Synthetic and Mechanistic Studies on the Azabicyclo[7.3.1]enediyne Core and Naphtho[2,3-*h*]quinoline Portions of Dynemicin A

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Abstract: The synthesis of the 13-keto-10-azabicyclo[7.3.1]enediyne core structure of dynemicin A has been achieved by two routes, Schemes 4 and 6. The chemistry of the 13-keto core structure is dominated by the unusually facile bridgehead enolization. Comparison of the rates of cycloaromatization of a variety of enediynes revealed that substantial rate differences occurred even though the distance between the bonding acetylenes was virtually identical. A non-radical cycloaromatization pathway, initiated by thiol addition to the enediyne system, was discovered, and the simple core amine **26** exhibits modest *in vitro* and *in vivo* antitumor activity. Finally, two methods for the synthesis of the naphtho[2,3-*h*]quinoline portion of dynemicin A are described, and both these compounds also exhibit antitumor activity.

Introduction

The isolation and structural elucidation of dynemicin A **1** (R = H) was reported in 1989.[1] It was the first enediyne antitumor agent whose structure **1** (R = Ac) was confirmed by X-ray crystallography, Scheme 1.[2,3] The source of **1** was the fermentation broth of a new *Micromonospora* strain, isolated from a soil sample collected in Gujarat State, India, and identified as *Micromonospora chersina* sp. nov. no. M956-1. Dynemicin A was found to exhibit strong growth inhibition of Gram-positive bacteria, especially of recombination-deficient mutants such as *Bacilus subtillis* M45 strain. Most importantly, both dynemicin A and its triacetate show potent *in vivo* antitumor activity. Dynemicin A is a member of the family of antitumor antibiotics commonly known as the enediyne natural products;[4] this group includes the calicheamicins, esperamicins,[5] neocarzinostatin,[6] kedarcidin,[7] C-1027,[8] and maduropeptin.[9]

In 1990, Semmelhack[10] speculated that dynemicin A undergoes bioreductive activation with concomitant epoxide ring opening to give the extended quinone methide **1a**. Hydration and oxidation of **1a** followed by Bergman cycloaromatization of the diol **1b** lead to the diyl **1c** which can hydrogen abstract to provide the adduct **1d**.[11] Consequently if dynemicin A or one of the subsequent adducts is bound to DNA,[12] the diyl is fully capable of backbone scission, Scheme 2. Generally, it is thought that, prior to bioreduction, dynemicin forms an intercalation complex with the DNA. A model for this complex has been constructed (using energy minimization and molecular dynamics techniques), and appeared to be consistent with the available experimental data.[4]

Studies to design models that mimic dynemicin A have been based upon this working hypothesis.[13] It has been generally assumed that the formation of a diradical intermediate is a prerequisite for biological activity. The diradical (*p*-benzyne) intermediates in simple prototype enediynes were proposed by Bergman in 1972.[14] There have been many reports of different strategies for the synthesis of the core structure of dynemicin A,[15] and recently the Myers[16] and Danishefsky[17] groups have completed its total synthesis.

⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1997.

(1) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. Konishi, M.; Ohkuma, H.; Matsumoto, K.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1991**, *44*, 1300.

(2) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

(3) The Wender and Langley groups have utilized computational docking protocols in an effort to determine the absolute stereochemistry. These findings predict that the absolute stereochemistry is (2*S*,3*S*,4*S*,7*R*,8*R*). Wender, P.; Kelly, R.; Beckham, S.; Miller, B. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8835. Langley, D. R.; Doyle, T. W.; Beveridge, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 4395.

(4) *Enediyne Antibiotics as Antitumor Agents*; Borders, D. B., Doyle, T. W., Eds.; Dekker, Inc.: New York, 1995.

(5) Lee, M. D.; Durr, F. E.; Hinman, L. M.; Hamann, P. R.; Ellestad, G. A. In *Advances in Medicinal Chemistry*; Maryanoff, B. E., Maryanoff, C. A., Eds.; JAI Press: Greenwich, CT, 1993; Vol. 2. Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res*. **1991**, *24*, 235. Nicolaou, K. C.; Smith, A. L. *Acc. Chem. Res.* **1992**, *25*, 497. Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1387.

(6) Ishida, N. K.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot. (Tokyo), Ser. A* **1965**, *18*, 63. Ohnuma, T.; Nogeire, C.; Cuttner, J.; Holland, J. F. *Cancer* **1978**, *42*, 1670. Goldberg, I. H. *Acc. Chem. Res*. **1991**, *24*, 191. Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Edo, K.; Akiyama, Y.; Saito, K.; Mizugaki, M.; Koide, Y.; Ishida, N. *J. Antibiot*. **1986**, *39*, 1615. Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc*. **1988**, *110*, 7212.

(7) Leet, J. E.; Schroeder, D. R.; Langley, D. R.; Colson, K. L.; Huang, S.; Klohr, S. E.; Lee, M. S.; Golik, J.; Hofstead, S. J.; Doyle, T. W.; Matson, J. A. *J. Am. Chem. Soc*. **1993**, *115*, 8432.

(8) Minami, Y.; Yoshida, K.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett.* **1993**, *34*, 2633. Yoshida, K.; Minami, Y.; Azuma, R.; Saeki, M.; Otani, T. *Tetrahedron Lett*. **1993**, *34*, 2637. Iida, K.; Ishii, T.; Hirama, M.; Otani, T.; Minami, Y.; Yoshida, K. *Tetrahedron Lett*. **1993**, *34*, 4079.

(9) Hanada, M.; Ohkuma, H.; Yonemoto, T.; Tomita, K.; Ohbayashi, M.; Kamei, H.; Miyaki, T.; Konishi, M.; Kawaguchi, H.; Forenza, S. *J. Antibiot.* **1991**, *44*, 403.

(10) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett*. **1990**, *31*, 1521.

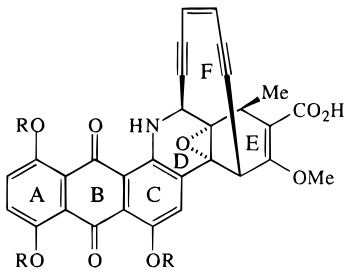
(11) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3831. Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, *29*, 9795. Sugiura, Y.; Arakawa, T.; Uesugi, M.; Shiraki, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, *30*, 2989.

(12) De Voss, J. J.; Hangeland, J. J.; Townsend, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 4554.

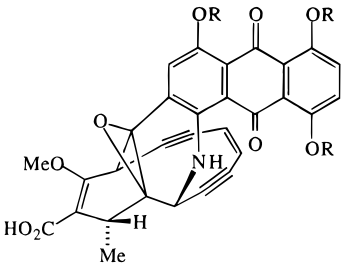
(13) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106.

S0002-7863(97)00435-6 CCC: $14.00

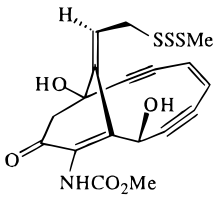
Scheme 1



1, Dynemicin A (R = H), (R = Ac)

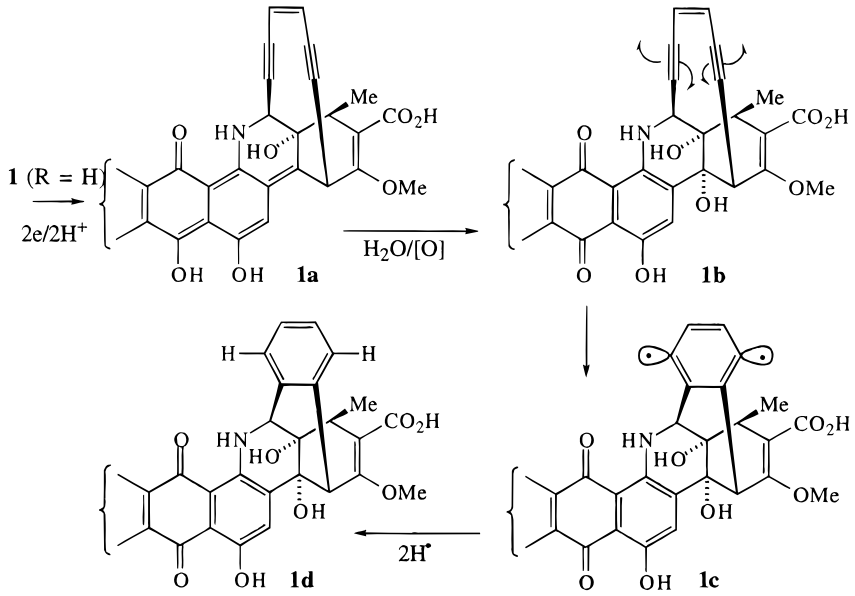


1, drawn to show its relationship to calicheamicinone.



2, Calicheamicinone

Scheme 2



Retrosynthetic Analysis (X = H or OR)

In Scheme 1 dynemicin A is drawn in two ways. The first emphasizes the enediyne (F-ring), and is a particularly good representation for illustrating the diradical mechanism, Scheme 2. The second drawing more readily shows the bicyclo[7.3.1]-enediyne core in relation to calicheamicinone (**2**). A third way of drawing dynemicin A is shown in Scheme 3 that lends itself to providing a clear picture of our retrosynthetic analysis. The enediyne bisects the two fused six-membered rings, providing a pseudo-axis of symmetry. While this may seem to be a mute point, the structural relationships between compounds and the subsequent analysis of possible pathways for their synthesis can frequently be strongly influenced by how the compounds are drawn.

As an extension of our research on esperamicin and calicheamicin,[18] we have applied the key $\eta^2Co_2(CO)_6$-propargyl cation cyclization strategy for the synthesis of cyclic ten-membered ring enediynes to the synthesis of the azabicyclo-[7.3.1]enediyne core structure **3**, Scheme 3.[19]

We considered that the core structure **3** should be a stable molecule with respect to cycloaromatization at ambient temperatures, and could be derived from **4**, which in turn should be available from a cobalt-mediated cyclization of **5**. The enediyne section can be constructed from a 3-(silyloxy)-quinolinium intermediate, **7**, leading directly to **6**.

Synthesis of the Azabicyclo[7.3.1]enediyne Core

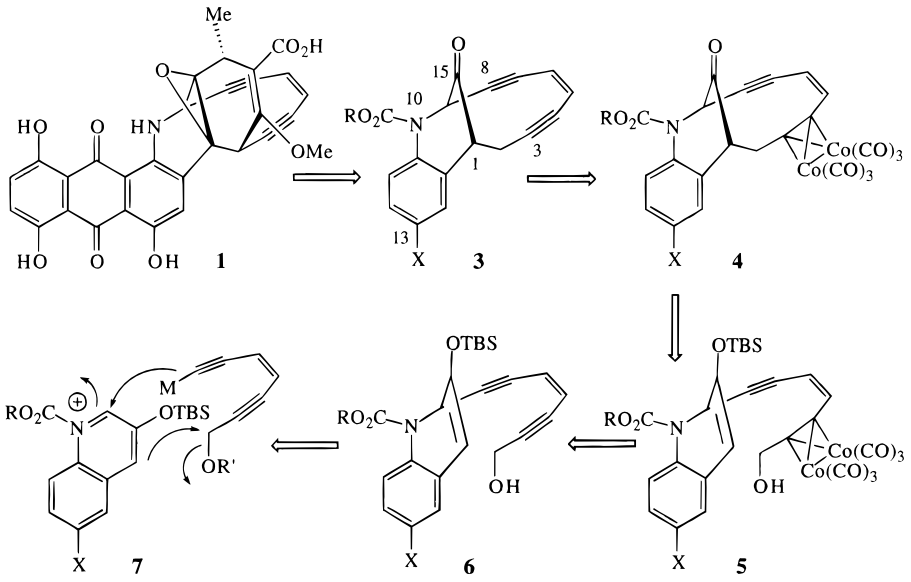
The protected enediyne **9** was prepared using two consecutive palladium(0)-catalyzed acetylenic coupling reactions. Coupling

(14) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. For biradical activity, see: Chapman, O. L.; Chang, C. V. C.; Kole, J. *J. Am. Chem. Soc.* **1976**, *98*, 5703. Darby, N; Kim, C. U.; Salaun, J. A.; Shelton, K. W.; Takeda, S.; Masamune, S. *J. Chem. Soc.* **1971**, 1516. Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217.

