3305, 2951, 2931, 1716, 1611, 1506, 1385, 1310, 1094, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–6.78 (m, 13 H, aromatic), 5.65 (d, J = 2.0 Hz, 0.79 H, H6), 5.60 (br s, 0.21 H, H6), 5.06 (s, 2 H, benzylic), 4.95 (br, 0.79 H, H10), 4.64 (br, 0.21 H, H10), 2.50–1.60 (m, 7 H, acetylenic, H7, H8, and H9), 0.94 (s, 1.89 H, $SiC(CH_3)_3$), 0.82 (s, 7.11 H, $SiC(CH_3)_3$), 0.26 (s, 0.63 H, $SiCH_3$), 0.19 (s, 0.63 H, $SiCH_3$), 0.10 (s, 2.37 H, $SiCH_3$), 0.08 (s, 2.37 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 698 (M + Cs, 26), 540 (12), 508 (35), 434 (19); HRMS for $C_{35}H_{39}NO_4SiCs$ (M + Cs) calcd 698.1703, found 698.1754. Anal. Calcd for $C_{35}H_{39}NO_4Si$: C, 74.30; H, 6.95; N, 2.48. Found: C, 74.30; H, 6.99; N, 2.55.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6-ethynyl-3-[(2-nitrobenzyl)oxy]-5,6,7,8,9,10-hexahydrophenanthridine (35).** Prepared from **29** in 98% yield as a 79:21 mixture. **35**: white foam; R_f = 0.33 (silica, 20% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3306, 3018, 2952, 2933, 1717, 1612, 1527, 1505, 1385, 1344, 1306, 1199, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 7.8 Hz, 1 H, aromatic), 7.89 (d, J = 7.8 Hz, 1 H, aromatic), 7.62 (t, J = 7.2 Hz, 1 H, aromatic), 7.59 (d, J = 8.7 Hz, 0.21 H, H1), 7.46–7.12 (m, 7.79 H, H1, H4, and aromatic), 6.86–6.79 (m, 1 H, H2), 5.64 (d, J = 1.8 Hz, 0.79 H, H6), 5.59 (br s, 0.21 H, H6), 5.51 (s, 2 H, benzylic), 4.95 (br s, 0.79 H, H10), 4.64 (br s, 0.21 H, H10), 2.51–1.55 (m, 7 H, acetylenic, H7, H8, and H9), 0.94 (s, 1.89 H, $SiC(CH_3)_3$), 0.82 (s, 7.11 H, $SiC(CH_3)_3$), 0.26 (s, 0.63 H, $SiCH_3$), 0.19 (s, 0.63 H, $SiCH_3$), 0.09 (s, 2.37 H, $SiCH_3$), 0.08 (s, 2.37 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 743 (M + Cs, 78), 610 (11), 553 (32), 479 (24), 222 (9), 133 (100); HRMS for $C_{35}H_{38}N_2O_6SiCs$ (M + Cs) calcd 743.1553, found 743.1554. Anal. Calcd for $C_{35}H_{38}N_2O_6Si$: C, 68.83; H, 6.27; N, 4.59. Found: C, 68.98; H, 6.38; N, 4.42.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6a,10a-epoxy-6-ethynyl-3-(trimethylacetoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (38).** To a solution of **36** (6.4 g, 12.25 mmol) in CH_2Cl_2 (100 mL) cooled at 0 °C was added *m*-CPBA (50%, 8.46 g, 24.51 mmol) followed by stirring at 25 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (silica gel, benzene) to furnish **38** (7.0 g, 99%) as a 71:29 diastereomeric mixture. Diastereomerically pure samples of **38** were obtained by preparative TLC (silica gel plate, benzene). **38, major isomer**: white foam; R_f = 0.38 (silica, benzene); IR ($CHCl_3$) ν_{max} 3307, 2956, 1748 (shoulder), 1724, 1382, 1306, 1202, 1183, 1119, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.6 Hz, 1 H, H1), 7.42–7.11 (m, 6 H, H4 and aromatic), 6.99 (d, J = 8.6 Hz, 1 H, H2), 5.57 (br s, 1 H, H6), 4.77 (dd, J = 9.8, 5.7 Hz, 1 H, H10), 2.33 (dd, J = 13.9, 5.9 Hz, 1 H, H7), 1.96–1.81 (m, 2 H, H7 and H8 or H9), 1.80–1.53 (m, 3 H, H8 and H9), 1.34 (s, 9 H, $COC(CH_3)_3$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 0.21 (s, 3 H, $SiCH_3$), 0.07 (br s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 576 (M + H, 25), 518 (100), 444 (8), 330 (7); HRMS for $C_{33}H_{42}NO_6Si$ (M + H) calcd 576.2781, found 576.2760. Anal. Calcd for $C_{33}H_{41}NO_6Si$: C, 68.84; H, 7.18; N, 2.43. Found: C, 69.04; H, 7.31; N, 2.35. **38, minor isomer**: colorless gum; R_f = 0.27 (silica, benzene); IR ($CHCl_3$) ν_{max} 3306, 2958, 2934, 1748 (shoulder), 1721, 1683, 1495, 1382, 1307, 1201, 1178, 1122, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.6 Hz, 1 H, H1), 7.39–7.11 (m, 6 H, H4 and aromatic), 6.96 (dd, J = 8.6, 2.4 Hz, 1 H, H2), 5.53 (d, J = 2.1 Hz, 1 H, H6), 4.90 (d, J = 2.6 Hz, 1 H, H10), 2.49–2.37 (m, 1 H, H7), 2.09–1.82 (m, 4 H, H7, H8, and H9), 1.77–1.66 (m, 1 H, H8 or H9), 1.33 (s, 9 H, $COC(CH_3)_3$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 0.26 (s, 3 H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 576 (M + H, 92), 559 (34), 529 (22), 518 (100), 444 (86), 360 (8), 266 (13), 238 (29); HRMS for $C_{33}H_{42}NO_6Si$ (M + H) calcd 576.2781, found 576.2799.

***N*-[(Phenyloxy)carbonyl]-6-ethynyl-10-oxo-3-(trimethylacetoxy)-5,6,7,8,9,10-hexahydrophenanthridine (40).** To a solution of **38** (7.0 g, 12.16 mmol) in wet $CHCl_3$ (100 mL) was added $BF_3{\cdot}OEt_2$ (7.48 mL, 60.82 mmol). The mixture was stirred at 25 °C (1.5 h) until TLC indicated complete conversion. Silica gel (10.0 g) was added to the reaction mixture followed by stirring at 25 °C for another 12 h. Silica gel was filtered off using Celite and washed with ethyl ether (100 mL). The solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, 10% ethyl ether in benzene) to provide **40** (3.91 g, 73%). A more polar component (ca. 1.0 g) was also isolated; this compound was not converted to **40** in the presence of silica gel after prolonged reaction time. **40**: white crystalline solid, mp 163–165 °C dec (from ethyl ether/petroleum ether); R_f = 0.44 (silica, 10% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3305, 2977, 1737 (shoulder), 1720, 1705, 1684, 1607, 1577, 1495, 1382, 1306, 1201, 1178, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 8.7 Hz, 1 H, H1), 7.43–7.35 (m, 3 H, H4 and aromatic), 7.28–7.16 (m, 3 H, aromatic), 6.98 (dd, J = 8.7, 2.4 Hz, 1 H, H2), 5.86 (d, J = 2.4 Hz, 1 H, H6), 2.87–2.51 (m, 4 H, H7 and H9), 2.26 (d, J = 2.4 Hz, 1 H, acetylenic), 2.24–2.08 (m, 2 H, H8), 1.33 (s, 9 H, $COC(CH_3)_3$); MS (FAB^+) m/e (relative intensity) 444 (M + H, 82), 350 (15), 266 (20), 238 (15); HRMS for $C_{27}H_{26}NO_5$ (M + H) calcd 444.1811, found 444.1842. Anal. Calcd for $C_{27}H_{25}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 73.00; H, 5.70; N, 3.16.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-ethynyl-10-oxo-3-(trimethylacetoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (41).** To a mixture of **40** (2.15 g, 4.85 mmol) in CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) cooled at 0 °C was added *m*-CPBA (50%, 2.01 g, 5.82 mmol) followed by stirring at 25 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Flash column chromatography of the residue (silica gel, 10% ethyl ether in benzene) afforded **41** (1.5 g, 67%): white crystalline solid; mp 164–166 °C (from ethyl ether/petroleum ether); R_f = 0.56 (silica, 10% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3306, 2976, 1749 (shoulder), 1721, 1494, 1379, 1305, 1203, 1181, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 8.8 Hz, 1 H, H1), 7.41–7.33 (m, 3 H, H4 and aromatic), 7.25–7.10 (m, 3 H, aromatic), 7.00 (dd, J = 8.8, 2.3 Hz, 1 H, H2), 5.73 (d, J = 2.3 Hz, 1 H, H6), 2.75 (ddd, J = 15.6, 5.2, 5.2 Hz, 1 H, H9), 2.60 (ddd, J = 15.6, 10.0, 6.5 Hz, 1 H, H9), 2.38–2.22 (m, 3 H, acetylenic and H7), 2.08–1.85 (m, 2 H, H8), 1.34 (s, 9 H, $COC(CH_3)_3$); MS *m/e* (relative intensity) 460 (M + H,

91), 376 (16), 255 (4), 215 (23), 154 (100); HRMS for $C_{27}H_{26}NO_6$ (M + H) calcd 460.1760, found 460.1760.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-10-oxo-3-(trimethylacetoxy)-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (43).** A mixture of $Pd(PPh_3)_4$ (185 mg, 0.16 mmol), vinyl chloride **42** (0.776 g, 4.89 mmol), and diethylamine (0.51 mL, 4.93 mmol) in degassed benzene (5 mL) was stirred at 25 °C for 15 min. The resultant solution was added to a mixture of **41** (1.50 g, 3.26 mmol) and CuI (124 mg, 0.65 mmol) in degassed benzene (15 mL) via a syringe followed by stirring at 25 °C for 1 h. The reaction mixture was quenched by saturated aqueous NH_4Cl, extracted with ethyl ether (80 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash column chromatography (silica gel, 25% ethyl ether in petroleum ether) provided **43** (0.606 g, 32%): white foam; R_f = 0.43 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2964, 1721, 1494, 1378, 1305, 1270, 1253, 1202, 1181, 1122, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 8.7 Hz, 1 H, H1), 7.44–7.10 (m, 6 H, H4 and aromatic), 6.99 (dd, J = 8.7, 2.4 Hz, 1 H, H2), 5.98 (d, J = 1.5 Hz, 1 H, H6), 5.84 (d, J = 11.1 Hz, 1 H, olefinic), 5.69 (br d, J = 11.1 Hz, 1 H, olefinic), 2.81–2.66 (m, 2 H, H9), 2.41–2.26 (m, 2 H, H7), 2.10–1.86 (m, 2 H, H8), 1.33 (s, 9 H, $COC(CH_3)_3$), 0.22 (s, 9 H, $SiC(CH_3)_3$); MS (FAB^+) m/e (relative intensity) 582 (M + H, 100), 525 (13), 460 (48), 406 (8), 360 (6), 320 (8), 279 (25), 246 (5); HRMS for $C_{34}H_{36}NO_6Si$ (M + H) calcd 582.2312, found 582.2322.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-[3(*Z*)-hexene-1,5-diynyl]-10-oxo-3-(trimethylacetoxy)-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (44). Method A.** To a solution of **43** (0.38 g, 0.65 mmol) in THF/EtOH/H_2O (1:1:1, 12 mL) cooled at 0 °C was added silver nitrate (0.442 g, 2.60 mmol) followed by stirring at 25 °C for 1 h. Potassium cyanide (0.296 g, 4.55 mmol) was added to the reaction mixture followed by stirring at 25 °C for another 10 min. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 33% ethyl ether in petroleum ether) to give the product **44** (0.22 g, 66%).

Method B. To a mixture of **48** (3.50 g, 7.09 mmol) in CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (10 mL) cooled at 0 °C was added *m*-CPBA (50%, 2.94 g, 8.51 mmol) followed by stirring at 25 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 33% ethyl ether in petroleum ether) afforded **44** (1.12 g, 45% based on 71% conversion of **48**; 1.0 g of **48** was recovered): white foam; R_f = 0.60 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3304, 2976, 1748 (shoulder), 1720, 1495, 1377, 1305, 1202, 1181, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.7 Hz, 1 H, H1), 7.42–7.33 (m, 3 H, H4 and aromatic), 7.27–7.10 (m, 3 H, aromatic), 6.99 (dd, J = 8.8, 2.2 Hz, 1 H, H2), 5.94 (s, 1 H, H6), 5.80 (s, 2 H, olefinic), 3.30 (s, 1 H, acetylenic), 2.82–2.63 (m, 2 H, H9), 2.41–2.27 (m, 2 H, H7), 2.09–1.88 (m, 2 H, H8), 1.33 (s, 9 H, $COC(CH_3)_3$); MS (FAB^+) m/e (relative intensity) 510 (M + H, 38), 434 (23), 350 (4), 307 (14), 215 (11); HRMS for $C_{31}H_{28}NO_6$ (M + H) calcd 510.1917, found 510.1966.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-3-(trimethylacetoxy)-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,7,8,9,10-hexahydrophenanthridine (45).** A mixture of $Pd(PPh_3)_4$ (1.65 g, 1.43 mmol), vinyl chloride **42** (5.80 g, 36.6 mmol), and *n*-propylamine (3.5 mL, 42.9 mmol) in degassed benzene (100 mL) was stirred at 25 °C for 15 min. The resultant solution was added to a mixture of **36** (69:31 mixture of stereomers, 16.0 g, 28.6 mmol) and CuI (1.09 g, 5.7 mmol) in degassed benzene (300 mL) via a syringe followed by stirring at 25 °C for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ethyl ether (300 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel, 10% ethyl ether in petroleum ether) gave **45** (13.0 g, 67%) as a mixture of diastereomers. **45, major isomer**: white foam, R_f = 0.44 (silica, 10% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2958, 2932, 1748 (shoulder), 1730 (shoulder), 1718, 1494, 1383, 1310, 1181, 1118, 1028, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.16 (m, 7 H, H1, H4, and aromatic), 6.88 (dd, J = 8.6, 2.3 Hz, 1 H, H2), 5.87 (s, 1 H, H6), 5.74 and 5.71 (AB q, J = 11.1 Hz, 2 H, olefinic), 4.93 (br s, 1 H, H10), 2.59–2.46 (m, 1 H, H7), 2.23 (br d, J = 18.2 Hz, 1 H, H7), 2.00–1.82 (m, 3 H, H8 and H9), 1.74–1.61 (m, 1 H, H8 or H9), 1.30 (s, 9 H, $COC(CH_3)_3$), 0.80 (s, 9 H, $SiC(CH_3)_3$), 0.16 (s, 9 H, $Si(CH_3)_3$), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity), 814 (M + Cs, 100), 681 (9), 624 (42), 588 (7), 534 (22); HRMS for $C_{40}H_{51}NO_5Si_2Cs$ (M + Cs) calcd 814.2360, found 814.2360. **45, minor isomer**: white foam; R_f = 0.40 (silica, 10% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2958, 2934, 1745 (shoulder), 1727 (shoulder), 1717, 1494, 1382, 1310, 1182, 1118, 1018, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 8.6 Hz, 1 H, H1), 7.50 (br s, 1 H, H4), 7.40–7.32 (m, 2 H, aromatic), 7.24–7.15 (m, 3 H, aromatic), 6.89 (dd, J = 8.6, 2.3 Hz, 1 H, H2), 5.83 (s, 1 H, H6), 5.75 (s, 2 H, olefinic), 4.63 (br s, 1 H, H10), 2.55 (dd, J = 17.7, 4.8 Hz, 1 H, H7), 2.27–1.95 (m, 3 H, H7 and H8 or H9), 1.76–1.53 (m, 2 H, H8 or H9), 1.29 (s, 9 H, $COC(CH_3)_3$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.22 (s, 3 H, $SiCH_3$), 0.17 (s, 9 H, $Si(CH_3)_3$), 0.16 (s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 814 (M + Cs, 100), 681 (45), 624 (27), 588 (26), 534 (60); HRMS for $C_{40}H_{51}NO_5Si_2Cs$ (M + Cs) calcd 814.2360, found 814.2361.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-6a,10a-epoxy-3-(trimethylacetoxy)-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (46).** To a solution of **45** (mixture of diastereomers, 13.0 g, 19.06 mmol) in CH_2Cl_2 (100 mL) cooled at 0 °C was added *m*-CPBA (50%, 7.9 g, 22.98 mmol) followed by stirring at 25 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 10% ethyl ether in petroleum ether) to afford **46** (9.5 g, 71%) as a mixture of diastereomers. **46, major isomer**: white foam; R_f = 0.38 (silica, 10% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2958, 2933, 1730 (shoulder), 1721, 1382, 1307, 1118, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 1 H, H1), 7.40–7.10 (m, 6 H, H4 and aromatic), 6.95 (dd, J = 8.6, 1.9 Hz, 1 H, H2), 5.84–5.62 (m, 3 H, H6 and olefinic), 4.76 (dd, J = 9.6, 5.7 Hz, 1 H, H10), 2.45 (dd, J = 14.5, 4.6 Hz, 1 H, H7), 1.97–1.57 (m, 5 H, H7, H8, and H9), 1.31 (br s, 9 H, $COC(CH_3)_3$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 0.19 (s, 12 H, $Si(CH_3)_3$ and $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 830 (M + Cs, 100), 681 (6), 624 (9), 534 (11); HRMS for $C_{40}H_{51}NO_6Si_2Cs$ (M + Cs) calcd 830.2309, found 830.2361. **46, minor isomer**: white foam; R_f = 0.22 (silica, 10% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2958, 2933, 1747 (shoulder), 1721, 1494, 1381, 1306, 1256, 1181, 1118, 909, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.7 Hz, 1 H, H1), 7.40–7.10 (m, 6 H, H4 and aromatic), 6.95 (dd, J = 8.7, 2.5 Hz, 1 H, H2), 5.80–5.60 (m, 3 H, H6 and olefinic), 4.89 (d, J = 2.4 Hz, 1 H, H10), 2.66–2.50 (m, 1 H, H7), 2.18–1.63 (m, 5 H, H7, H8, and H9), 1.31 (br s, 9 H, $COC(CH_3)_3$), 0.94 and 0.79 (s, 9 H, $SiC(CH_3)_3$), 0.23, 0.21, and 0.19 (s, 9 H, $Si(CH_3)_3$), 0.14 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$); MS (FAB^+) m/e (relative intensity) 830 (M + Cs, 100), 708 (8), 640 (13), 534 (7); HRMS for $C_{40}H_{51}NO_6Si_2Cs$ (M + Cs) calcd 830.2309, found 830.2296.