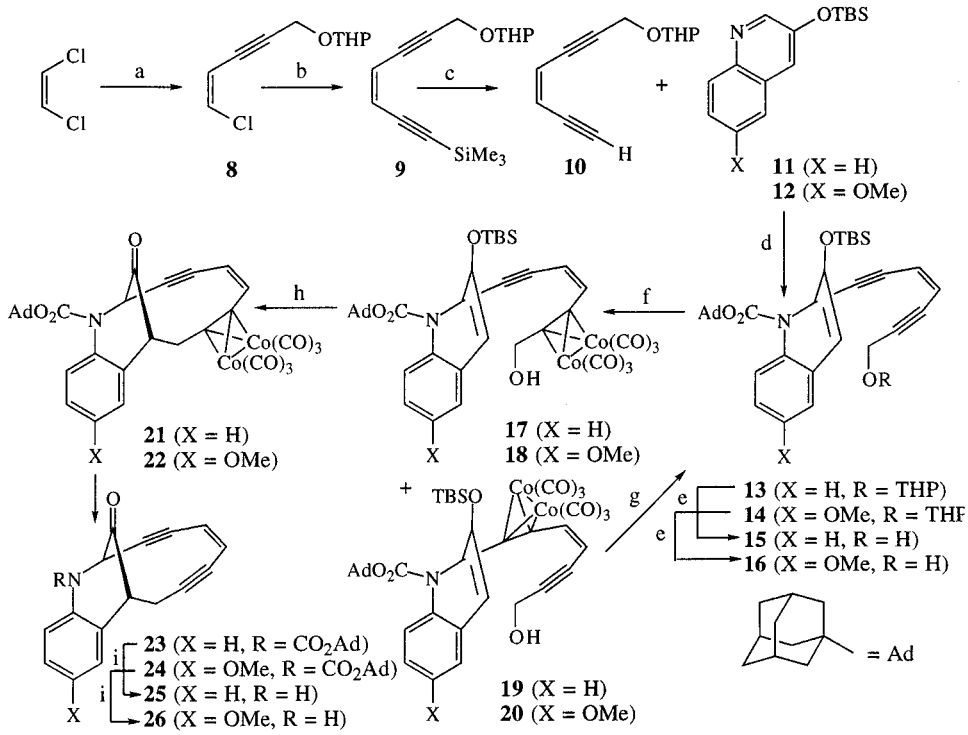
(15) Wood, J. L.; Porco, Jr. J. A.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. Porco, Jr. J. A.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378. Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendeborn, S. V.; Dai, W.-M.; Chadha, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8890. Nicolaou, K. C.; Hong, Y.-P.; Torisawa. Y.; Tsay, S.-C.; Dai, W.-M. *J. Am. Chem. Soc.* **1991**, *113*, 9878. Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172. Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908. Dai, W.-M. *J. Org. Chem.* **1993**, *58*, 7581. Shair, M. D.; Yoon, T.; Danishefsky, S. J.*J. Org. Chem.* **1994**, *59*, 3755. Shair, M. D.; Yoon, T.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2477. Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. Nishikawa, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 5621. Maier, M. E.; Abel, U. *Synlett* **1994**, 38. Wender, P. A.; Beckham, S.; Mohler, D. L. *Tetrahedron Lett.* **1995**, *36*, 209. Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867. Wender, P. A.; Beckham, S.; O'Leary, J. O. *Synthesis* **1994**, 1278. Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chem. Lett.* **1991**, 1271. Nishikawa, T.; Yoshikai, M.; Obi, K.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7997. Nishikawa, T.; Ino, A.; Isobe, M. *Tetrahedron* **1994**, *50*, 1449. Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 99. Sakamoto, Y.; Takahashi, T. *Synlett* **1995**, 513. Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1345.

(16) Myers, A. G.; Fraley, M. E.; Tom, N. J.; Cohen, S. B.; Madar, D. J. *Chem. Biol.* **1995**, *2*, 33. Myers, A. G.; Fraley, M. E.; Tom, N. J. *J. Am. Chem. Soc.* **1994**, *116*, 11556.

Scheme 3



Scheme 4[a]



[a] Conditions: (a) $HCCCH_2OTHP/THF/n\text{-}BuNH_2/Pd(PPh_3)_4$ (2.5 mol %)/CuI (5 mol %), **8** (72%). (b) $HCCSiMe_3/THF/n\text{-}BuNH_2/Pd(PPh_3)_4$ (2.5 mol %)/CuI (5 mol%), **9** (90%). (c) TBAF·H_2O/Et_2O, **10** (100%). (d) **10**/EtMgBr/THF, followed by **11** or **12** and AdOCOCl, **13** (64%), **14** (75%). (e) *p*-TsOH·H_2O/EtOH, **15** (87%), pyridinium tosylate/EtOH, **16** (86%). (f) $Co_2(CO)_8$/EtOAc, **17** (60%), $Co_2(CO)_8$/THF, **18** (59%) and **20** (33%). (g) $Ce(NH_4)_2(NO_2)_6$/acetone/2,6-di-*tert*-butyl-4-methylpyridine, **16** (76%). (h) Tf_2O/2-nitropropane/2,6-di-*tert*-butyl-4-methylpyridine at −10 °C for 15 min, followed by $Ce(NH_4)_2(NO_2)_6$/acetone, **23** (55%), **24** (53%). (i) TFA/CH_2Cl_2, **25** (81%), **26** (78%).

of propargyl *O*-THP ether, with *cis*-1,2-dichloroethylene gave **8** (72%), Scheme 4.[20] (Trimethylsilyl)acetylene was coupled to **8** to give the enediyne tetrahydropyranyl ether **9** (90%). Treatment of **9** with tetrabutylammonium fluoride (or, alternatively, lithium hydroxide in aqueous THF) gave the terminal acetylene **10** in quantitative yield. This sequence provides large quantities of **10** (70 g), which was used immediately since it is difficult to store without extensive decomposition.

Initially, we used 3-hydroxyquinoline to test the viability of the strategy, and we also experimented with several chloroformates to convert **10** and **11** into **13**. Eventually, it was found that the most suitable carbamate derivative that could be readily removed to provide access to the unprotected aniline derivatives was the adamantyl carbamate adduct, Scheme 4.[21] Treatment of **11**[22] with the magnesioacetylide salt of **10** in the presence of

(17) Shair, M. D.; Yoon, T. Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1996**, *118*, 9509. Shair, M. D.; Danishefsky, S. J. *J. Org. Chem*. **1996**, *61*, 16. Shair, M. D.; Yoon, T. Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1721.

(18) Magnus, P. *Tetrahedron* **1994**, *50*, 1397.

(19) Preliminary communications: Magnus, P., Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 544. Magnus, P.; Parry, D.; Illiadis, T.; Eisenbeis, S. A.; Fairhurst, R. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1543.

(20) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313. Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001. Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811. Coste, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967. Sonogashira, K.; Tohda, Y.; Hashigara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

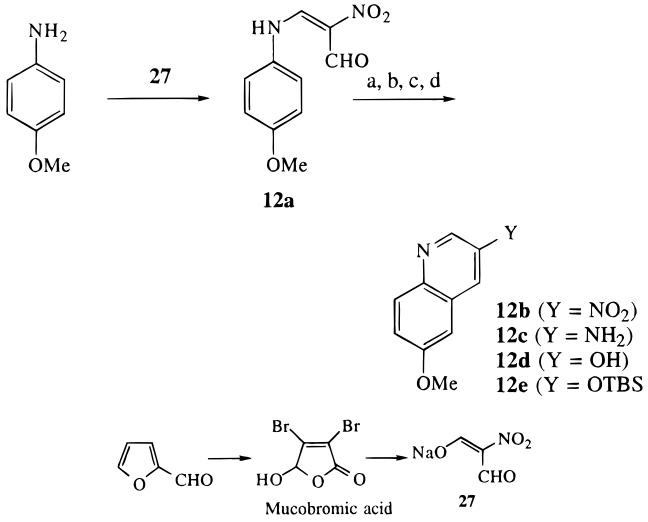
adamantyl chloroformate (Ad = adamantyl) gave, in a completely regiospecific reaction,[23] the dihydroquinoline **13** (64%). Selective deprotection of the THP ether **13** to give **15** (87%) was accomplished using *p*-TsOH·H_2O.

Complexation of **15** with $Co_2(CO)_8$ gave **17** (60%) along with some complexation at the other acetylene **19** (ca. 15%) and small amounts (<5%) of biscomplexation. In this series the minor regioisomer was not recycled. When the alcohol **17** was exposed to triflic anhydride/2,6-di-*tert*-butyl-4-methylpyridine (DBMP) in CH_2Cl_2 at −10 °C, a rapid transformation took place to give a symmetrical ether (69%).[24] None of the desired adduct **21** could be detected. We reasoned that the alcohol **17** could be intermolecularly hydrogen bonded, and as a consequence ionization of the hydroxyl group to the η^2-$Co_2(CO)_6$-propargylic cation takes place when it is solvated by un-ionized molecules of **17** (in CH_2Cl_2).[25] This solvate collapses to the ether faster than intramolecular enol ether trapping to give **21**. This simple notion predicts that a cation-solvating solvent might stabilize the η^2-$Co_2(CO)_6$-propargylic cation long enough to be trapped by the TBS enol ether. Treatment of **17** with triflic anhydride/DBMP in $(Me)_2CHNO_2$ (ϵ 35.9)/CH_2Cl_2 (ϵ 8.9) (1:2) at −10 °C gave the cyclized product **21**, and none of the ether. The cobalt-complexed cyclization product **21** was quite unstable and could not be readily purified without extensive decomposition, and therefore it was immediately oxidatively decomplexed using ceric ammonium nitrate (CAN) to give **23** (55% from **17**). Treatment of the newly generated enediyne core **23** with trifluoroacetic acid in dichloromethane cleanly generated the *sec*-amine **25** (81%).

The next stage required the synthesis of 3-hydroxy-6-methoxyquinoline (**12d**), which despite its apparent simplicity proved to be a tedious compound to synthesize, especially on a large scale. The classical sequence shown in Scheme 5 proved to be the most practical.[26]

O-Sodionitromalonodialdehyde (**27**) (made by treatment of mucobromic acid with NaOH)[27] was condensed with *p*-anisidine to give the vinylogous enamide **12a**. Treatment of **12a** with *p*-anisidine hydrochloride/AcOH in the presence of a catalytic amount of thiophenol gave **12b**. The function of thiophenol (it clearly accelerates the reaction) is presumably to equilibrate the *E/Z*-isomers of **12a**, thus facilitating cyclization into **12b**. Reduction, diazotization, and hydrolysis of **12b** gave **12d**, *via* **12c**. Standard silylation conditions gave **12e**.

Scheme 5[a]



[a] Conditions: (a) *p*-$MeOC_6H_4NH_3Cl$/AcOH/PhSH (catalytic), reflux, **12b** (48%). (b) $SnCl_2$/HCl, **12c** (86%). (c) $NaNO_2/H_2SO_4$, **12d** (95%). (d) *t*-$BuMe_2SiCl$/DMF, **12e** (91%).

Following the same reaction protocols **12e** was converted into **14** and then into **16**.[28] Complexation of **16** with $Co_2(CO)_8$ in tetrahydrofuran gave **18** (59%) along with some complexation at the other acetylene **20** (33%) and traces of biscomplexation. The undesired regioisomer **20** was recycled by ceric ammonium nitrate oxidation to give **16** (76%). All attempts to make this complexation more selective did not improve the above ratio (1.8:1). The uncomplexed propargyl alcohol **16**, and the η^2-$Co_2(CO)_6$ isomer **20** *do not* cyclize to the dynemicin core structure using the conditions described below.

Treatment of the cobalt adduct **18** with triflic anhydride/DBMP in $(Me)_2CHNO_2$ at −10 °C for 30 min gave **22**. Direct oxidative workup by ceric ammonium nitrate oxidation gave the cyclized enediyne **24** (53%, for the two steps). The structure of **24** was confirmed by X-ray crystallography.[29] The adamantyl carbamate was removed by treatment of **24** with trifluoroacetic acid in dichloromethane to give the amine **26** (78%). While the route to the azabicyclo[7.3.1]enediyne core structure **24** is short (five steps from **12,** overall 15% yield), the 3-(silyloxy)-quinoline **12** is tedious to make, and lacks flexibility for more substituted systems.

Alternative Synthesis of the Azabicyclo[7.3.1]enediyne Core

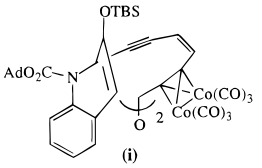
Commercially available 6-hydroxyquinoline, was treated with triisopropylsilyl trifluoromethanesulfonate and 2,6-lutidine to give **28** in >95% yield, Scheme 6. Treatment of the quinoline **28** with the magnesioacetylide salt of **10** resulted in exclusive 1,2-addition, affording **29**. When **29** was treated with MCPBA

(21) Haas, W. L.; Krumkalns, E. V.; Gerzon, K. *J. Am. Chem. Soc.* **1966**, *88*, 1988.

(22) *Organic Syn*theses; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, p 635.

(23) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. *Tetrahedron Lett.* **1983**, *24*, 1801.

(24) For examples of η^2-$Co_2(CO)_6$-propargylic cation reactions and cyclizations, see: Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, 3475. Nicholas, K. M.; Nestle, M. O.; Seyferth, D. In *Transition Metal Organometallics in Organic Synthesis*; Alper, H., Ed.; Academic Press: New York, 1978; Vol. 2. Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. Nicholas, K. M.; Mulraney, M.; Bayer, M. *J. Am. Chem. Soc.* **1980**, *102*, 2508. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Schreiber, S. L.; Klimas, M. Y.; Sammakia,T. *J. Am. Chem. Soc.* **1987**, *109*, 5749. Montana, A. M.; Nicholas, K. M.; Khan, M. A. *J. Org. Chem.* **1988**, *22*, 5193. The symmetrical ether is formulated as **i**, and is a mixture of diastereomers.



(i)

(25) For general discussions of the effects of solvent polarity on reaction rates see: *Solvents and Solvent Effects in Organic Chemistry*; Reichardt, C., Ed.; VCH: Weinheim, Germany, 1988. *Kinetics and Mechanism. A Study of Homogeneous Chemical Reactions*; Frost, A. A., Pearson, R. G., Eds.; Wiley: New York, 1963. *Mechanism in Organic Chemistry*; Alder, R. W., Baker, R., Brown, J. M., Eds.; Wiley: New York, 1975.