***N*-[(Phenyloxy)carbonyl]-10-oxo-3-(trimethylacetoxy)-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,7,8,9,10-hexahydrophenanthridine (47).** To a solution of **46** (9.5 g, 13.6 mmol) in wet $CHCl_3$ (150 mL) cooled at 0 °C was added $BF_3{\cdot}OEt_2$ (8.4 mL, 68.0 mmol) followed by stirring at 25 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (400 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was then dissolved in THF (50 mL) and treated with 48% aqueous HBr (5 mL) at 25 °C for 40 min with stirring. The reaction mixture was diluted with ethyl ether (400 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 33% ethyl ether in petroleum ether) gave **47** (2.80 g, 34%) and **48** (1.30 g, 18%). **47**: white foam; R_f = 0.52 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2970, 1719, 1681, 1606, 1494, 1381, 1307, 1179, 1123, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.7 Hz, 1 H, H1), 7.45–7.18 (m, 6 H, H4 and aromatic), 6.98 (dd, J = 8.7, 2.4 Hz, 1 H, H2), 6.11 (d, J = 0.9 Hz, 1 H, H6), 5.84 (d, J = 11.1 Hz, 1 H, olefinic), 5.72 (dd, J = 11.1, 1.7 Hz, 1 H, olefinic), 2.90 (dt, J = 18.9, 4.5 Hz, 1 H, H9), 2.77–2.53 (m, 3 H, H7 and H9), 2.24–2.12 (m, 2 H, H8), 1.34 (s, 9 H, $COC(CH_3)_3$), 0.21 (s, 9 H, $Si(CH_3)_3$); MS (FAB^+) m/e (relative intensity) 698 (M + Cs, 100), 565 (6); HRMS for $C_{34}H_{35}NO_5SiCs$ (M + Cs) calcd 698.1339, found 698.1339.

***N*-[(Phenyloxy)carbonyl]-6-[3(*Z*)-hexene-1,5-diynyl]-10-oxo-3-(trimethylacetoxy)-5,6,7,8,9,10-hexahydrophenanthridine (48).** To a solution of **47** (2.80 g, 4.95 mmol) in THF/EtOH/H_2O (1:1:1, 300 mL) was added silver nitrate (3.36 g, 19.8 mmol) followed by stirring at 25 °C for 1 h. Potassium cyanide (2.26 g, 34.65 mmol) was added to the reaction mixture followed by stirring at 25 °C for another 10 min. The reaction mixture was diluted with CH_2Cl_2 (300 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 50% ethyl ether in petroleum ether) to furnish **48** (2.20 g, 90%): white foam; R_f = 0.43 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3302, 2959, 1740 (shoulder), 1725 (shoulder), 1719, 1680, 1606, 1494, 1381, 1307,

1177, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 1 H, H1), 7.50–7.17 (m, 6 H, H4 and aromatic), 6.95 (dd, J = 8.8, 1.1 Hz, 1 H, H2), 6.06 (s, 1 H, H6), 5.79 (s, 2 H, olefinic), 3.32 (d, J = 1.0 Hz, 1 H, acetylenic), 2.86 (dt, J = 18.9, 4.5 Hz, 1 H, H9), 2.76–2.51 (m, 3 H, H7 and H9), 2.23–2.16 (m, 2 H, H8), 1.33 (s, 9 H, COC(CH_3)$_3$); MS (FAB$^+$) m/e (relative intensity) 626 (M + Cs, 16), 418 (13); HRMS for $C_{31}H_{27}NO_5Cs$ (M + Cs) calcd 626.0944, found 626.0975.

Dynemicin A Model Compound 49. To a solution of **44** (1.12 g, 2.20 mmol) in dry toluene (220 mL, 0.01 M) cooled in a dry ice/acetone (−78 °C) bath was added LDA (1.5 M in cyclohexane, 1.47 mL, 2.20 mmol) followed by stirring at −78 °C for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl at −78 °C and allowed to warm to room temperature. Saturated aqueous $NaHCO_3$ was added to the mixture, followed by extraction with ethyl ether (200 mL), drying over anhydrous Na_2SO_4, and concentration in vacuo. The residue was flash column chromatographed (silica gel, 40% ethyl ether in petroleum ether) to afford crystalline **49** (900 mg, 80%): colorless platelike crystals, mp 181–183 °C dec (from ethyl ether, 1:1 complex with ethyl ether as determined by ^{1}H NMR, X-ray, and elemental analysis); R_f = 0.44 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3593, 2979, 1748 (shoulder), 1723, 1494, 1382, 1306, 1196, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J = 8.7 Hz, 1 H, aromatic), 7.41–7.32 (m, 2 H, aromatic), 7.25–7.13 (m, 4 H, aromatic), 6.96 (dd, J = 8.7, 2.4 Hz, 1 H, aromatic), 5.84 (d, J = 9.9 Hz, 1 H, olefinic), 5.69 (dd, J = 9.9, 1.6 Hz, 1 H, olefinic), 5.53 (d, J = 1.6 Hz, 1 H, NC*H*), 2.43 (br s, 1 H, O*H*), 2.32 (dd, J = 14.7, 7.8 Hz, 1 H, CH_2), 2.25–2.09 (m, 2 H, CH_2), 2.08–1.86 (m, 2 H, CH_2), 1.78–1.67 (m, 1 H, CH_2), 1.32 (s, 9 H, COC(CH_3)$_3$); MS (FAB$^+$) m/e (relative intensity) 510 (M + H, 100), 416 (28), 332 (11), 288 (17), 258 (11); HRMS for $C_{31}H_{28}NO_6$ (M + H) calcd 510.1917, found 510.1920. Anal. Calcd for $C_{31}H_{27}NO_6 \cdot (CH_3CH_2)_2O$: C, 72.02; H, 6.39; N, 2.40. Found: C, 72.02; H, 6.43; N, 2.38.

X-ray Crystal Structure Analysis of 49. A colorless platelike crystal of **49** formed from ethyl ether, having approximate dimensions of 0.14 × 0.38 × 0.75 mm, was mounted on a glass fiber along the longest dimension. Data collections were performed on a Siemens R3m/V diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Crystal data were obtained as follows: a = 9.140 (5) Å, b = 13.017 (5) Å, c = 14.645 (7) Å, α = 65.31 (3)°, β = 82.80 (4)°, γ = 76.50 (4)°; triclinic unit cell with space group $P\bar{1}$ (No. 2 C_i^1), Z = 2; calculated density 1.260 mg/m^3. Experimental and crystal details are available as supplementary material. Figure 1 is a computer-generated perspective drawing of **49** from the final X-ray coordinates.

Deoxygenation of 49. Compound 50. A mixture of **49** (120 mg, 0.235 mmol), thiocarbonyldiimidazole (126 mg, 0.705 mmol), and DMAP (14.4 mg, 0.118 mmol) in CH_2Cl_2 (1 mL) was stirred at 25 °C for 22 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography (silica gel, 66% ethyl ether in petroleum ether) to afford **50** (85 mg, 58%), together with recovery of **49** (40 mg, 33%). **50**: pale yellow solid, mp >320 °C dec; R_f = 0.24 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2979, 2932, 1749 (shoulder), 1725, 1494, 1386, 1334, 1307, 1286, 1247, 1231, 1195, 1117, 1104, 967 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (br s, 1 H, imidazole), 7.65 (d, J = 8.9 Hz, 2 H, imidazole and aromatic), 7.44–7.18 (m, 6 H, imidazole and aromatic), 7.05 (br s, 1 H, aromatic), 6.90 (dd, J = 8.7, 2.4 Hz, 1 H, aromatic), 5.95 (d, J = 10.1 Hz, 1 H, olefinic), 5.76 (dd, J = 10.1, 1.6 Hz, 1 H, olefinic), 5.60 (d, J = 1.6 Hz, 1 H, NC*H*), 3.09 (br d, J = 12.1 Hz, 1 H, CH_2), 2.50–2.05 (m, 4 H, CH_2CH_2), 1.92–1.78 (m, 1 H, CH_2), 1.31 (s, 9 H, COC(CH_3)$_3$); MS (FAB$^+$) m/e (relative intensity) 752 (M + Cs, 56), 642 (10), 560 (15), 492 (39), 372 (13), 336 (9), 288 (36), 258 (38), 232 (36), 207 (37), 169 (41); HRMS for $C_{35}H_{29}N_3O_6SCs$ (M + Cs) calcd 752.0831, found 752.0803.