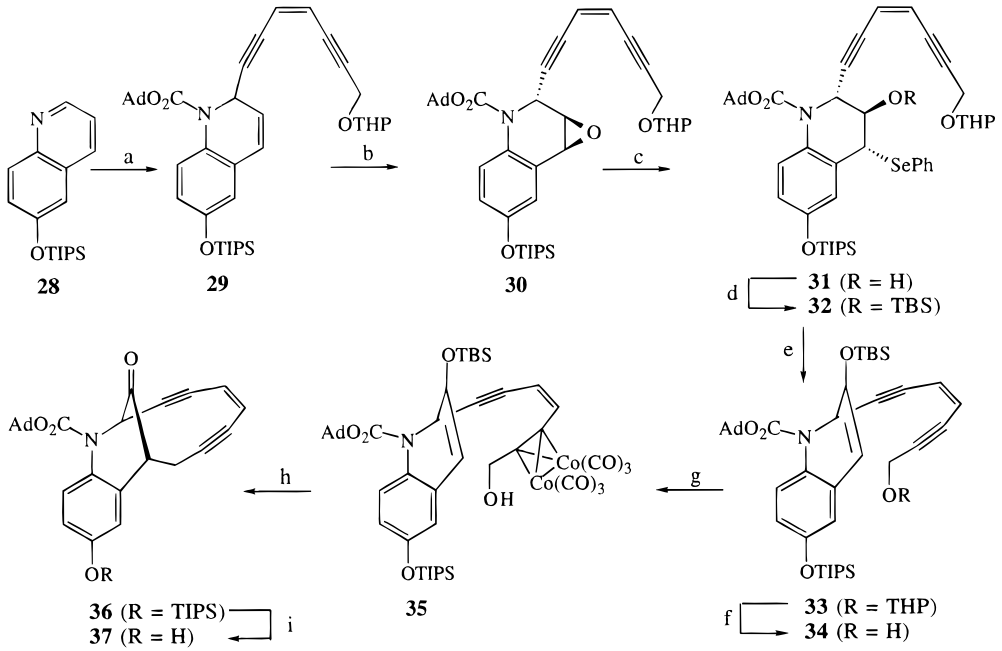
(26) Weissberg, A.; Taylor, E. C. *The Chemistry of Heterocyclic Compounds. Quinoline. Parts I-III*; Jones, G., Ed.; Interscience Publications, John Wiley & Sons: London, 1977; Vol. 32. Van der Plas, H. C.; Yamaguchi, T. *Recl. Trav. Chim. Pays-Bas*. **1977**, *96*, 89. Cho, I.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288. Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833. Arnold, Z. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1168. Lloyd, D.; McNab, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 459.

(27) Uhle, F. C.; Jacobs, W. A. *J. Org. Chem.* **1945**, *10*, 76. Morley, J. S.; Simpson, J. S. C. *J. Chem. Soc.* **1948**, 2024. Fanta, P. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 844.

(28) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(29) Lynch, V. M.; Iliadis, T.; Fairhurst, R.; Magnus, P.; Davis, B. E. *Acta Crystallogr., Sect. C* **1995**, *C51*, 782.

Scheme 6[a]



[a] Conditions: (a) **10**/EtMgBr/THF, followed by **28** and AdOCOCl. (b) MCPBA/CH_2Cl_2/$NaHCO_3$, **30** (100%). (c) $(PhSe)_2$/EtOH/$NaBH_4$, **31** (64%). (d) *t*-$BuMe_2SiCl$/DMF/imidazole, **32** (95%). (e) MCPBA/CH_2Cl_2, followed by pyridine, reflux, **33** (95%). (f) Pyridinium tosylate/EtOH, **34** (95%). (g) $Co_2(CO)_8$/EtOAc, **35** (60%). (h) Tf_2O/2-nitropropane/2,6-di-*tert*-butyl-4-methylpyridine at −10 °C for 15 min, followed by $Ce(NH_4)_2(NO_2)_6$/acetone, **36** (55%). (i) CsF/MeCN/H_2O, **37** (95%).

in dichloromethane, a 1:1 mixture of epoxides was formed in low yield, whereas exposure of **29** to MCPBA in the presence of aqueous sodium bicarbonate gave **30** as a single stereoisomer, presumably with the stereochemistry as shown. Treatment of diphenyl diselenide with sodium borohydride resulted in a selenyl/borate complex which when added to **30** generated the *anti*-adduct **31**.[30] The hydroxyl group was protected as the *tert*-butyldimethylsilyl ether **32** under standard conditions, and oxidation with MCPBA generated the selenoxide, which upon warming in the presence of excess pyridine undergoes *syn*-elimination to produce the dihydroquinoline **33** (>95%). This alternative synthesis is efficient, with **33** being produced in good overall yield (ca. 40%). Conversion of **33** into **36** proceeded without complications. Treatment of **36** with cesium fluoride in wet acetonitrile afforded the desired phenol **37** in 97% yield. The phenol **37** is only moderately stable at room temperature, and slowly decomposes due to air oxidation.

Bridgehead Enolate Reactivity

Having established a concise route to gram quantities of the core structure, we examined some of the chemistry of **24**. The bridged ketone **24** was readily enolized using $LiN(TMS)_2$/THF/−78 °C, and quenching with PhSeBr gave the bridgehead selenide **38** (93%), Scheme 7.[31] The X-ray structure of **24** shows that the bridgehead proton is in the plane of the π-orbitals of the carbonyl group, and therefore ideally aligned for enolization. Oxidation of **38** (MCPBA) gave the selenoxide **39** which was sufficiently stable to be isolated. Heating **39** at 40 °C resulted in rearrangement to the selenite ester **40**, and eventually the alcohol **41** (68%). If **39** is heated in the presence of the trimethylsilyl enol ether of acetone, the bridgehead acetonyl compound **42** is formed. These transformations indicate that the iminoquinomethide **39a** is formed from **39**, and does not lose a proton to form the α,β-unsaturated ketone **39b**. The formation of the iminoquinomethide intermediate **39a** is completely analogous to the chemistry exhibited by dynemicin, and speculated to be an intermediate formed from opening of the epoxide in **1**.

Direct oxidation of the enolate **24a** with dibenzoyl peroxide gave the bridgehead benzoate **43**. The enolate **24a** was readily alkylated; for example, treatment of **24a** with chloromethyl methyl ether gave **44** in excellent yield. Quite surprisingly, attempts to form the enol triflate in tetrahydrofuran by treatment with a variety of triflating reagents only resulted in the *C*-triflate **45** with small amounts of the desired *O*-triflate **46**.[32] Eventually, it was found that the *O*-triflate **46** became the major product if toluene was used as the solvent, but the yield is a modest 33%. While **46** underwent Pd^{II}-catalyzed carboxymethylation to give **47**,[33] which potentially allows access to the E-ring of dynemicin, the low yields did not make it practical for further investigation.

Rates of Cycloaromatization

We have found that, for a series of enediynes where the bonding distance between the acetylenes (*r*, 3, 8) is virtually identical, their relative rates of cycloaromatization are dramatically different, Scheme 8.[34] Measuring the rate of cycloaromatization of **24** (r = 3.4 Å, X-ray) to give **48** (68%) in 3,6-dihydrotoluene from 65 to 114 °C gave the thermodynamic parameters. The data were extrapolated to 37 °C (Table 1), and clearly show that **24** is very stable under physiological conditions. There is a modest solvent effect on the rate of cyclization of **24** to **48**, $t_{1/2}$(cyclohexadiene, 81 °C) = 10.9 h versus $t_{1/2}$(3,6-dihydrotoluene, 81 °C) = 35.0 h and $t_{1/2}$(THF, 67 °C) = 114.9 h versus $t_{1/2}$(3,6-dihydrotoluene, 67 °C) = 167.4 h.[35]

The bridgehead alkylated adduct **44** undergoes cycloaromatization to give **50** (>95%), in an exceptionally clean reaction

(30) Liotta, D.; Markiewicz, W.; Santiesteban, H. *Tetrahedron Lett.* **1977**, 4365.

(31) Magnus, P.; Carter, P.; Elliot, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544. Magnus, P.; Lewis, R.; Bennett, F. *J. Am. Chem. Soc.* **1992**, *114*, 2560.

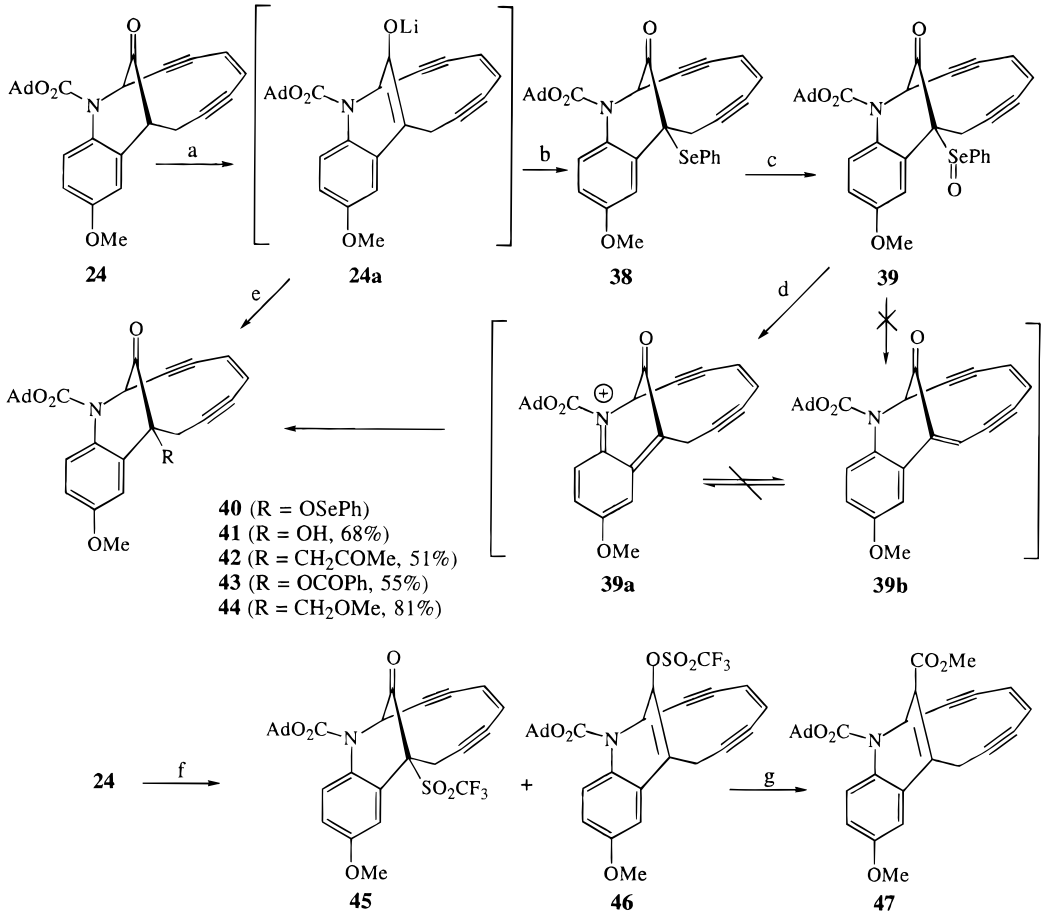
(32) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

(33) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(34) Magnus, P.; Fairhurst, R. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1541.

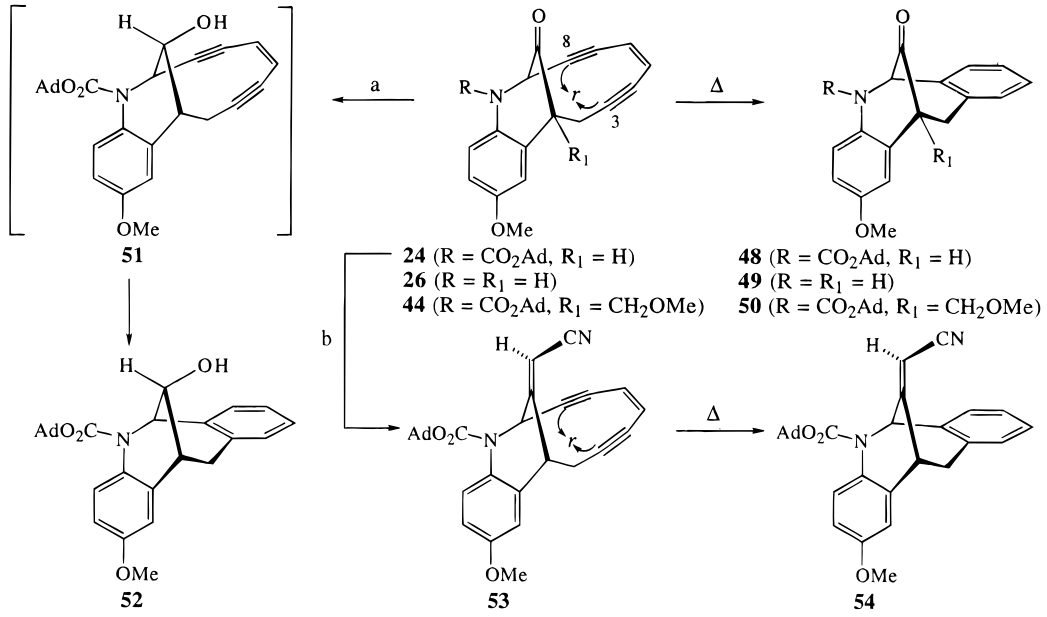
(35) While the $t_{1/2}$ differ by a factor of 3.2, this represents a very small change in $\Delta G^{\ddagger}$.