Dynemicin A Model Compound 1. To a solution of **50** (75 mg, 0.121 mmol) in dry toluene (3 mL) was added AIBN (5 mg, 0.03 mmol) and ^{n}Bu$_3$SnH (65 μL, 0.242 mmol) followed by heating at 80 °C for 1 h. The solvent was removed in vacuo, and the residue was purified by preparative TLC (silica gel plate, 33% ethyl ether in petroleum ether) to give **1** (41 mg, 69%) and the hydrolyzed product **49** (5.6 mg, 9%). **1**: colorless crystalline solid, mp 99–101.0 °C (from ethyl ether); R_f = 0.25 (silica, 20% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2960, 2937, 1748 (shoulder), 1723, 1494, 1379, 1304, 1273, 1199, 1182, 1116, 909 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.6 Hz, 1 H, aromatic), 7.41–7.33 (m, 2 H, aromatic), 7.25–7.13 (m, 4 H, aromatic), 6.99 (dd, J = 8.6, 2.3 Hz, 1 H, aromatic), 5.79 (dd, J = 9.8, 1.3 Hz, 1 H, olefinic), 5.68 (dd, J = 9.8, 1.4 Hz, olefinic), 5.53 (br s, 1 H, NC*H*), 3.77 (br s, 1 H, C≡CC*H*), 2.41 (dd, J = 14.2, 8.0 Hz, 1 H, CH_2), 2.22 (dd, J = 15.2, 9.0 Hz, 1 H, CH_2), 2.09–1.88 (m, 2 H, CH_2), 1.87–1.77 (m, 1 H, CH_2), 1.66–1.58 (m, 1 H, CH_2), 1.32 (s, 9 H, COC(CH_3)$_3$); MS (FAB$^+$) m/e (relative intensity) 626 (M + Cs, 28), 179 (23); HRMS for $C_{31}H_{27}NO_5Cs$ (M + Cs) calcd 626.0944, found 626.0944. Anal. Calcd for $C_{31}H_{27}NO_5$: C, 75.44; H, 5.51; N, 2.84. Found: C, 75.24; H, 5.68; N, 2.89.

***N*-[(Phenyloxy)carbonyl]-10-[(*tert*-butyldimethylsilyl)oxy]-3-[(2-nitrobenzyl)oxy]-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,7,8,9,10-hexahydrophenanthridine (51).** A mixture of $Pd(PPh_3)_4$ (1.12 g, 0.97 mmol), vinyl chloride **42** (4.60 g, 28.98 mmol), and *n*-propylamine (2.38 mL, 28.98 mmol) in degassed benzene (100 mL) was stirred at 25 °C for 15 min. The resultant solution was added to a mixture of **35** (ca. 79:21, mixture of the diastereomers, 11.80 g, 19.32 mmol) and CuI (0.74 g, 3.86 mmol) in degassed benzene (300 mL) via a syringe followed by stirring at 25 °C for 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ethyl ether (500 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel, 20% ethyl ether in petroleum ether) gave **51** (12.3 g, 87%): pale yellow foam; R_f = 0.51 (silica, 25% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2957, 2932, 1716, 1613, 1506, 1495, 1384, 1344, 1306, 1253, 1200, 1093, 1025, 858, 844 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.1 Hz, 1 H, aromatic), 7.97 (d, J = 7.7 Hz, 1 H, aromatic), 7.80–7.17 (m, 9 H, H1, H4 and aromatic), 6.93–6.84 (m, 1 H, H2), 5.96 (br s, 0.79 H, H6), 5.93 (br s, 0.21 H, H6), 5.88–5.77 (m, 2 H, olefinic), 5.58 (s, 2 H, benzylic), 5.03 (br s, 0.79 H, H10), 4.73 (br s, 0.21 H, H10), 2.67–2.50 (m, 1 H, H7), 2.39–2.26 (m, 1 H, H7), 2.16–1.91 (m, 3 H, H8 and H9), 1.84–1.70 (m, 1 H, H8 or H9), 1.02 (s, 1.89 H, SiC(CH_3)$_3$), 0.90 (s, 7.11 H, SiC(CH_3)$_3$), 0.27 (s, 9 H, Si(CH_3)$_3$), 0.18 (s, 3 H, SiCH_3), 0.16 (s, 3 H, SiCH_3); MS (FAB$^+$) m/e (relative intensity) 865 (M + Cs, 72), 732 (42), 675 (82), 639 (28), 585 (100), 450 (34), 330 (39), 279 (52), 198 (42); HRMS for $C_{42}H_{48}N_2O_6Si_2Cs$ (M + Cs) calcd 865.2105, found 865.2111.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-10-hydroxy-3-[(2-nitrobenzyl)oxy]-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (53).** To a solution of **51** (0.40 g, 0.546 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C was added *m*-CPBA (50%, 188 mg, 0.546 mmol) followed by stirring at 25 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield crude product **52**. To a solution of the crude **52** obtained above in wet $CHCl_3$ (10 mL) was added $BF_3 \cdot OEt_2$ (0.20 mL, 1.64 mmol) followed by stirring at 25 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 20% ethyl ether in benzene) to afford **53** (0.28 g, 81% from **51**): pale yellow foam; R_f = 0.45 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3568, 2961, 1723, 1615, 1527, 1379, 1343, 1305, 1253, 1202, 1026, 846 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.1 Hz, 1 H, aromatic), 7.82 (d, J = 7.7 Hz, 1 H, aromatic), 7.58 (t, J = 7.5 Hz, 1 H, aromatic), 7.47 (br s, 1 H, H4), 7.41–7.17 (m, 5 H, aromatic), 7.06 (d, J = 7.9 Hz, 2 H, H1 and aromatic), 6.86 (dd, J = 8.6, 2.4 Hz, 1 H, H2), 5.86 (d, J = 11.1 Hz, 1 H, olefinic), 5.74 (dd, J = 11.1, 1.6 Hz, 1 H, olefinic), 5.61 (d, J = 1.6 Hz, 1 H, H6), 5.47 (s, 2 H, benzylic), 4.34 (s, 1 H, H10), 2.64–2.50 (m, 2 H, H7), 2.44 (dt, J = 12.8, 4.8 Hz, 1 H, H9), 2.37–2.18 (m, 1 H, H8), 2.16–2.03 (m, 1 H, H8), 1.93 (br d, J = 13.2 Hz, 1 H, H9), 0.21 (s, 9 H, Si(CH_3)$_3$); MS (FAB$^+$) m/e (relative intensity) 767 (M + Cs, 100), 359 (8), 312 (20), 286 (8); HRMS for $C_{36}H_{34}N_2O_7SiCs$ (M + Cs) calcd 767.1190, found 767.1114.

***N*-[(Phenyloxy)carbonyl]-3-[(2-nitrobenzyl)oxy]-10-oxo-6-[6-(trimethylsilyl)-3(*Z*)-hexene-1,5-diynyl]-5,6,7,8,9,10-hexahydrophenanthridine (54). Method A.** A solution of **53** (0.26 g, 0.41 mmol) in THF (10 mL) and 48% aqueous HBr (1 mL) was stirred at 25 °C for 2 h. The reaction mixture was diluted with ethyl ether (30 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography of the residue (silica gel, 50% ethyl ether in petroleum ether) gave **54** (0.208 g, 82%).

Method B (Large-Scale Synthesis). To a solution of **51** (12.3 g, 16.78 mmol) in CH_2Cl_2 (300 mL) cooled at 0 °C was added *m*-CPBA (50%, 5.79 g, 16.78 mmol) followed by stirring at 25 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield crude product **52**. To a solution of the crude **52** obtained above in wet $CHCl_3$ (300 mL) was added $BF_3 \cdot OEt_2$ (6.2 mL, 50.34 mmol) followed by stirring at 25 °C for 10 min. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford a crude product **53**. A solution of the crude **53** obtained above in THF (300 mL) and 48% aqueous HBr (30 mL) was stirred at 25 °C for 1.5 h. The reaction mixture was diluted with ethyl ether (500 mL),

washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 50% ethyl ether in petroleum ether) to afford **54** (5.50 g, 53% from **51**): pale yellow foam; R_f = 0.45 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2957, 1717, 1681, 1612, 1527, 1504, 1382, 1343, 1306, 1253, 1201, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 9.0 Hz, 1 H, H1), 8.08 (d, J = 8.0 Hz, 1 H, aromatic), 7.84 (d, J = 7.7 Hz, 1 H, aromatic), 7.59 (t, J = 7.5 Hz, 1 H, aromatic), 7.43–7.05 (m, 7 H, H4 and aromatic), 6.89 (dd, J = 8.9, 2.4 Hz, 1 H, H2), 6.08 (d, J = 1.8 Hz, 1 H, H6), 5.83 (d, J = 11.1 Hz, 1 H, olefinic), 5.72 (dd, J = 11.1, 1.8 Hz, 1 H, olefinic), 5.53 (s, 2 H, benzylic), 2.86 (dt, J = 18.9, 4.6 Hz, 1 H, H9), 2.78–2.50 (m, 3 H, H7 and H9), 2.23–2.09 (m, 2 H, H8), 0.20 (s, 9 H, $Si(CH_3)_3$); MS (FAB^+) m/e (relative intensity) 749 (M + Cs, 12), 312 (7), 286 (8), 133 (100); HRMS for $C_{36}H_{32}N_2O_6SiCs$ (M + Cs^+) calcd 749.1084, found 749.1095.

***N*-[(Phenyloxy)carbonyl]-6-[3(*Z*)-hexene-1,5-diynyl]-3-[(2-nitrobenzyl)oxy]-10-oxo-5,6,7,8,9,10-hexahydrophenanthridine (55).** To a solution of **54** (5.50 g, 8.92 mmol) in THF/EtOH/H_2O (1:1:1, 450 mL) was added silver nitrate (6.06 g, 35.67 mmol) followed by stirring at 25 °C for 1 h. Potassium cyanide (4.07 g, 62.44 mmol) was added to the reaction mixture followed by stirring at 25 °C for another 10 min. The reaction mixture was diluted with CH_2Cl_2 (500 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 50% ethyl ether in petroleum ether) to furnish **55** (4.03 g, 83%): pale yellow foam; R_f = 0.38 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3304, 2929, 1717, 1680, 1611, 1527, 1504, 1494, 1382, 1343, 1306, 1270, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 1 H, H1), 8.08 (d, J = 8.1 Hz, 1 H, aromatic), 7.82 (d, J = 7.8 Hz, 1 H, aromatic), 7.59 (t, J = 7.4 Hz, 1 H, aromatic), 7.43–7.05 (m, 7 H, H4 and aromatic), 6.89 (dd, J = 8.9, 2.4 Hz, 1 H, H2), 6.03 (s, 1 H, H6), 5.79 (s, 2 H, olefinic), 5.53 (s, 2 H, benzylic), 3.16 (s, 1 H, acetylenic), 2.84 (dt, J = 18.8, 4.7 Hz, 1 H, H9), 2.75–2.49 (m, 3 H, H7 and H9), 2.22–2.07 (m, 2 H, H8); MS (FAB^+) m/e (relative intensity) 677 (M + Cs, 5), 653 (19), 419 (16), 312 (29), 286 (24); HRMS for $C_{33}H_{24}N_2O_6Cs$ (M + Cs) calcd 677.0689, found 677.0639.

***N*-[(Phenyloxy)carbonyl]-6a,10a-epoxy-6-[3(*Z*)-hexene-1,5-diynyl]-3-[(2-nitrobenzyl)oxy]-10-oxo-5,6,6a,7,8,9,10,10a-octahydrophenanthridine (56).** To a solution of **55** (4.00 g, 7.35 mmol) in CH_2Cl_2 (70 mL) and saturated aqueous $NaHCO_3$ (70 mL) was added *m*-CPBA (50%, 5.07 g, 14.70 mmol) followed by stirring at 25 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield crude product. Flash column chromatography (silica gel, 50% ethyl ether in petroleum ether) gave pure **56** (2.43 g, 59%): pale yellow foam; R_f = 0.45 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3303, 2952, 1720, 1615, 1528, 1506, 1494, 1380, 1344, 1307, 1253, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, J = 9.0 Hz, 1 H, H1), 8.11 (d, J = 8.0 Hz, 1 H, aromatic), 7.81 (d, J = 7.7 Hz, 1 H, aromatic), 7.59 (t, J = 7.2 Hz, 1 H, aromatic), 7.44–6.98 (m, 7 H, H4 and aromatic), 6.90 (dd, J = 9.0, 2.0 Hz, 1 H, H2), 5.91 (s, 1 H, H6), 5.79 (s, 2 H, olefinic), 5.52 (s, 2 H, benzylic), 3.20 (d, J = 1.1 Hz, 1 H, acetylenic), 2.80–2.62 (m, 2 H, H9), 2.38–2.25 (m, 2 H, H7), 2.09–1.85 (m, 2 H, H8); MS (FAB^+) m/e (relative intensity) 693 (M + Cs, 14), 653 (12), 468 (7), 417 (8), 377 (9), 312 (33), 215 (23); HRMS for $C_{33}H_{24}N_2O_7Cs$ (M + Cs) calcd 693.0638, found 693.0651.

Dynemicin A Model Compound 2. To a solution of **56** (2.43 g, 4.33 mmol) in dry toluene (400 mL) cooled at −78 °C was added LDA (1.5 M in cyclohexane, 2.90 mL, 4.35 mmol) followed by stirring at −78 °C for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ethyl ether (200 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 50% ethyl ether in petroleum ether) to afford **2** (1.01 g, 42%) along with recovered **56** (260 mg, 11%). **2**: pale yellow foam; R_f = 0.24 (silica, 50% ethyl ether in petroleum ether); IR (C_6H_6) ν_{max} 3554, 2954, 2927, 1728, 1615, 1529, 1506, 1494, 1378, 1343, 1302, 1280, 1202 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.97 (d, J = 9.0 Hz, 1 H, aromatic), 7.72 (d, J = 8.3 Hz, 1 H, aromatic), 7.52 (d, J = 7.7 Hz, 1 H, aromatic), 7.13–7.01 (m, 5 H, aromatic), 6.97–6.87 (m, 2 H, aromatic), 6.81 (br d, J = 8.9 Hz, 1 H, aromatic), 6.66 (t, J = 7.9 Hz, 1 H, aromatic), 5.90 (br s, 1 H, NC*H*), 5.31 (d, J = 10.1 Hz, 1 H, olefinic), 5.17 (dd, J = 10.1, 1.7 Hz, 1 H, olefinic), 5.13 and 5.04 (AB q, J = 16.0 Hz, 2 H, benzylic), 2.29 (br s, O*H*), 2.15–1.85 (m, 4 H, CH_2CH_2), 1.70–1.60 (m, 1 H, CH_2), 1.37–1.29 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, C_6D_6) δ 157.8, 151.7, 146.9, 138.0, 134.0, 133.5, 133.3, 129.6, 128.5, 125.5, 124.6, 124.3, 122.3, 122.2, 113.5, 102.0, 94.8, 93.9, 89.0, 74.1, 73.5, 67.0, 64.9, 51.1, 35.2, 23.1, 19.6 (other peaks corresponding to the aromatic carbons overlap with the solvent peaks); MS (FAB^+) m/e (relative intensity) 561 (M + H, 13), 340 (9), 306 (9), 281 (10), 253 (14), 239 (16), 221 (21), 202 (27), 191 (31), 178 (37), 165 (59); HRMS for $C_{33}H_{25}N_2O_7$ (M + H) calcd 561.1162, found 561.1162.

Base-Induced Bergman Cycloaromatization of 49. Compound 57. A solution of **49** (16.0 mg, 0.0314 mmol) in EtOH/H_2O (3:1, 6.23 mL) containing 0.02 M LiOH (0.125 mmol, pH ~11.5) was stirred at 25 °C for 6 h. The solvent was removed in vacuo to give a residue, to which brine was added followed by acidification with 5% HCl, extraction with CH_2Cl_2 (20 mL), drying over anhydrous Na_2SO_4, and removal of the solvent in vacuo. The crude product was purified by preparative TLC (silica gel plate, 50% ethyl ether in benzene) to afford **57** (7.5 mg, 56%): colorless gum; R_f = 0.33 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3583, 3375, 2929, 1725 (shoulder), 1701, 1614, 1502, 1447, 1398, 1381, 1299, 1276, 1255, 1087, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.32 (m, 2 H, aromatic), 7.29 (d, J = 8.6 Hz, 1 H, aromatic), 7.25–7.15 (m, 3 H, aromatic), 6.49 (dd, J = 8.6, 2.5 Hz, 1 H, aromatic), 5.54 (s, 1 H, NC*H*), 5.35 (br s, 1 H, ArO*H*), 4.40–4.24 (m, 2 H, NC(O)OCH_2CH_3), 3.99 (dq, J = 9.7, 7.0 Hz, 1 H, OCH_2CH_3), 3.50 (dq, J = 9.7, 7.0 Hz, 1 H, OCH_2CH_3), 2.60 (br s, 1 H, O*H*), 2.35 (td, J = 12.8, 4.6 Hz, 1 H, CH_2), 2.23 (td, J = 13.9, 6.2 Hz, 1 H, CH_2), 1.77 (dd, J = 13.4, 4.8 Hz, 1 H, CH_2), 1.64 (br s, 1 H, O*H*), 1.56–1.45 (m, 1 H, CH_2), 1.41 (t, J = 7.0 Hz, 3 H, NC(O)OCH_2CH_3), 1.39–1.26 (m, 1 H, CH_2), 1.24 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 0.82–0.63 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 154.7, 140.3, 137.4, 133.5, 130.3, 128.9, 127.5, 127.2, 124.3, 111.0, 109.6, 81.0, 80.4, 72.2, 64.8, 62.6, 62.0, 35.9, 32.2, 19.1, 16.3, 14.6; MS (FAB^+) m/e (relative intensity) 425 (M, 10), 362 (8), 290 (4), 217 (5), 165 (13); HRMS for $C_{24}H_{27}NO_6Cs$ (M + Cs) calcd 558.0893, found 558.0893.

Based-Induced Bergman Cyclization of 1. Compound 58. A solution of **1** (10.0 mg, 0.0201 mmol) in EtOH/H_2O (3:1, 4.0 mL) containing 0.02 M LiOH (0.080 mmol) was stirred at 25 °C for 4 h. The reaction mixture was extracted with CH_2Cl_2 (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (silica gel plate, 33% ethyl ether in benzene) to afford **58** (3.4 mg, 42%): colorless gum; R_f = 0.40 (silica, 33% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3594, 2927, 1732, 1707, 1612, 1377, 1250, 1109, 1050 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.20 (s, 1 H, ArO*H*), 7.34 (dd, J = 6.8, 2.1 Hz, 1 H, aromatic), 7.22 (d, J = 8.5 Hz, 1 H, aromatic), 7.15–7.04 (m, 3 H, 1 H, aromatic), 6.85 (dd, J = 6.7, 2.1 Hz, 1 H, aromatic), 6.51 (dd, J = 8.5, 2.4 Hz, 1 H, aromatic), 5.55 (s, 1 H, NC*H*), 4.25 (q, J = 7.0 Hz, 2 H, NC(O)OCH_2CH_3), 3.95 (dq, J = 9.9, 7.0 Hz, 1 H, OCH_2CH_3), 3.85 (s, 1 H, O*H*), 3.48 (dq, J = 9.0, 7.0 Hz, 1 H, OCH_2CH_3), 3.12 (t, J = 3.0 Hz, 1 H, ArC*H*), 2.38 (tdd, J = 12.6, 3.6, 3.6 Hz, 1 H, CH_2), 2.30 (td, J = 13.8, 6.0 Hz, 1 H, CH_2), 1.80 (dd, J = 13.2, 4.8 Hz, 1 H, CH_2), 1.38–1.32 (m, 1 H, CH_2), 1.35 (t, J = 7.0 Hz, 3 H, NC(O)OCH_2CH_3), 1.26–1.15 (m, 1 H, CH_2), 1.14 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 0.88–0.75 (m, 1 H, CH_2); MS (FAB^+) m/e (relative intensity) 542 (M + Cs, 18), 409 (35), 364 (15), 318 (29), 286 (25), 233 (15), 221 (29), 178 (20), 165 (31); HRMS for $C_{24}H_{27}NO_5Cs$ (M + Cs) calcd 542.0944, found 542.0961.