Scheme 7[a]



[a] Conditions: (a) $Li(TMS)_2$/THF/−78 °C. (b) PhSeBr, **38** (93%). (c) MCPBA/CH_2Cl_2/−78 °C. (d) 1-[(Trimethylsilyl)oxy]-1-methylethylene followed by TMSOTf, **41** (22%) and **42** (51%), dimethyldioxirane/acetone, **41** (68%). (e) $(PhCO)_2O_2$, **43** (55%), $ClCH_2OMe$, **44** (81%). (f) $LiN(TMS)_2$/PhMe/Tf_2O/−78 °C, **45** (10%) and **46** (33%). (g) $Pd(OAc)_2$/DMF/PPh_3/MeOH/Et_3N/CO at 25 °C, **47** (55%).

Scheme 8[a]



[a] Conditions: (a) $NaBH_4$/THF/MeOH, **52** (43%). (b) *n*-BuLi/$(EtO)_2P(O)CH_2CN$/THF, **53** (85%).

compared to **24**. The thermodynamic parameters are very similar to those of **24**, and indicate that it is more resistant to cycloaromatization even though the distance between the two bonding acetylene carbon atoms (*r*) must be virtually the same.

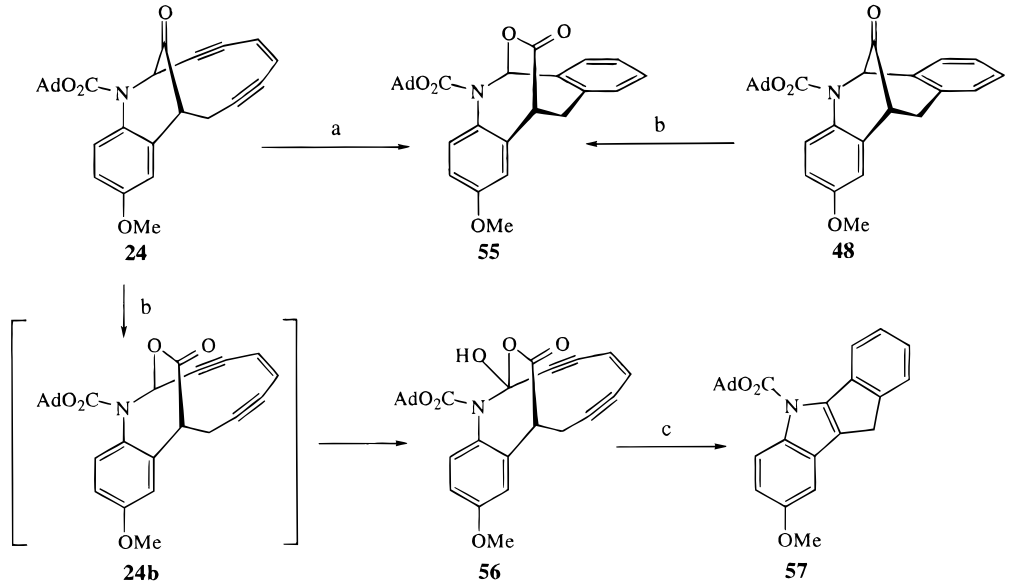
The amine **26** was heated in THF at temperatures from 51 to 67 °C to give **49** (72%). The most notable feature is that the rate of cycloaromatization of **26** increases more rapidly with increasing temperature than that of the carbamates **24** and **44**. At 37 °C **26** cycloaromatizes 1.6 times faster than **24**, and at 65 °C the difference increases to 20 times ($\Delta G^{\ddagger} = 29$ and 28.1, respectively). The origin of this difference lies in the $T\Delta S^{\ddagger}$ term.[36]

The remarkable change in entropy (**26**, $\Delta S^{\ddagger} = +28.3$ cal·mol^{-1}, **24**, $\Delta S^{\ddagger} = -9.3$ cal·mol^{-1}) appears to be caused by

Table 1.

substrate	$\Delta G^{\ddagger}$ (kcal·mol^{-1})	$\Delta H^{\ddagger}$ (kcal·mol^{-1})	$\Delta S^{\ddagger}$ (cal·mol^{-1}·K^{-1})	E_a (kcal·mol^{-1})	rate (s^{-1}) (37 °C)	$t_{1/2}$
24	29.0	26.1	−9.3	26.8	2.48×10^{-8}	324 d
26	28.1	36.9	28.3	37.6	4.10×10^{-8}	196 d
53	25.1	21.7	−10.9	22.2	1.26×10^{-5}	15.3 h
44	30.2	26.1	−9.3	33.0	3.50×10^{-9}	6.28 y

Scheme 9[a]



[a] Conditions: (a) Heating in 2,5-dihydrotoluene (air leakage). (b) MCPBA/CH_2Cl_2, **55** (59%), **56** (82%). (c) Heating in 2,5-dihydrotoluene at 140 °C, **57** (15%).

hydrogen bonding. Both the NH and C═O infrared bands of **26** change as a function of concentration, indicating intermolecular hydrogen bonding. Variable concentration ^{1}H NMR also confirmed this phenomenon. The degree of intermolecular hydrogen bonding (aggregation) is a function of temperature, and therefore causes the entropy of activation to increase and become positive (dissociation).

The ketone **24** reacted with $(EtO)_2P(O)CH_2CN$/*n*-BuLi to give **53** (85%) as a single stereoisomer. While the distance (*r*) between the bonding acetylenic carbon atoms in **24** and **53** is virtually the same, and the hybridization at the bridging carbon atom is trigonal in both compounds, **53** cycloaromatizes to give **54** (X-ray) *500 times* faster than **24** at 37 °C! An even more dramatic change in rate occurs when the bridging trigonal carbon atom is made tetrahedral. Reduction of **24** with sodium borohydride in methanol at 25 °C gave directly the cycloaromatized alcohol **52** (43%). We could not detect the intermediate enediyne **51**. Using a conservative estimate, the alcohol **51** cycloaromatizes 10^6 *times faster* than **24** at 37°C!

While the above cycloaromatization rate studies were conducted with the exclusion of air, for the slower reactions, for example, **24** to **48** at 65 °C, it was found that a new product slowly accumulated as air leaked into the reaction. The new compound turned out to be the cycloaromatized lactone **55**, and an authentic sample was made by treating **48** with *m*-chloroperoxybenzoic acid, Scheme 9. Surprisingly, when **24** was exposed to *m*-chloroperoxybenzoic acid, the amide−acetal **56** (82%) was the only isolable product.[37] Even if less than 1 equiv of oxidant was used, **56** and **24** were the only materials present. Apparently, the further Baeyer−Villiger oxidation of the presumed intermediate **24b** (in the open iminium ion form) is faster than **24**! When **56** was heated at 140 °C, it extruded carbon dioxide, cycloaromatized, and eliminated water to give the indole derivative **57** (15%).

Quantitative investigations indicate that the overall change in strain energy from enediyne to cycloaromatized adduct provides the closure driving force. We have presented computational evidence that factors controlling the ease of cycloaromatization are directly related to strain energy in the transition state rather than to proximity of the acetylenic carbon atoms (*r*) in the ground state.[38] The experimental data reported above support the strain hypothesis, but the relative rates are not predicted by computational methods that worked in the esperamicin/calicheamicin core compound(s).[39] It therefore appears that the small changes in $\Delta G^{\ddagger}$, which are manifested in substantial rate differences, are difficult to match by computational methods.

Non-Radical Cycloaromatization Pathway for the Azabicyclo[7.3.1]enediyne Core Structure Initiated by Thiolate Addition

It has been assumed that the formation of a diradical intermediate is a prerequisite for biological activity.[4] The simple azabicyclo[7.3.1]enediyne dynemicin core analogue **23** undergoes cycloaromatization *via* a polar non-radical pathway, and exhibits both *in vitro* and *in vivo* antitumor activity.[40]

Treatment of **23** with sodium 3,5-dimethylthiophenolate/THF at 0 °C gave a mixture of two compounds, **58** (ca. 1:1), which

(36) Isaacs, N. S. *Physical Organic Chemistry*; Longman Scientific & Technical: Birmingham, AL, 1987.

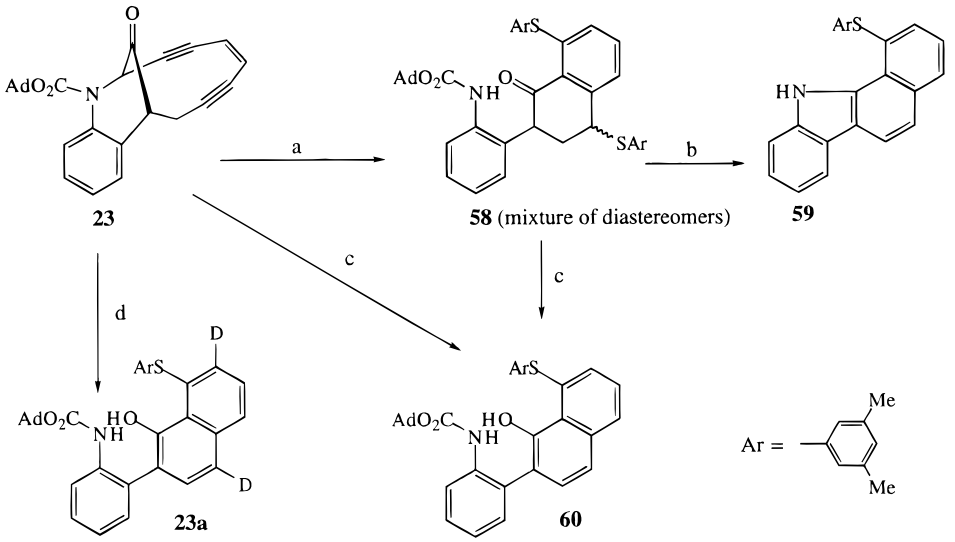
(37) The double Baeyer−Villiger oxidation of diethyl ketals gives a mixture of orthocarbonates and carbonate. Bailey, W. F.; Shih, M.-J. *J. Am. Chem. Soc.* **1982**, *104*, 1769.

(38) For calculations concerning the rate of diyl formation, see: Snyder, J. P.; Tipword, G. E. *J. Am. Chem. Soc.* **1990,** *112*, 4040 3. Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630. Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367. Magnus, P.; Fortt, S. M.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986. Semmelhack, M. F.; Gallagher, J.; Minami, T.; T. Date, T. *J. Am. Chem. Soc.* **1993**, *115*, 11618.

(39) Dr. David Langley (Bristol-Myers Squibb) is thanked for his efforts to match the relative $\Delta G^{\ddagger}$ values by computational methods.

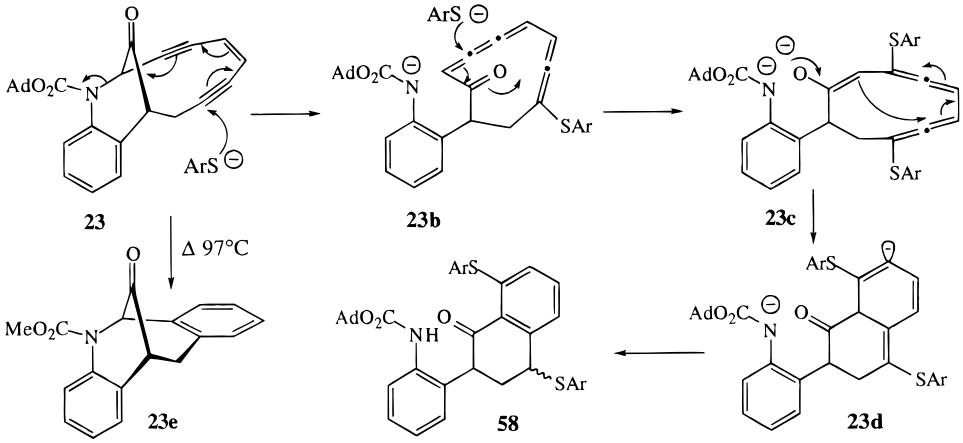
(40) Magnus, P.; Eisenbeis, S. A. *J. Am. Chem. Soc.* **1993**, *115*, 12627.

Scheme 10[a]



[a] Conditions: (a) 3,5-Dimethylthiophenol/NaH/THF/0 °C, **58** (73%). (b) TFA/CH_2Cl_2, **59** (25%). (c) NaH/THF/25 °C, **60** (72%). (d) NaH/THF/MeOD.

Scheme 11



upon deprotection (TFA) gave a single completely aromatized adduct, **59** (structure by X-ray), Scheme 10. Conducting the above reaction in THF-d_8 did not result in any deuterium incorporation into **58** or **59**, thus precluding a radical intermediate in the conversion of **23** into **58**. Treatment of **23** with sodium 3,5-dimethylthiophenolate/THF/excess NaH at 0 °C gave the naphthol **60** (72%). Carrying out the same transformation in the presence of MeOD gave **23a** with the incorporation of two deuterium atoms in the positions shown. Excess NaH converted **58** into **60** (72%). Irradiation of **23** in the presence of PhSSPh/benzene resulted in slow decomposition to an intractable mixture.

A plausible mechanistic explanation for this unprecedented reaction involves thiolate addition to the enediyne **23** to give the cumulene **23b**, which can undergo further thiolate addition resulting in the enolate **23c**. Enolate anion ring closure to **23d** followed by protonation and tautomerism results in **58**, which gives **60**. It should be noted that **23** does not undergo the normal Bergman cycloaromatization to give **23e** at an appreciable rate until it is heated to at least 97 °C ($t_{1/2}$ = 8.26 h). The mechanism shown in Scheme 11 is consistent with the MeOD experiment, and it is probable that the deuterium *para* to the −OH was introduced by base-catalyzed exchange after elimination of ArS−.

Myers has shown that neocarzinostatin chromophore undergoes thiol addition to trigger cycloaromatization. The actual cycloaromatization reaction involves a diradical which has been trapped by THF-d_8.[41] It has been shown by Saito that there is a second pathway available for the cycloaromatization of neocarzinostatin. Under physiological conditions (D_2O/buffered 2-mercaptoethanol) neocarzinostatin cycloaromatizes with the incorporation of one deuterium atom (80%) in the aromatic ring.[42] This duality of cycloaromatization mechanisms, diradical and polar, has not been seen in any other enediynes. This study shows that the dynemicin core analogue **23** can undergo cycloaromatization to **23e** *via* the "normal" thermal (97 °C) diradical cycloaromatization pathway, and in the presence of thiolate (0 °C), a polar cycloaromatization pathway intervenes to give **58**/**60**.[43]

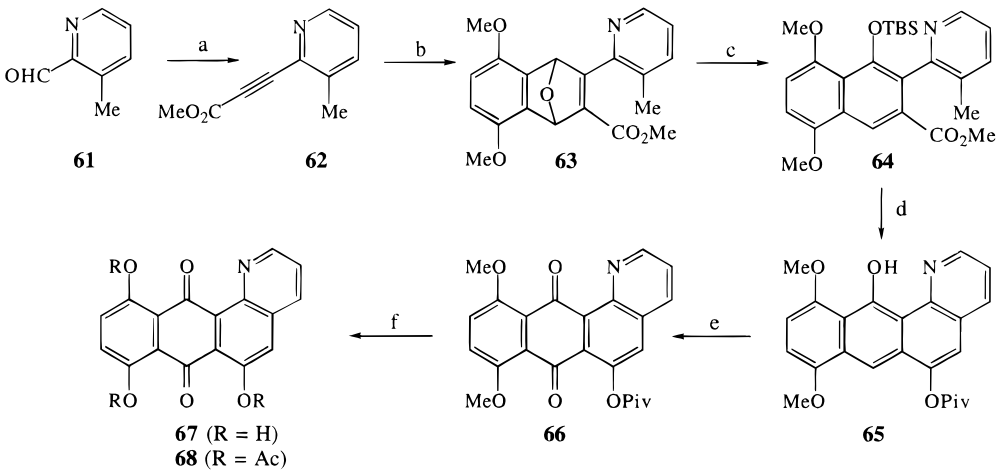
Naphtho[2,3-*h*]quinoline Portion of Dynemicin

The biological activity of anthraquinones and methods for their synthesis have been the subject of numerous reviews.[44] A number of anthraquinones exhibit *in vitro* activity versus murine L1210 leukemia cell lines, as well as *in vivo* activity against P388 leukemia cell lines.[45] This raises the intriguing possibility

(41) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130. Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146. Nicolaou, K. C.; Skokotas, G.; Furuya, S.; Suemune, H.; Nicolaou, C. *Angew. Chem., Int. Ed. Engl.* **1990**, 1064.

(42) Sugiyama, H.; Yamashita, K.; Nishi, M.; Saito, *Tetrahedron Lett.* **1992**, *33*, 515. Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc*. **1989**, *111*, 4120. Fujiwara, K.; Kurisaki, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329.

Scheme 12[a]



[a] Conditions: (a) (i) PPh_3/CBr_4, (72%). (ii) $LiN(TMS)_2$/THF followed by *n*-BuLi and $ClCO_2Me$, **62** (95%). (b) 4,7-Dimethoxyisobenzofuran/PhH/reflux for 18 h, **63** (100%). (c) TBSOTf/2,6-lutidine/CH_2Cl_2, **64** (99.6%). (d) LDA/THF/25 °C, followed by PivCl/py, **65** (72%). (e) $Ag^{II}O$/dioxane HNO_3, **66** (72%). (f) HBr/AcOH/reflux followed by Ac_2O/py, **68** (68%).

that the anthraquinone portion of dynemicin could have antitumor activity, rather than simply serving as a DNA intercalating partner.[46,47]

The aldehyde **61**[48] was converted into the alkyne **62** using standard methodology,[49] and heated with 4,7-dimethoxyisobenzofuran in benzene at reflux to afford the adduct **63** in quantitative yield, Scheme 12.[50] The bridging ether in **63** was cleaved with *tert*-butyldimethylsilyl trifluoromethanesulfonate, affording a 5:1 ratio of (*tert*-butyldimethylsilyl)oxy-protected phenols **64** (only one regioisomer shown). Treatment of **64** with lithium diisopropylamide in tetrahydrofuran, followed by pivaloyl chloride, gave **65**.[51] The mixture of **65** (and regioisomer) was readily oxidized to the anthraquinone **66** (72%, $Ag^{II}O$, HNO_3/dioxane).[52] The minor regioisomer was destroyed under these conditions. Deprotection of the anthraquinone **66** proved to be quite difficult; however, warming **66** with 48% aqueous HBr/AcOH gave **67**. Although the triol **67** could be isolated, it was found to be extremely insoluble in the majority of organic solvents, thus making characterization difficult. Acetylation of **67** gave the triacetate **68** (68% from **66**). Due to the instability of the triacetate **68** (deacetylation), and the inability to purify the trihydroxyanthraquinone **67**, neither were submitted for biological evaluation. However, **66** showed promising results. The *in vitro* assays against HCT-116 cell lines provided an IC_{50} value of 500 ng/mL. Comparisons to dynemicin A and its triacetate reveal that **66** is less active *in vitro*, with dynemicin A **1** (R = H) and its triacetate **1** (R = Ac) having IC_{50} values of 0.28 and 0.18 ng/mL, respectively, in HCT-116 cell lines.[43]

An alternative synthesis of the naphtho[2,3-*h*]quinoline core structure was examined that avoided the construction of 4,7-dimethoxyisobenzofuran, and is regiospecific, Scheme 13.

ortho Lithiation of 2,5-dimethoxybenzyl alcohol using *n*-butyllithium in tetrahydrofuran at reflux, followed by quenching the resulting dianion with carbon dioxide and acidification, gave the lactone **70** (80%). Addition of the lactone **70** to a solution of lithium diisopropylamide in tetrahydrofuran, followed by ethyl 3-(3-methylpyrid-2-yl)propenoate gave the adduct **71** (and stereoisomer) in excellent yield.

Exposure of **71** to *p*-toluenesulfonic acid in chloroform at 40 °C resulted in clean aromatization to give, after pivaloylation, the naphthalene derivative **72**. When the derived pivaloyl ester derivative **72** was treated with lithium diisopropylamide in tetrahydrofuran at −70 to +26 °C, it was converted into **73**

(43) The core azabicyclo[7.3.1]enediyne compounds **25** showed *in vivo* potency and activity (efficacy, *T/C* > 125%) in P388 leukemia assays using CDF1 mice (2 mg/kg gave *T/C* values of 175% and 170%, respectively. Kedarcidin gave a *T/C* of 175% at 2.4 mg/kg. In a distal solid tumor model, which measured delay in tumor growth of a subcutaneous M109 lung carcinoma, **26** was active ($T - C$ = 7.5 days) when administered intervenously every two days beginning on the day of tumor implant for a total of five doses of 1.2 (mg/kg)/dose. Using the same model and schedule, **25** was found to be marginally active ($T - C = 3.0$ days) while esperamicin ($T - C = 11.0$ days at 0.05 (mg/kg)/dose) and neocarzinostatin ($T - C =$ 19.3 days at 0.6 (mg/kg)/dose) were more active. *In vitro* cytotoxicity, assessed in HCT116 human colon carcinoma cells, showed that **25** was 350 times more potent than **23** (IC_{50} values of 0.21 and 75 μM, respectively). Dr.'s William C. Rose, Nada Zein, and Wyle Solomon, Bristol-Myers Squibb, Pharmaceutical Research Institute, Oncology Drug Discovery, P.O. Box 4000, Princeton, NJ 08543.

(44) Kelly, T. R. *Tetrahedron* **1984**, *40*, 4537.

(45) **(45)** Showalter, H. D. H.; Johnson, J. L.; Hoftiezer, J. M. *J. Heterocycl. Chem.* **1986**, *23*, 1491. Showalter, H. D. H.; Johnson, J. L.; Hoftiezer, J. M.; Turner, W. R.; Werbel, L. M.; Leopold, W. R.; Shillis, J. L.; Jackson, R. C.; Elslager, E. F. *J. Med. Chem.* **1987**, *30*, 121.

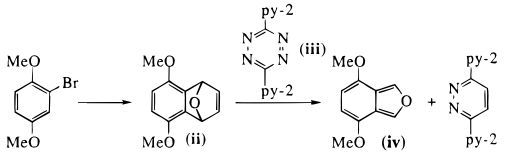
(46) Magnus, P.; Eisenbeis, S. A.; Magnus, N. *J. Chem. Soc., Chem. Commun.* **1994**, 1545.

(47) Chikashita, H.; J. A. Porco. J. A. Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 1692. Nicolaou, K. C.; Gross, J. L.; Kerr, M. A.; Lemus, R. H.; Ikeda, K.; Ohe, K. *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 781. Okita, T.; Isobe, M. *Tetrahedron*, **1994**, *50*, 11143. Okita, T.; Isobe, M. *Tetrahedron* **1995**, *51*, 3737. Okita, T.; Isobe, M. *Synlett* **1994**, 589.

(48) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534. Boekelheide, V.; Lynn, W. J. *J. Am. Chem. Soc.* **1954**, *76*, 1286. Ginsburg, S.; Wilson, I. *J. Am. Chem. Soc.* **1957**, *79*, 481. Mathes, W.; Sauermilch, W. *Chem. Ber.* **1957**, *90*, 758. Jones, G.; Mouat, D. J.; Tonkinson, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2719.

(49) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769. McIntosh, M.; Weinreb, S. *J. Org. Chem.* **1993**, *58*, 4823.

(50) 4,7-Dimethoxyisobenzofuran (**iv**) was made by treatment of **ii** with the tetrazine **iii**.

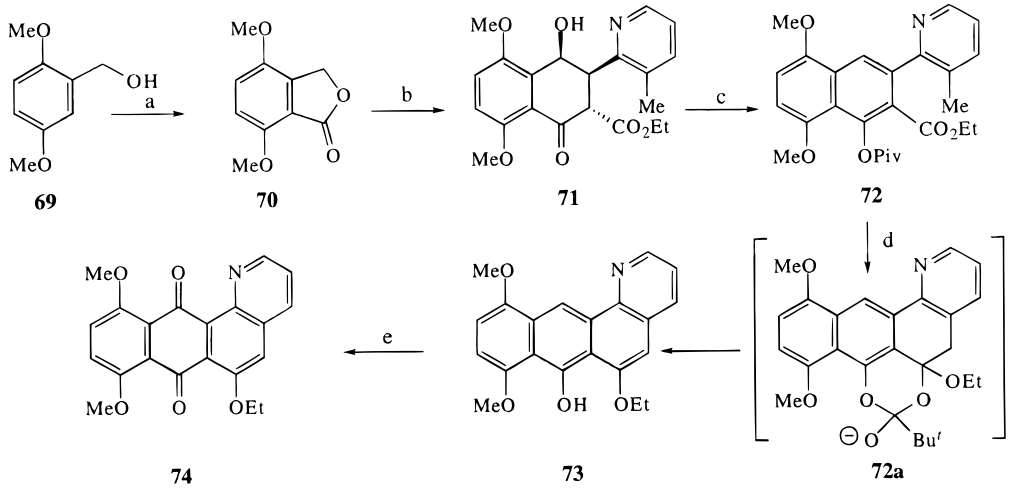


While **iv** has been reported as an intermediate in various [2 + 4] cycloaddition reactions, it has not been previously isolated presumably because of its assumed instability. For the synthesis of **ii** see: Cragg, G. M. L.; Giles, R. G. F.; Roos, G. P. H. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1339. **iii**: Geldard,J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318. Lynch, V. M.; Fairhurst, R.; Magnus, P.; Davis, B. E. *Acta Crystallogr., Sect. C* **1995**, *C51*, 780−782. Warrener, R. N. *J. Org. Chem.* **1971**, *93*, 2346. Priestly, G. M.; Warrener, R. N. *Tetrahedron Lett.* **1972**, *13*, 4295. Recently Danishefsky has reported the *in situ* use of 4,7-dimethoxyisobenzofuran for the synthesis of dynemicin analogs; see: Shair, M. D.; Yoon, T.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2477.