Acetylation of 2. Compound 62. A solution of **2** (100.0 mg, 0.178 mmol) and DMAP (2.2 mg, 0.0178 mmol) in pyridine (2.0 mL) and Ac_2O (1.0 mL) was stirred for 2 h at 25 °C. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 40% ethyl ether in petroleum ether) to afford **62** (82.5 mg, 77%): pale yellow foam; R_f = 0.43 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2956, 1723, 1615, 1526, 1506, 1494, 1379, 1343, 1303, 1288, 1162, 1150, 1071, 1035, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 1 H, aromatic), 7.86 (d, J = 9.1 Hz, 1 H, aromatic), 7.83 (d, J = 10.0 Hz, 1 H, aromatic), 7.60 (t, J = 7.3 Hz, 1 H, aromatic), 7.45–7.02 (m, 7 H, H4 and aromatic), 6.87 (dd, J = 8.9, 2.5 Hz, 1 H, H2), 5.90 (d, J = 10.2 Hz, 1 H, olefinic), 5.73 (dd, J = 9.8, 1.7 Hz, 1 H, olefinic), 5.52 (s, 1 H, H6), 5.51 (s, 2 H, benzylic), 2.22 (s, 3 H, $COCH_3$), 2.56–2.08 (m, 5 H, $CH_2CH_2CH_2$), 1.79–1.70 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, C_6D_6) δ 169.3, 157.4, 150.8, 146.7, 137.1, 134.0, 133.4, 131.1, 129.4, 129.4, 128.4, 128.3, 125.9, 125.0, 125.0, 124.4, 123.0, 121.5, 121.5, 120.5, 113.2, 112.2, 97.5, 95.5, 93.7, 88.8, 77.8, 73.6, 66.9, 63.0, 50.4, 29.5, 22.9, 21.9, 18.4; HRMS for $C_{35}H_{26}N_2O_8Cs$ (M + Cs) calcd 735.0743, found 735.0749. Anal. Calcd for $C_{35}H_{26}N_2O_8$: C, 69.76; H, 4.35; N, 4.65. Found: C, 69.78; H, 4.35; N, 4.70.

Photodeprotection of 2. Compound 63. A solution of **2** (5.0 mg, 0.0089 mmol) in THF-d_8 (0.5 mL) and D_2O (50 μL) charged in an NMR tube was irradiated with a Hanover high-pressure mercury arc (Pyrex filter) cooled in an ice–water bath (0–5 °C). The reaction was monitored by ^1H NMR; after irradiation for 40 min, **2** was completely converted into **63**. Attempts at purification of **63** led to decomposition. **63**: R_f = 0.63 (silica, 50% ethyl ether in benzene); ^1H NMR (300 MHz, THF-d_8/D_2O, 10:1) δ 8.53 (d, J = 8.8 Hz, 1 H, H1), 7.45–7.10 (m, 5 H, aromatic), 6.88 (d, J = 2.5 Hz, 1 H, H4), 6.63 (dd, J = 2.5, 8.8 Hz,

1 H, H2), 5.97 (d, J = 10.0 Hz, 1 H, olefinic), 5.78 (dd, J = 10.0, 1.6 Hz, 1 H, olefinic), 5.46 (br s, 1 H H6), 2.35–1.55 (m, 6 H, H7, H8, and H9).

Photodeprotection of 62. Compound 64. A solution of **62** (34.0 mg, 0.0564 mol) in THF (5 mL) and H_2O (0.5 mL) charged in a test tube was irradiated with a Hanover high-pressure mercury arc (Pyrex filter) cooled in an ice–water bath (0–5 °C) for 40 min. The reaction mixture was extracted with ethyl ether (30 mL), washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, 50% ethyl ether in petroleum ether) to afford **64** (22.0 mg, 83%): yellow foam; R_f = 0.20 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3302, 2955, 2928, 1723, 1619, 1494, 1381, 1293, 1163, 1150, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 1 H, H1), 7.36 (t, J = 7.6 Hz, 2 H, aromatic), 7.22 (t, J = 7.3 Hz, 1 H, aromatic), 7.13 (d, J = 7.9 Hz, 2 H, aromatic), 6.97 (br s, 1 H, H4), 6.67 (dd, J = 9.0, 2.6 Hz, 1 H, H2), 5.89 (d, J = 10.1 Hz, 1 H, olefinic), 5.71 (dd, J = 10.1, 1.7 Hz, 1 H, olefinic), 5.51 (d, J = 1.7 Hz, 1 H, H6), 5.18 (br s, 1 H, ArO*H*), 2.20 (s, 3 H, $COCH_3$), 2.53–1.97 (m, 5 H, $CH_2CH_2CH_2$), 1.78–1.68 (m, 1 H, CH_2); HRMS for $C_{28}H_{21}NO_6Cs$ (M + Cs) calcd 600.0423, found 600.0441.

Acetylation of 64. Compound 65. A solution of **64** (16.0 mg, 0.0342 mmol) in pyridine (0.5 mL) and Ac_2O (1.0 mL) was stirred for 30 min at 25 °C. The reaction was diluted with ethyl ether (10 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel plate, 67% ethyl ether in petroleum ether) to afford **65** (16.0 mg, 92%): pale yellow foam; R_f = 0.24 (silica, 50% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2958, 1725, 1614, 1502, 1494, 1372, 1307, 1252, 1247, 1182, 1150, 1072, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 1 H, H1), 7.37 (t, J = 7.7 Hz, 2 H, aromatic), 7.29 (br s, 1 H, H4), 7.22 (t, J = 7.1 Hz, 1 H, aromatic), 7.16 (d, J = 8.1 Hz, 2 H, aromatic), 7.00 (dd, J = 9.2, 2.4 Hz, 1 H, H2), 5.90 (d, J = 10.3 Hz, 1 H, olefinic), 5.72 (br d, J = 10.3 Hz, 1 H, olefinic), 5.54 (br s, 1 H, H6), 2.55–2.48 (m, 1 H, CH_2), 2.41–2.07 (m, 4 H, CH_2CH_2), 2.27 (s, 3 H, $COCH_3$), 2.21 (s, 3 H, $COCH_3$), 1.79–1.70 (m, 1 H, CH_2); HRMS for $C_{30}H_{23}NO_7Cs$ (M + Cs) calcd 642.0529, found 642.0529. Anal. Calcd for $C_{30}H_{23}NO_7$: C, 70.72; H, 4.55; N, 2.75. Found: C, 70.73; H, 4.56; N, 2.63.

Reaction of 63 with Nucleophiles. General Procedure. A crude solution of **63** prepared from **2** (20.0 mg, 0.0357 mmol) in THF (2.0 mL) and H_2O (0.2 mL) as described above was diluted to 3.0 mL in THF. Potassium phosphate monobasic–sodium hydroxide buffer (0.05 M, pH 8.0, 3.0 mL) and EtOH (3.0 mL), or EtSH (0.6 mL), or $^nPrNH_2$ (3.0 mL) was added. The resultant mixture was then stirred under argon at 25 °C until TLC showed that **63** was completely consumed (1.5 h). The reaction mixture was diluted with brine, extracted with CH_2Cl_2 (10 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (silica gel plate, 50% ethyl ether in benzene for **66** and **67** and 3.2% MeOH in CH_2Cl_2 for **68**) to give the Bergman cycloaromatization products **66**, **67**, and **68**, respectively.

66: 31% from **2**; pale yellow gum; R_f = 0.48 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3587, 3390 (br), 2929, 1718, 1615, 1494, 1383, 1345, 1298, 1277, 1163, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.44 (m, 1 H, aromatic), 7.41–7.35 (m, 4 H, aromatic), 7.26–7.16 (m, 5 H, aromatic), 7.11 (br s, 1 H, aromatic), 6.36 (dd, J = 8.6, 2.5 Hz, 1 H, aromatic), 5.89 (br s, 1 H, ArO*H*), 5.67 (s, 1 H, NC*H*), 3.97 (dq, J = 9.6, 6.9 Hz, 1 H, OCH_2CH_3), 3.51 (dq, J = 9.6, 6.9 Hz, 1 H, OCH_2CH_3), 2.72 (br s, 1 H, O*H*), 2.44 (br s, 1 H, O*H*), 2.35 (td, J = 12.7, 4.5 Hz, 1 H, CH_2), 2.22 (td, J = 13.9, 6.0 Hz, 1 H, CH_2), 1.81 (dd, J = 13.0, 3.8 Hz, 1 H, CH_2), 1.50 (br d, J = 14.0 Hz, 1 H, CH_2), 1.35 (br d, J = 11.3 Hz, 1 H, CH_2), 1.23 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 0.71 (ddddd, J = 13.8, 13.8, 13.8, 4.5, 4.5 Hz, 1 H, CH_2); MS (FAB^+) m/e (relative intensity) 606 (M + Cs, 55), 473 (M, 13); HRMS for $C_{28}H_{27}NO_6Cs$ (M + Cs) calcd 606.0893, found 606.0903. Anal. Calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96. Found: C, 71.11; H, 5.59; N, 3.01.