(51) Brandão, M. A. F.; de Oliveira, A. B.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 2437.

(52) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.

Scheme 13[a]



[a] Conditions: (a) *n*-BuLi/THF/reflux, followed by CO_2, **70** (80%). (b) LDA/THF/**70**, followed by ethyl 3-(3-methylpyrid-2-yl)propenoate/−78 °C, **71** (96%). (c) *p*-TsOH/$CHCl_3$, followed by PivCl/Et_3N/DMAP/CH_2Cl_2, **72** (87%). (d) LDA/THF/−70 to +26 °C, **73** (95%). (e) $Ce(NH_4)_2(NO_2)_6$/MeCN/H_2O, **74** (74%).

(95%). Presumably, the origin of the ethyl ether **73** is *via* the intermediate ortho ester **72a**, which prefers to eliminate pivaloate anion rather than ethoxide anion, thus providing *in situ* protection of the newly formed anthracene **73**.

Oxidation of **73** with ceric ammonium nitrate in acetonitrile−water gave the anthraquinone **74** as an orange crystalline solid (74%).[53] Tests for cytotoxicity and DNA cleavage were conducted using etoposide (UP-16) as the reference. The inhibitory concentration (IC_{50}) of anthraquinone **74** was 2.8×10^{-3} mg/mL, while the reference had an IC_{50} of 1.5×10^{-3} mg/mL.[43]

Summary

In all of the $\eta^2Co_2(CO)_6$-acetylene-mediated cyclizations, the blank reaction without the cobalt metallocycle was unsuccessful. This strategy has provided short synthetic routes to the core structures of the other enediyne antitumor agents.[54] The rate studies clearly show that ring strain and conformational factors control the ease of cycloaromatization. This information should assist the design of non-natural enediynes with potential antitumor activity.

Experimental Section

Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone under nitrogen prior to use. *N*,*N*-Dimethylformamide (DMF), hexane, and benzene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide and stored over 3 Å molecular sieves under argon. Triethylamine was distilled from calcium hydride and stored under argon. All reactions involving organometallic reagents or other moisture sensitive reactants were executed under an atmosphere of dry nitrogen or argon using oven-dried and/or flame-dried glassware.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a General Electric QE-300 (300 MHz) spectrometer as solutions in deuteriochloroform ($CDCl_3$), unless otherwise indicated. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CDCl_3$ (7.24 ppm) as internal standard. Coupling constants are given in hertz (Hz). ^{13}C NMR spectra were recorded on General Electric QE-300 (75 MHz) instrument as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. IR spectra were recorded either neat on sodium chloride plates or as solutions in solvent as indicated using a Perkin-Elmer 1600 FT-IR spectrometer, and are reported in wavenumbers (cm^{-1}). Low-resolution chemical ionization (CI) mass spectra were obtained on a TSQ 70 instrument, and the exact mass determinations were obtained on a VG Analytical ZAB2-E instrument.

Routine monitoring of reactions was performed using Merck Alufolien Kieselgel 60 F_{254} silica gel and aluminum-backed TLC plates. Flash chromatography was performed using silica gel Merck Kieselgel 60H F_{254} and Florisil 100−200 mesh with the solvent indicated.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-[(tetrahydro)-pyranyloxy]hept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]-quinoline (13).** Ethylmagnesium bromide (36.0 mL, 1 M, 0.036 mol) was added to a cooled solution of **10** (5.7 g, 0.030 mol) in tetrahydrofuran (45 mL), and the mixture was stirred for 20 min followed by addition of **11** (7.00 g, 0.027 mol) in tetrahydrofuran (30 mL). Adamantyl chloroformate (7.31 g, 0.034 mol) was slowly added over a period of 2 h and the mixture stirred for 15 h and poured into saturated aqueous NH_4Cl (100 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3×100 mL). The extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed over silica gel eluting with 5% Et_2O/pentane to give the product **13** (10.4 g, 64%) as a pale yellow foam: IR ($CDCl_3$) 2973, 2956, 2196, 1702, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.55 (1H, m), 7.09−6.97 (3H, m), 5.76−5.68 (4H, m), 4.75 (1H, bs), 4.35−4.19 (2H, q), 3.87 (1H, m), 3.57 (1H, m), 2.17 (9H, s), 1.83−1.52 (12H, m), 0.97 (9H, s), 0.26 (3H, s), 0.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 150.1, 131.6, 129.0, 127.7, 126.9, 125.2, 124.9, 124.8, 124.3, 119.5, 119.3, 103.5, 96.9, 93.1, 92.9, 82.7, 81.9, 80.2, 61.9, 54.7, 48.9, 41.5, 36.2, 31.0, 30.1, 25.6, 19.1, −4.4, −4.7; HRMS (CI) calcd for $C_{38}H_{49}NO_5Si$ (M^+) 627.338, found 627.338.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-hydroxyhept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]quinoline (15).** A solution of **13** (1.34 g, 2.64 mmol) and *p*-TsOH·H_2O (0.15 g) in ethanol (30 mL) was stirred at 55 °C for 10 h. The mixture was concentrated *in vacuo*, dissolved in Et_2O (50 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*, and the residue chromatographed over silica gel eluting with 40% Et_2O/pentane to give **15** (0.98 g, 87%): IR ($CHCl_3$) 3460, 2918, 1689 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, br s), 7.11−6.98 (3H, m), 5.78−5.69 (3H, m), 4.25 (2H, s), 2.61 (9H, s), 2.17 (6H, s), 0.97 (9H, s), 0.27 (3H, s), 0.26 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 131.6, 127.7, 125.3, 124.3, 119.9, 119.8, 119.0, 103.5, 95.2, 93.2, 82.6, 82.2, 80.3, 51.4, 48.9, 41.5, 36.1, 30.9,

(53) Ho, T.-L.; Hall, T.-W.; Wong, C. M. *Synthesis* **1973**, 206.

(54) Magnus, P. *The Use of $\eta^2Co_2(CO)_6$-Acetylene Complexes for the Synthesis of Enediyne Antitumor Antibiotics*; SmithKline Beecham Research Symposium, Organometallic Reagents in Organic Synthesis; Academic Press Ltd.: New York, 1994; Chapter 1, p 1. Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283.

25.6, 18.2, −4.4, −4.67; HRMS (CI) calcd for $C_{33}H_{42}NO_4Si$ ($M^+ + 1$) 544.288, found 544.288.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-hydroxy(5,6-η^2-hexacarbonyldicobaltio)hept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]quinoline (17).** To a solution of **15** (1.0 g, 2.36 mmol) in EtOAc (50 mL) at 0 °C was added $Co_2(CO)_8$ (0.89 g, 1.1 equiv) as a solid. Immediate evolution of gas was observed. The mixture was stirred for 15 min, and concentrated to dryness. The crude product was chromatographed over silica gel (200 times the original weight of starting material) and eluted with 20% Et_2O/pentane (60% yield): IR ($CHCl_3$) 3215, 2863, 2605, 2030, 1963, 1685, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61−7.54 (1H, br d), 7.19−7.02 (3H, m), 6.71 (1H, d, J = 9.2 Hz), 5.83 (1H, s), 5.76 (1H, s), 5.63 (1H, dd, J = 9.2, 2.3 Hz), 4.82−4.60 (2H, m), 2.17 (9H, s), 1.72 (6H, s), 0.97 (9H, s), 0.27 (3H, s), 0.26 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0−198.8, 151.9, 149.9, 138.2, 131.4, 127.6, 125.5, 125.1, 124.4, 124.3, 110.0, 103.6, 97.6, 95.9, 82.3, 81.7, 81.3, 64.1, 49.0, 41.4, 36.1, 30.9, (25.5), 18.1, −4.4, −4.7. This compound was used directly in the next step.

***N*-[(Adamantyloxy)carbonyl]-15-oxobenzo[10a,14a]bicyclo[7.3.1]-trideca-3,7-diyn-5-ene (23).** To a solution of **17** (0.913 g, 1.10 mmol) in 2-nitropropane (39.0 mL) and 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) (1.13 g, 5.50 mmol) at −10 °C was rapidly added triflic anhydride (Tf_2O) (0.56 mL, 3.30 mmol). The mixture was stirred at −10 °C for 15 min followed by the addition of saturated aqueous $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with 2-nitropropane (3 × 10 mL) and dried ($MgSO_4$). The extracts were filtered and diluted with acetone (70 mL) and cooled to −10 °C, followed by the addition of ceric ammonium nitrate (CAN) (4.82 g, 8.80 mmol) in three portions (over 5 min). The mixture was stirred for an additional 15 min with rapid evolution of gas occurring. Addition of NEt^iPr_2 (4.80 mL, 27.5 mmol) resulted in the formation of a brown precipitate. The mixture was poured onto a column of silica (50 g) and eluted with EtOAc (500 mL). The organic layers were concentrated, and the crude product was chromatographed over silica gel eluting with dichloromethane to give **23** (0.25 g, 55%): IR ($CHCl_3$) 3013, 2917, 2341, 1736, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, J = 7.31 Hz), 7.29−7.21 (3H, m), 5.82 (1H, s), 5.75 (1H, d, J = 9.3 Hz), 5.63 (1H, d, J = 9.6 Hz), 3.71 (1H, br s), 3.54−3.50 (1H, m), 3.48−3.20 (1H, dd, J = 14.5, 3.0 Hz), 2.15 (9H, s), 1.66 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 151.7, 136.1, 128.2, 127.2, 126.3, 126.2, 125.8, 125.6, 121.2, 99.3, 91.4, 89.7, 83.3, 82.7, 49.1, 41.4, 36.2, 36.0, 30.9, 21.5; HRMS (CI) calcd for $C_{27}H_{25}NO_3$ (M^+) 411.183, found 411.183.

15-Oxo-10-azabenzo[10a,14a]bicyclo[7.3.1]trideca-3,7-diyn-5-ene (25). To a solution of **23** (0.247 g, 0.60 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2.31 mL, 30.0 mmol), and the mixture was stirred at 25 °C for 2 h. The mixture was quenched by the addition of solid $NaHCO_3$ (5.0 g), and extracted with dichloromethane (3 × 25 mL). The extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo*, and chromatographed over silica gel eluting with dichloromethane to give **25** (0.14 g, 81%): IR (CH_2Cl_2) 3379, 2986, 2305, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.22 (1H, d, J = 9.7 Hz), 7.15 (1H, t, J = 7.5 Hz), 6.95 (1H, t, J = 7.5 Hz), 6.74 (1H, d, J = 7.9 Hz), 5.73 (2H, q, J = 22.4, 9.1 Hz), 4.62 (1H, s), 4.23 (1H, br s), 3.63 (1H, t, J = 4.1 Hz), 3.51 (1H, dd, J = 2.9 Hz), 3.39 (1H, qd, J = 17.7, 4.8, 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 142.4, 127.9, 126.6, 125.8, 122.3, 121.3, 120.9, 116.5, 100.1, 92.7, 90.0, 83.0, 54.0, 53.4, 21.7; HRMS (CI) calcd for $C_{16}H_{11}NO$ (M^+) 233.084, found 233.083.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-[(tetrahydropyranyl)oxy]hept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]-6-methoxyquinoline (14).** A solution of ethylmagnesium bromide in tetrahydrofuran (43 mL, 1 M solution, 43 mmol) was added to a solution of **10** (6.89 g, 36.2 mmol) and **12** (9.41 g, 32.5 mmol) in tetrahydrofuran (210 mL) at 0 °C. After the initial evolution of gas, the mixture was stirred for 20 min at 0 °C, and a solution of adamantyl chloroformate (11.51 g, 53.6 mmol) in tetrahydrofuran (40 mL) was added *via* syringe pump over 90 min, maintaining the temperature at 0 °C. The mixture was allowed to warm to 25 °C, stirred for 18 h, and quenched with saturated aqueous $NaHCO_3$ (60 mL). The resulting mixture was extracted with Et_2O (300 mL and 2 × 150 mL), and the combined extracts were dried ($MgSO_4$) and evaporated to give a brown oil. Flash column chromatography over silica gel eluting with 4:1 pentane/Et_2O gave **14** (16.11 g, 75%): IR ($CHCl_3$) 1687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (1H, s), 6.62 (1H, dd, J = 8.8, 2.8 Hz), 6.52 (1H, d, J = 2.8 Hz), 5.74 (1H, dd, J = 11.0, 1.4 Hz), 5.68−5.79 (1H, s), 5.67 (1H, d, J = 11.0 Hz), 5.62 (1H, s), 4.75 (1H, s), 4.31 (1H, dd, J = 16.0, 1.4 Hz), 4.23 (1H, dd, J = 16.0, 1.4 Hz), 3.77−3.89 (1H, m), 3.76 (3H, s), 3.46−3.58 (1H, m), 2.15 (9H, s), 1.64 (6H, s), 1.45−1.89 (6H, m), 0.96 (9H, s), 0.25 (3H, s), 0.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 152.0, 128.9, 125.5, 124.8, 119.5, 119.3, 110.5, 109.9, 103.5, 96.8, 93.1, 92.8, 82.7, 81.6, 80.1, 61.9, 55.3, 54.7, 48.8, 41.5, 36.1, 30.9, 30.2, 25.5, 25.3, 19.0, 18.1, −4.3, −4.7; HRMS (FAB) calcd for $C_{39}H_{51}NO_6Si$ (M^+) 657.349, found 657.351.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-hydroxyhept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]-6-methoxyquinoline (16).** Pyridinium *p*-toluenesulfonate (1.23 g, 4.9 mmol) was added to a solution of **14** (16.1 g, 24.5 mmol) in ethanol (320 mL) at 25 °C and the solution heated at reflux for 18 h. After the solution was cooled to 25 °C, the solvent was evaporated *in vacuo*, and water (150 mL) added to the residue. The mixture was extracted with Et_2O (200 mL and 2 × 100 mL), dried ($MgSO_4$), and evaporated to give the crude product. Flash chromatography over silica gel eluting with 3:2 pentane/Et_2O gave **16** (12.58 g, 89%). Alternatively **16** can be obtained from the crude product by crystallization from 4:1 pentane/Et_2O (50 mL) (12.15 g, 86%): IR ($CHCl_3$) 3474, 1685, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, s), 6.63 (1H, dd, J = 8.9, 2.7 Hz), 6.52 (1H, d, J = 2.7 Hz), 5.77 (1H, m), 5.70−5.80 (1H, m), 5.68 (1H, m), 5.64 (1H, s), 4.27 (2H, s), 3.77 (3H, s), 2.15 (9H, s), 1.64 (6H, s), 0.96 (3H, s), 0.26 (3H, s), 0.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 152.2, 128.9, 125.3, 124.8, 119.9, 119.6, 110.5, 109.9, 103.6, 95.3, 93.2, 82.5, 81.9, 80.2, 55.3, 51.3, 48.9, 41.5, 36.1, 30.9, 25.5, 18.1, −4.33, −4.71; HRMS (FAB) calcd for $C_{34}H_{43}NO_5Si$ (M^+) 579.291, found 573.290.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-hydroxy(5,6-η^2-hexacarbonyldicobaltio)hept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]-6-methoxyquinoline (18).** A solution of dicobalt octacarbonyl (2.67 g, 7.81 mmol) in tetrahydrofuran (60 mL) was added rapidly in a single portion to a stirred solution of **16** (4.27 g, 7.44 mmol) in tetrahydrofuran (80 mL) at 25 °C. After the initial evolution of gas the mixture was stirred at 25 °C for 40 min, and evaporated to give a viscous brown oil. Flash column chromatography over silica gel eluting with 9:1 pentane/Et_2O gave a trace of the biscobalt complex as a black amorphous solid, followed by **18** (3.77 g, 59%) as a red-brown amorphous solid. Further elution with 7:3 pentane/Et_2O gave **20** (2.02 g, 33%) as a red brown amorphous solid. Finally, elution with 3:2 pentane/Et_2O gave **16** (0.25 g, 6%). Data for **18**: IR ($CHCl_3$) 2092, 2056, 2026, 1687, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4 (1H, s), 6.6−6.72 (2H, m), 6.54 (1H, d, J = 2.8 Hz), 5.80 (1H, s), 5.66 (1H, s), 5.62 (1H, dd, J = 10.5, 2.0 Hz), 4.82 (1H, m), 4.70 (1H, d, J = 14.5 Hz), 3.77 (3H, s), 2.16 (9H, s), 1.65 (6H, s), 0.95 (9H, s), 0.25 (3H, s), 0.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 152.3, 138.2, 128.9, 125.4, 124.6, 110.7, 110.1, 103.7, 97.7, 96.0, 82.1, 81.8, 81.2, 64.1, 64.0, 55.4, 41.5, 36.1, 30.9, 25.5, 18.1, −4.3, −4.7. This compound was used directly in the next step.

Recycling Incorrect Cobalt Regioisomer 20. Ceric ammonium nitrate (5.15 g, 9.40 mmol) was added portionwise over 3−4 min to a solution of **20** (2.02 g, 2.35 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (3.86 g, 18.8 mmol) in acetone (24 mL) at −10 °C. After an initial evolution of gas the mixture was stirred for 20 min at −10 °C and quenched with *N*,*N*-diisopropylethylamine (6.07 g, 47.0 mmol). The resulting dark brown slurry was eluted through a short column of silica gel with 1:1 Et_2O/dichloromethane to give a viscous brown oil. Flash column chromatography over silica gel eluting with 3:2 pentane/Et_2O gave **16** (1.03 g, 76%).

***N*-[(Adamantyloxy)carbonyl]-15-oxo-13-methoxy-10-azabenzo-[10a,14a]bicyclo[7.3.1]trideca-3,7-diyn-5-ene (24).** Trifluoromethanesulfonic anhydride (1.71 mL, 10.2 mmol) was added rapidly in a single portion to a stirred solution of **18** (2.18 g, 2.54 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (3.13 g, 15.2 mmol) in 2-nitropropane (55 mL) at −10 °C. After being stirred for 30 min at −10 °C, the mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL), and the layers were separated. The aqueous layer was extracted with 2-nitropropane (15 mL), and the combined extracts were dried ($MgSO_4$), filtered, and diluted with acetone (80 mL) to give an opaque red-brown solution. After cooling to −10 °C, ceric ammonium nitrate (13.93 g, 25.4 mmol)

was added portionwise over 3−4 min. After the initial gas evolution, the mixture was stirred for 20 min, and quenched with *N*,*N*-diisopropylethylamine (8.85 mL, 50.8 mmol). Elution of the mixture through a short column of silica gel with 1:1 Et_2O/dichloromethane gave a viscous brown oil. Flash column chromatography over silica gel eluting with dichloromethane gave **24** (0.59 g, 53%). Recrystallization from Et_2O/dichloromethane gave small white prisms: mp 115−119 °C dec (rapid heating in sealed capillary tube); IR ($CHCl_3$) 1733, 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (1H, d, J = 8 Hz), 6.81 (1H, dd, J = 2.4, 8.9 Hz), 6.76 (1H, s), 5.77 (1H, s), 5.75 (1H, d, J = 9.5 Hz), 5.62 (1H, d, J = 9.5 Hz), 3.79 (3H, s), 3.68 (1H, X of ABX), 3.47 (1H, A of ABX), 3.19 (1H, B of ABX), 2.13 (9H, s), 1.64 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 157.1, 151.8, 129.5, 129.3, 126.8, 126.3, 121.1, 112.3, 111.6, 99.1, 91.5, 90.0, 83.3, 82.3, 55.4, 54.2, 49.2, 41.4, 36.0, 30.9, 21.5; HRMS (CI) calcd for $C_{28}H_{28}NO_4$ (M^+ + 1) 442.201, found 442.201.

15-Oxo-13-methoxy-10-azabenzo[10a,14a]bicyclo[7.3.1]trideca-3,7-diyn-5-ene (26). Trifluoroacetic acid (2.1 mL, 27.3 mmol) was added dropwise to a stirred solution of **24** (481 mg, 1.09 mmol) in dichloromethane (22 mL) at 0 °C. The mixture was warmed to room temperature, and after 1.5 h the mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with dichloromethane (3 × 15 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a brown amorphous solid. Chromatography over silica gel eluting with 9:1 dichloromethane/Et_2O gave **26** (224 mg, 78%) as a white amorphous solid: mp 101−105 °C dec (rapid heating in sealed capillary tube); ^1H NMR (300 MHz, $CDCl_3$) δ 6.6−6.8 (3H, m), 5.78 (1H, d, J = 9.2 Hz), 5.66 (1H, d, J = 9.2 Hz), 4.58 (1H, s), 3.76 (3H, s), 3.59 (1H, X of ABX), 3.55 (1H, A of ABX), 3.22 (1H, B of ABX); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 153.9, 136.3, 125.6, 123.5, 121.2, 117.0, 112.9, 112.4, 99.9, 93.2, 89.9, 82.9, 55.5, 54.2, 48.6, 21.6; HRMS (CI) calcd for $C_{17}H_{14}NO_2$ (M^+ + 1) 264.102, found 264.102.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-[(tetrahydropyranyl)oxy]hept-3-ene-1,5-diynyl]-3,4-dihydro-3,4-epoxy-6-[(triisopropylsilyl)oxy]quinoline (30).** A solution of **29** (7.7 g, 11.5 mmol), water (850 mL), and saturated $NaHCO_3$ (850 mL) in dichloromethane (850 mL) was treated with *m*-chloroperoxybenzoic acid (7.94 g, 46.0 mmol). After 10 min the mixture was diluted with dichloromethane (850 mL). After 24 h the reaction mixture was quenched with 1-pentene (200 mL) and extracted with dichloromethane (3 × 150 mL). The extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give **30** (7.87 g, 100%), which was used directly in the next step: IR ($CDCl_3$) 2944, 1693, 1614 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (1H, s), 6.88 (1H, m), 6.81 (1H, d, J = 5.6 Hz), 5.91 (1H, br s), 5.76 (1H, d, J = 10.9 Hz), 5.62 (1H, d, J = 10.9 Hz), 4.84 (1H, m), 4.40 (2H, m), 4.0 (1H, m), 3.85−3.8 (2H, m), 3.60−3.50 (1H, m), 2.20−2.00 (9H, br d), 1.90−1.40 (14H, m), 1.30−1.20 (3H, m), 1.09 (12H, s), 1.07 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 126.2, 119.9, 119.8, 118.7, 96.3, 96.2, 93.0, 92.9, 90.8, 82.5, 82.4, 81.9, 81.2, 81.1, 61.6, 61.5, 61.0, 54.3, 50.6, 41.2, 35.9, 30.7, 30.0, 25.2, 18.7, 17.7, 12.4; HRMS (CI) calcd for $C_{41}H_{44}NO_6Si$ (M^+) 685.380, found 685.378.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-[(tetrahydropyranyl)oxy]hept-3-ene-1,5-diynyl]-3,4-dihydro-3-hydroxy-4-(phenylseleno)-6-[(triisopropylsilyl)oxy]quinoline (31).** To a slurry of diphenyl diselenide (31.9 g, 102.1 mmol) in EtOH (735 mL) was added $NaBH_4$ (3.22 g, 85.1 mmol) in small portions. The slurry was stirred for 1 h followed by slow addition (ca. 30 min) of **30** (23.3 g, 34.0 mmol) dissolved in tetrahydrofuran (365 mL). The mixture was stirred for 4 h and quenched with water (2 L). The mixture was extracted with Et_2O (3 × 200 mL), dried ($MgSO_4$), and evaporated *in vacuo*, and the crude material was purified by chromatography over silica gel eluting with 10% Et_2O/pentane to give **31** (18.3 g, 64%) as a yellow oil: IR ($CDCl_3$) 3399, 2944, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (2H, m), 7.43 (1H, d, J = 8.5 Hz), 7.32−7.25 (3H, m), 7.13 (1H, d, J = 3.9 Hz), 6.73 (1H, dd, J = 8.9, 2.8 Hz), 5.78 (2H, s), 5.38 (1H, s), 4.90 (1H, dt, J = 10.3, 3.1 Hz), 4.40−4.25 (3H, m), 3.80 (1H, m), 3.57 (3H, m), 3.18 (1H, m), 2.15 (9H, s), 1.8−1.57 (12H, m), 1.19 (5H, m), 1.06 (12H, s), 1.04 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.5, 132.6, 131.6, 129.3, 129.1, 128.7, 127.1, 126.0, 120.4, 119.4, 119.3, 119.2, 118.9, 96.1, 93.8, 92.5, 83.0, 82.1, 81.4, 75.5, 61.5, 54.5, 47.0, 41.3, 36.0, 30.7, 29.9, 25.2, 18.6, 17.8, 12.4; HRMS (CI) calcd for $C_{47}H_{61}NO_6SiSe$ (M^+) 843.343, found 843.342.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-[(tetrahydropyranyl)oxy]hept-3-ene-1,5-diynyl]-3,4-dihydro-3-[(*tert*-butyldimethylsilyl)oxy]-4-(phenylseleno)-6-[(triisopropylsilyl)oxy]quinoline (32).** A solution of **31** (18.3 g, 21.9 mmol) in DMF (200 mL) was treated with *tert*-butyldimethylsilyl chloride (18.0 g) and imidazole (18.0 g). The mixture was stirred for 24 h, quenched with water (1.0 L), and extracted with Et_2O (3 × 100 mL). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo*, and heated (50 °C) under reduced pressure to give **32** (20.9 g, >95% yield): IR ($CHCl_3$) 3059, 2927, 1687, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, m), 7.40−7.25 (4H, m), 7.03 (1H, d, J = 2.2 Hz), 6.70 (1H, br d, J = 8.9 Hz), 5.76 (2H, dd, J = 11.1, 7.0 Hz), 5.55 (1H, br s), 4.82 (1H, br s), 4.67 (1H, br s), 4.39 (2H, m), 4.24 (1H, s), 3.82 (1H, m), 3.56 (1H, m), 2.14 (9H, s), 1.85−1.47 (12H, m), 1.24−1.15 (5H, m), 1.06 (12H, s), 1.04 (6H, s), 0.75 (9H, s), −0.03 (3H, s), −0.11 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 151.8, 134.4, 132.1, 129.2, 129.1, 128.7, 128.6, 127.7, 121.0, 119.2, 119.1, 118.8, 96.7, 93.3, 92.8, 83.2, 83.0, 81.0, 74.6, 61.8, 54.7, 54.6, 46.9, 41.5, 36.1, 30.8, 30.2, 25.7, 25.3, 18.9, 17.8, 12.4, −4.9, −5.2; HRMS (CI) calcd for $C_{53}H_{75}NO_6Si_2Se$ (M^+) 957.430, found 957.434.