67: 34% from **2**; pale yellow gum; R_f = 0.56 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3590, 3365 (br), 3013, 2956, 2931, 1717, 1616, 1494, 1456, 1385, 1299, 1070, 921 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.7 Hz, 1 H, aromatic), 7.51–7.33 (m, 5 H, aromatic), 7.31–7.19 (m, 4 H, aromatic), 7.08 (br s, 1 H, aromatic), 6.56 (dd, J = 8.7, 2.7 Hz, 1 H, aromatic), 5.78 (s, 1 H, NC*H*), 5.02 (br s, 1 H, ArO*H*), 2.74 (s, 1 H, O*H*), 2.68–2.54 (m, 2 H, SCH_2CH_3), 2.32–2.22 (m, 1 H, CH_2), 2.18 (dd, J = 12.9, 8.4 Hz, 1 H, CH_2), 2.13 (s, 1 H, O*H*), 1.85 (dd, J = 13.5, 4.9 Hz, 1 H, CH_2), 1.46 (dd, J = 13.5, 4.8 Hz, 1 H, CH_2), 1.33–1.22 (m, 1 H, CH_2), 1.20 (t, J = 7.5 Hz, 3 H, SCH_2CH_3), 0.81–0.63 (m, 1 H, CH_2); HRMS (FAB^+) for $C_{28}H_{27}NO_5SCs$ (M + Cs) calcd 622.0664, found 622.0670.

68: 46% from **2**; pale yellow gum; R_f = 0.33 (silica, 4.8% MeOH in CH_2Cl_2); IR ($CHCl_3$) ν_{max} 3591, 3439, 3270, 2964, 2935, 1727, 1645, 1613, 1500, 1459, 1416, 1252, 1188, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.43 (dd, J = 5.3, 3.5 Hz, 1 H, aromatic), 7.25–7.10 (m, 4 H, aromatic), 6.56 (dd, J = 8.4, 2.2 Hz, 1 H, aromatic), 6.53 (d, J = 2.2 Hz, 1 H, aromatic), 5.58 (s, 1 H, NC*H*), 5.46 (t, J = 5.6 Hz, 1 H, $CONHCH_2$), 3.19–2.95 (m, 2 H, $CONHCH_2CH_2$), 2.80 (dt, J = 11.3, 6.3 Hz, 2 H, $NHCH_2CH_2$), 2.53–2.26 (m, 4 H, $NHCH_2CH_2$, CH_2, O*H*), 1.84 (s, 1 H, O*H*), 1.68 (dd, J = 12.4, 4.7 Hz, 1 H, CH_2), 1.61–1.36 (m, 5 H, $CONHCH_2CH_2$, $NHCH_2CH_2$, CH_2), 0.94 (t, J = 7.3 Hz, 3 H, $CONHCH_2CH_2CH_3$), 0.89 (dd, J = 4.8, 2.4 Hz, 1 H, CH_2), 0.83 (t, J = 7.3 Hz, 3 H, $NHCH_2CH_2CH_3$), 0.78–0.59 (m, 1 H, CH_2); MS (FAB^+) m/e (relative intensity) 584 (M + Cs, 19), 452 (M + H, 20); HRMS for $C_{26}H_{34}N_3O_4$ (M + H) calcd 452.2549, found 452.2549.

Reaction of 64 with Ethanol. Compounds 69 and 70. The reaction was carried out as described above for compound **63**. The Bergman cycloaromatization products **69** and **70** were isolated by preparative TLC (silica gel plate, 50% ethyl ether in benzene) as a mixture (ca. 65:35, 20% combined yield). **69** + **70**: pale yellow gum; R_f = 0.56 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3302, 2952, 1724, 1613, 1494, 1384, 1368, 1297, 1255, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 9.0 Hz, 1 H, aromatic), 7.60–7.15 (m, 6.25 H, aromatic), 7.02 (br s, 1 H, aromatic), 6.60–6.53 (m, 2 H, aromatic), 5.91 (s, 0.65 H, NC*H*), 5.69 (s, 0.35 H, NC*H*), 5.12 (s, 0.65 H, ArO*H*), 5.04 (s, 0.35 H, ArO*H*), 4.00–3.92 (m, 0.7 H, $NC(O)OCH_2CH_3$), 3.60–3.49 (m, 0.65 H, OCH_2CH_3), 3.21 (td, J = 13.0, 4.5 Hz, 0.65 H, OCH_2CH_3), 2.90 (td, J = 13.3, 4.6 Hz, 0.7 H, OCH_2CH_3), 2.66 (s, 1 H, O*H*), 2.62 (br d, J = 13.3 Hz, 1 H, CH_2), 2.40–2.14 (m, 3 H, CH_2CH_2), 2.25 (s, 1.95 H, $COCH_3$), 2.16 (s, 1.05 H, $COCH_3$), 1.95 (dd, J = 13.6, 4.4 Hz, 0.65 H, CH_2), 1.80 (dd, J = 13.1, 4.3 Hz, 0.35 H, CH_2), 1.23 (t, J = 7.0 Hz, 4.05 H, $NC(O)OCH_2CH_3$, OCH_2CH_3), 0.90–0.70 (m, 1 H, CH_2).

Reaction of 63 with Molecular Oxygen. Compound 71. A crude solution of **63** prepared from **2** (80.0 mg, 0.143 mmol) in THF (8.0 mL) and H_2O (0.8 mL) as described above was mixed with potassium phosphate monobasic–sodium hydroxide buffer solution (0.05 M, pH 8.0, 8.0 mL) and ethanol (8.0 mL) followed by stirring in open air at 25 °C for 1.5 h. The reaction mixture was diluted with brine, extracted with CH_2Cl_2 (30 mL × 2), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (silica gel plate, 50% ethyl ether in benzene) to provide **66** (22.6 mg, 33% from **2**) and **71** (5.6 mg, 9% from **2**). **71**: pale yellow gum; R_f = 0.41 (silica, 50% ethyl ether in benzene); UV ($CHCl_3$) λ_{max} (log ϵ) 310 (shoulder, 3.645), 290 (shoulder, 3.955), 258 (4.160) nm; IR ($CHCl_3$) ν_{max} 3545, 2927, 1733, 1666, 1608, 1403, 1381, 1349, 1296, 1285, 1198 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 10.4 Hz, 1 H, olefinic), 7.44–7.35 (m, 3 H, aromatic), 7.20–7.14 (m, 2 H, aromatic), 6.76 (d, J = 2.2 Hz, 1 H, olefinic), 6.51 (dd, J = 10.4, 2.2 Hz, 1 H, olefinic), 5.92 (d, J = 9.9 Hz, 1 H, olefinic), 5.86 (dd, J = 9.9, 1.7 Hz, 1 H, olefinic), 5.21 (d, J = 1.7 Hz, 1 H, NC*H*), 3.74 (d, J = 2.3 Hz, 1 H, O*H*, exchangeable with D_2O), 3.23 (dddd, J = 14.7, 9.7, 9.7, 2.3 Hz, 1 H, CH_2), 2.34–2.15 (m, 2 H, CH_2), 2.29 (s, 1 H, O*H*, exchangeable with D_2O), 2.15–1.95 (m, 2 H, CH_2), 1.88 (ddd, J = 14.7, 8.3, 1.8 Hz, 1 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.5, 151.8, 150.4, 147.6, 138.9, 134.2, 129.7, 129.7, 127.9, 126.3, 123.8, 123.3, 121.3, 121.3, 98.3, 93.9, 90.5, 89.1, 79.3, 74.9, 68.3, 59.8, 59.5, 33.6, 26.4, 14.2; HRMS (FAB^+) for $C_{26}H_{19}NO_6Cs$ (M + Cs) calcd 574.0267, found 574.0284.

Acetylation of 71. Compound 72. A solution of **71** (1.3 mg, 0.0029 mmol) in pyridine (0.5 mL), DMAP (1.0 mg), and Ac_2O (0.1 mL) was stirred for 2 h at 25 °C. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel plate, 50% ethyl ether in benzene) to afford **72** (1.2 mg, 84%): pale yellow gum; R_f = 0.61 (silica, 50% ethyl ether in benzene); UV ($CHCl_3$) λ_{max} (log ϵ) 310 (shoulder, 3.645), 290 (shoulder, 3.955), 258 (4.160) nm; IR ($CHCl_3$) ν_{max} 3552, 1738, 1667, 1608, 1403, 1296, 1287 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.37 (m, 3 H, aromatic), 7.30 (d, J = 10.4 Hz, 1 H, olefinic), 7.20–7.15 (m, 2 H, aromatic), 6.76 (d, J = 2.0 Hz, 1 H, olefinic), 6.53 (dd, J = 10.4, 2.0 Hz, 1 H, olefinic), 5.94 (d, J = 9.8 Hz, 1 H, olefinic), 5.84 (dd, J = 9.8, 1.8 Hz, 1 H, olefinic), 5.20 (d, J = 1.8 Hz, 1 H, NC*H*), 3.87 (d, J = 2.6 Hz, 1 H, O*H*, exchangeable with D_2O), 3.18 (dddd, J = 14.5, 9.3, 9.3, 2.6 Hz, 1 H, CH_2), 2.81 (ddd, J = 13.1, 8.7, 3.0 Hz, 1 H, CH_2), 2.30–2.23 (m, 1 H, CH_2), 2.18 (s, 3 H, $COCH_3$), 2.12–2.01 (m, 2 H, CH_2), 1.93 (ddd, J = 14.5, 8.3, 2.2 Hz, 1 H, CH_2); NOE experiments were carried out on a 500-MHz instrument, irradiation at δ 2.18 ($COCH_3$), 4.6% enhancement at δ 7.30 (olefinic), irradiation at δ 5.20 (NC*H*), 22% enhancement at δ 3.87 (O*H*) and 33% enhancement at δ 1.93 (CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 167.8, 151.9, 150.4, 147.9, 138.1, 134.4, 129.7, 129.7, 128.2, 126.3, 124.0, 123.9, 121.3, 121.3, 96.1, 94.0, 91.7, 89.3, 78.8, 75.2, 72.5, 59.5, 59.5, 28.5, 26.3, 14.0; HRMS

(FAB+) for $C_{28}H_{21}NO_7Cs$ (M + Cs) calcd 616.0372, found 616.0398.

Compound 75. The isolable compound **75** was obtained from **2** by methylation (Cs_2CO_3, MeI, 18-crown-6, CH_3CN, 25 °C)[1] and photodeprotection. **75**: pale yellow gum; R_f = 0.76 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3450, 3004, 2979, 2875, 1720, 1384, 1299, 1198, 1151, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 1 H, aromatic), 7.35-7.28 (m, 2 H, aromatic), 7.18 (t, J = 7.3 Hz, 1 H, aromatic), 7.12 (br d, J = 6.9 Hz, 2 H, aromatic), 6.89 (br s, 1 H, aromatic), 6.65 (dd, J = 8.8, 2.7 Hz, 1 H, aromatic), 5.82 (d, J = 10.0 Hz, 1 H, olefinic), 5.67 (dd, J = 10.0, 1.7 Hz, 1 H, olefinic), 5.48 (s, 1 H, NC*H*), 5.28 (br s, 1 H, ArO*H*), 3.47 (s, 3 H, OCH_3), 2.28 (dd, J = 15.1, 8.2 Hz, 1 H, CH_2), 2.23-2.10 (m, 2 H, CH_2), 2.00-1.87 (m, 2 H, CH_2), 1.78-1.70 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 150.9, 136.8, 133.2, 131.9, 130.1, 129.3, 129.3, 125.8, 124.2, 124.1, 122.2, 121.6, 120.5, 113.0, 99.5, 94.9, 93.9, 88.4, 79.3, 72.1, 63.2, 52.1, 50.5, 28.5, 23.2, 18.9; HRMS (FAB+) for $C_{27}H_{21}NO_5Cs$ (M + Cs) calcd 572.0474, found 572.0429.

Reaction of 75 with Molecular Oxygen. Compounds 76 and 77. The reaction of **75** with molecular oxygen was carried out as described above for compound **63** in a THF/pH 9.0 buffer solution (boric acid/potassium chloride/sodium hydroxide; 1:1) at 25 °C in open air for 48 h to provide **76** (35%) and **77** (25%). **76**: R_f = 0.31 (silica, ethyl ether); UV ($CHCl_3$) λ_{max} (log ϵ) 330 (3.09), 285 (shoulder, 3.38), 256 (3.17), 244 (shoulder, 3.58) nm; IR ($CHCl_3$) ν_{max} 3527, 3385, 2956, 2929, 2856, 1656, 1597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 10.3 Hz, 1 H, olefinic), 6.36 (dd, J = 10.4, 2.0 Hz, 1 H, olefinic), 5.85 (d, J = 9.8 Hz, 1 H, olefinic), 5.86 (dd, J = 9.8, 1.7 Hz, 1 H, olefinic), 4.13 (d, J = 4.0 Hz, 1 H, O*H*, exchangeable with D_2O), 4.07 (d, J = 3.0 Hz, 1 H, olefinic), 3.72 (dd, J = 4.2, 1.7 Hz, 1 H, NC*H*), 3.41 (s, 3 H, OCH_3), 3.20 (m, 1 H, CH_2), 2.36 (m, 1 H, CH_2), 2.10 (m, 2 H, CH_2), 1.88 (m, 1 H, CH_2), 1.74 (m, 1 H, CH_2); ^{13}C NMR (125 MHz, C_6D_6) δ 184.4, 157.2, 137.7, 134.8, 123.3, 122.6, 113.3, 98.8, 98.4, 90.7, 87.2, 78.1, 74.8, 74.0, 58.4, 57.8, 51.5, 27.5, 27.4, 14.3; HRMS (FAB+) for $C_{20}H_{17}NO_4Cs$ (M + Cs) calcd 468.0212, found 468.0254.

Acid-Induced Bergman Cyclization of 78. Compound 79. To a solution of **78** (10.0 mg, 0.023 mmol) in benzene (1.0 mL) and 1,4-cyclohexadiene (1.0 mL) was added $TsOH \cdot H_2O$ (4.4 mg, 0.023 mmol) followed by stirring at 25 °C for 1.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (silica gel plate, 50% ethyl ether in benzene) to afford **78** (3.3 mg, 32%): R_f = 0.14 (silica, 50% ethyl ether in benzene); IR ($CHCl_3$) ν_{max} 3294, 2917, 1718, 1616, 1511, 1498, 1380, 1294 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.8 Hz, 1 H, aromatic), 7.56-7.20 (m, 10 H, aromatic), 6.69 (dd, J = 8.9, 2.8 Hz, 1 H, aromatic), 5.88 (s, 1 H, NC*H*), 3.69 (s, 1 H, O*H*), 3.67 (s, 3 H, OCH_3), 2.89 (s, 1 H, O*H*), 2.29 (s, 1 H, O*H*), 2.48-2.18 (m, 3 H, CH_2), 1.87 (dd, J = 13.6, 5.0 Hz, 1 H, CH_2), 1.47 (br d, J = 12.8 Hz, 1 H, CH_2), 0.95-0.75 (m, 1 H, CH_2); HRMS for $C_{27}H_{25}NO_6Cs$ (M + Cs) calcd 592.0736, found 592.0700.

DNA Cleavage Assay. Supercoiled ΦX174 DNA (50 μM/bp) was incubated with the indicated enediynes (5.0 mM, final concentration) in buffer solution (50 mM Tris-HCl, pH 8.5) at 37 °C for 36 h and analyzed by agarose gel electrophoresis to separate the various forms of DNA. The DNA bands were visualized with ethidium bromide binding and UV illumination. Figure 2 shows the picture of the agarose gel after electrophoresis.

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Supplementary Material Available: X-ray crystallographic data for compound **49** (11 pages); table of observed and calculated structure factors (15 pages). Ordering information is given on any current masthead page.

Skipped Cyclic Ene- and Dienediynes. 1. Synthesis, Spectroscopic Properties, and Reactions of a New Hydrocarbon Ring Family†

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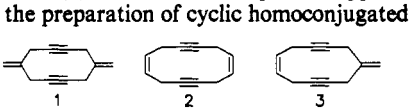
Abstract: The three skipped cyclic $C_{12}H_{12}$ dienediynes, 4,9-dimethylene-1,6-cyclodecadiyne (**1**), (*Z*,*Z*)-4,10-cyclododecadiene-1,7-diyne (**2**), and 10-methylene-(*Z*)-4-cycloundecene-1,7-diyne (**3**), have been synthesized by cyclization of dilithium salts of diterminal enediynes with the corresponding dihalogenides. This simple approach only worked (with approx. 5% yield) when no CuCl catalyst was used. Besides **1-3**, 4,9-diisopropylidene-1,6-cyclodecadiyne (**30**), the cyclic enediynes (*Z*)-4-cycloundecene-1,7-diyne (**19**) and (*Z*)-4-cyclododecene-1,7-diyne (**20**), as well as 4-methylene-1,6-cyclodecadiyne (**22**), 4-methylene-1,6-cycloundecadiyne (**23**), and their isopropylidene congeners **25** and **28** have been synthesized. Partial hydrogenation of **1-3** gives the corresponding homoconjugated tetraenes **37-39**. The reaction of **30** with dicarbonyl(η^5-cyclopentadienyl)cobalt yields a superphane of two cyclobutadiene units, stabilized by two CpCo moieties (**47**). The two cyclobutadiene rings are connected by four 2-isopropylidenepropano bridges. An X-ray investigation of the superphane shows that all four bridges adopt a pinwheel-like conformation.

Introduction

In "skipped" enynes a saturated carbon atom separates a double bond from a triple bond,[1] thus allowing at most homoconjugation between the π-units. We became interested in cyclic skipped ene- and dienediynes such as 4,9-dimethylene-1,6-cyclodecadiyne (**1**), (*Z*,*Z*)-4,10-cyclododecadiene-1,7-diyne (**2**), and 10-methylene-(*Z*)-4-cycloundecene-1,7-diyne (**3**) and related species for the following reasons: (1) These molecules provide appealing starting materials for the preparation of cyclic homoconjugated tetraenes.



1 2 3

(2) They are of interest with respect to the reactivity of their allylic

† Dedicated to Professor Klaus Hafner on the occasion of his 65th birthday.
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(1) Gensler, W. J.; Mahadevan, A. P. *J. Am. Chem. Soc.* **1955**, *77*, 3076.

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