***N*-[(Adamantyloxy)carbonyl]-1,2-dihydro-2-[(*Z*)-7-[(tetrahydropyranyl)oxy]hept-3-ene-1,5-diynyl]-3-[(*tert*-butyldimethylsilyl)oxy]-6-[(triisopropylsilyl)oxy]quinoline (33).** A solution of **32** (6.92 g, 7.24 mmol) in dichloromethane (250 mL) was cooled to 0 °C, followed by addition of *m*-chloroperoxybenzoic acid (1.50 g, 8.68 mmol) in small portions. After 1 h the mixture was warmed to 25 °C, pyridine (2.93 mL, 36.2 mmol) added, and the mixture heated at reflux for 5 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (250 mL) and extracted with dichloromethane (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by chromatography over silica gel eluting with 1:1 Et_2O/pentane to give **33** (5.8 g, >95% yield): IR ($CDCl_3$) 2929, 2360, 1688, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, br s), 6.59 (1H, d, J = 8.7 Hz), 6.50 (1H, d, J = 2.4 Hz), 5.74 (1H, d, J = 10.9 Hz), 5.66 (1H, d, J = 10.9 Hz), 5.59 (1H, s), 4.79 (1H, s), 4.32 (2H, m), 3.83 (1H, m), 3.57 (1H, m), 2.15 (9H, s), 1.89−1.40 (12H, m), 1.25 (5H, m), 1.09 (12H, s), 1.07 (6H, s), 0.96 (9H, s), 0.09 (3H, s), 0.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 134.9, 131.2, 130.6, 128.9, 128.6, 127.5, 125.0, 119.1, 115.9, 103.5, 96.5, 93.0, 82.5, 81.2, 79.9, 61.6, 54.4, 41.3, 36.0, 30.7, 30.0, 25.4, 25.2, 18.8, 17.9, 17.7, 12.4, −3.13, −4.5; HRMS (CI) calcd for $C_{47}H_{69}NO_6Si_2$ (M^+) 799.466, found 799.466.

***N*-[(Adamantyloxy)carbonyl]-13-hydroxy-15-oxo-10-azabenzo-[10a,14a]bicyclo[7.3.1]trideca-3,7-diyn-5-ene (37).** To a solution of **36** (10.0 mg, 0.017 mmol) in CH_3CN (10 mL) at 0 °C was added CsF (3.0 equiv), and the mixture was stirred for 4 h at 0 °C. The mixture was warmed to 25 °C for 2 h, poured onto saturated aqueous $NaHCO_3$ (30 mL), and extracted with Et_2O (3 × 15 mL). The combined extracts were dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed over silica gel eluting with 1:1 EtOAc/hexane to give **37** (7.1 mg, 95%): IR ($CDCl_3$) 3596, 2917, 1735, 1701, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, d, J = 8.8 Hz), 6.74 (2H, m), 5.80 (2H, m), 5.63 (1H, d, J = 8.8 Hz), 5.11 (1H, br s), 3.67 (1H, m), 3.65 (1H, m), 3.15 (1H, m), 2.17 (9H, br s), 1.63 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 153.3, 152.0, 129.8, 129.3, 127.1, 126.4, 121.2, 114.6, 112.7, 99.1, 91.6, 89.9, 83.3, 82.6, 65.9, 49.1, 41.5, 36.0, 30.9, 21.5; HRMS (CI) calcd for $C_{27}H_{25}NO_4$ (M^+ + 1) 428.186, found 428.187.

***N*-[(Adamantyloxy)carbonyl]-1-(phenylseleneno)-15-oxo-13-methoxy-10-azabenzo[10a,14a]bicyclo[7.3.1]trideca-3,7-diyn-5-ene (38).** A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 0.48 mL, 0.48 mmol) was added dropwise to a cold (−78 °C) solution of **24** (192 mg, 0.435 mmol) in tetrahydrofuran (3.5 mL). The resulting yellow solution was stirred under argon for 20 min and quenched by dropwise addition of a solution of phenylselenenyl bromide (140 mg, 0.58 mmol) in tetrahydrofuran (0.25 mL). The mixture was stirred at −78 °C, the cooling bath was removed, and saturated aqueous NH_4Cl (2.0 mL) was added. The mixture was diluted with Et_2O (8.0 mL), the phases were separated, and the aqueous phase was extracted with Et_2O (2 × 6 mL). The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was evaporated *in vacuo* to give the crude product (310 mg). Flash chromatography over silica gel eluting with Et_2O/pentane (1:4) gave **38** (241 mg, 93%) as a pale yellow amorphous solid: IR ($CDCl_3$) 2913, 1721, 1697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 7.15−7.50 (6H, m), 6.74 (1H, dd, J = 2.7, 10.0 Hz), 6.28 (1H, d, J = 2.7 Hz), 5.96 (1H, m), 5.69 (1H, d, J = 9.6 Hz), 5.60 (1H, d, J = 9.6 Hz), 3.66 (1H, d, J = 17.4 Hz), 3.59 (3H, s), 3.31 (1H, d, J = 17.4 Hz), 2.19 (9H, s), 1.67 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 156.9, 156.9, 151.9, 138.4, 130.5, 129.8, 129.1, 128.8, 128.8, 127.9, 127.6, 125.8, 120.8, 113.5, 110.9, 98.5, 92.6, 89.9, 84.3, 82.1, 55.3, 55.2, 41.5, 36.1, 30.9, 27.9; HRMS (FAB) calcd for $C_{34}H_{31}NO_4Se$ (M^+) 597.142, found 597.140.

***N*-[(Adamantyloxy)carbonyl]-1-(2-oxopropyl)-15-oxo-13-methoxy-10-azabenzo[10a,14a]bicyclo[7.3.1]trideca-3,7-diyn-5-ene (42).** A solution of *m*-chloroperoxybenzoic acid (23.2 mg, 0.134 mmol) in dichloromethane (0.2 mL) was added dropwise to a stirred solution of **38** (59.0 mg, 0.1 mmol), in dichloromethane (0.67 mL), under argon at −78 °C. The mixture was stirred at −78 °C for 45 min and treated with 1-[(trimethylsilyl)oxy]-1-methylethylene (200 mg, 1.54 mmol) followed by trimethylsilyl trifluoromethanesulfonate (33.4 mg, 0.15 mmol). After 10 min at −78 °C, the mixture was warmed to 0 °C, aqueous saturated $NaHCO_3$ (4.0 mL) was added, the mixture was diluted with dichloromethane (4.0 mL), and the phases were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (2.0 mL), dried ($MgSO_4$), and filtered, and the solvent evaporated *in vacuo* to give the crude product (79.3 mg). Purification by chromatography on a silica gel plate (1.0 mm, 1:1 Et_2O/pentane) gave **42** (25 mg, 51%) and **41** (10 mg, 22%). Data for **42**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, m), 6.82 (1H, dd, J = 2.7, 8.9 Hz), 6.70 (1H, d, J = 2.7 Hz), 6.11 (1H, m), 5.75 (1H, d, J = 9.6 Hz), 5.67 (1H, d, J = 9.6 Hz), 3.80 (3H, s), 3.25 (1H, d, J = 24 Hz), 3.20 (1H, d, J = 24 Hz), 3.0 (2H, m), 2.18 (9H, s), 1.86 (3H, s), 1.65 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 157.4, 153.4, 133.3, 130.8, 130.8, 128.9, 127.1, 122.1, 118.9, 112.8, 112.0, 99.9, 93.8, 89.9, 84.2, 82.1, 58.2, 56.5,53.5, 41.8, 36.4, 32.3, 32.2, 30.1; HRMS (FAB) calcd for $C_{31}H_{31}NO_5$ (M^+) 497.220, found 497.222.

Cycloaromatized Adduct 48. A solution of **24** (35 mg, 79.3 μmol) in 3,6-dihydrotoluene (4 mL) under an argon atmosphere was heated in an oil bath at 114 °C, and aliquots were removed after 20 (88%, **24**), 40 (69%, **24**), 60 (53%, **24**), 90 (42%, **24**), 150 (27%, **24**), and 210 (14%, **24**) min for ^{1}H NMR analysis. The combined aliquots were purified by PLC eluting with Et_2O to give **48** (23.8 mg, 68%): mp 126−129 °C (from EtOAc); IR ($CHCl_3$) 1743, 1698 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 247.5 (9.32×10^3), 295.5 (2.09×10^3) nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, d, br, J = 9.2 Hz), 7.37 (1H, dd, J = 6.9, 1.9 Hz), 7.13−7.25 (2H, m), 6.98 (1H, d, J = 6.9 Hz), 6.65 (1H, dd, J = 9.2, 2.9 Hz), 6.59 (1H, d, J = 2.9 Hz), 5.79 (X of ABX), 3.73 (3H, s), 3.64−3.55 (B of ABX), 3.39−3.30 (A of ABX), 2.22 (9H, s), 1.68 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 156.4, 152.4, 135.6, 133.5, 131.8, 130.1, 128.8, 128.7, 128.3, 127.4, 124.8, 113.0, 112.3, 82.2, 60.6, 55.4, 49.9, 43.9, 41.6, 36.1, 31.0; HRMS (CI) calcd for $C_{28}H_{29}NO_4$ (M^+) 443.210, found 443.210. The same experiment was carried out at 98, 81, and 65 °C to provide the data for an Arrhenius plot, Table 1. Prolonged reactions gave rise to by-product **52** (see below).

Cycloaromatized Adduct 49. A solution of **26** (13 mg, 49 μmol) in 3,6-dihydrotoluene (2 mL) under an argon atmosphere was heated in an oil bath at 114 °C, and aliquots were removed as above for ^{1}H NMR analysis. The combined aliquots were purified by PLC eluting with 10% Et_2O/dichloromethane to give **49** (9.3 mg, 72%): mp 218−220 °C (from dichloromethane); IR ($CHCl_3$) 3392, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.16 (3H, m), 7.06 (1H, d, J = 7.1 Hz), 6.65−6.53 (2H, m), 6.47 (1H, d, J = 8.6 Hz), 4.39 (1H, s), 3.71 (3H, s), 3.76−3.62 (2H, m), 3.45 (1H, d, J = 14.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.0, 153.8, 138.6, 134.8, 133.1, 128.9, 128.6, 128.4, 127.5, 126.7, 117.12, 114.4, 113.4, 61.1, 55.7, 49.4, 44.7; HRMS (FAB) calcd for $C_{17}H_{15}NO_2$ (M^+) 265.110, found 265.110.

Cycloaromatized Adduct 50. A solution of **44** (42.3 mg, 87.1 μmol) in 3,6-dihydrotoluene (4 mL) under an argon atmosphere was heated in an oil bath at 114 °C, and aliquots were removed as above for ^{1}H NMR analysis. The combined aliquots were purified by PLC eluting with 10% Et_2O/dichloromethane to give **50** (44.4 mg, >95%) as a viscous pale yellow oil: IR ($CHCl_3$) 1742, 1697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (1H, d, J = 9.1 Hz), 7.34 (1H, dd, J = 1.3, 6.9 Hz), 7.22−7.10 (2H, m), 7.09 (1H, d, J = 2.8 Hz), 6.93 (1H, d, J = 7.1 Hz), 6.64 (1H, dd, J = 2.8, 9.1 Hz), 5.83 (1H, s), 4.02 (1H, A of AB, J = 9.9 Hz), 3.97 (1H, B of AB, J = 9.9 Hz), 3.72 (3H, s), 3.42 (3H, s), 3.37 (1H, A of AB, J = 16.1 Hz), 3.24 (1H, B of AB, J = 16.1 Hz), 2.21 (9H, s), 1.68 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 156.5, 152.2, 135.4, 134.1, 129.7, 129.1, 128.7, 128.1, 127.3, 124.7, 112.6, 111.4, 82.1, 72.7, 60.5, 59.6, 55.3, 53.9, 46.3, 41.6, 36.1, 31.0, one quaternary resonance not detected; HRMS (CI) calcd for $C_{30}H_{33}NO_5$ (M^+) 487.236, found 487.235.

Cycloaromatized Adduct 52. Sodium borohydride (2.0 mg, 51.6 μmol) was added to a solution of **24** (22.8 mg, 51.6 μmol) in tetrahydrofuran (500 μL) and MeOH (500 μL). After 30 min an additional 1 equiv of sodium borohydride was added and the mixture stirred at 25 °C for 1.5 h. The reaction mixture was treated with 2 N HCl (1 mL) and neutralized with aqueous $NaHCO_3$ solution. The mixture was extracted with dichloromethane (3 × 10 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a residue which was purified by chromatography over silica gel eluting with dichloromethane/EtOAc (3:1) to give **52** (9.9 mg, 43%): mp 210−212 °C (from EtOAc); IR ($CHCl_3$) 3457, 1698, 1679 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, s), 7.43 (1H, d, J = 6.8 Hz), 7.19−7.06 (2H, m), 6.96 (1H, d, br, J = 6.9 Hz), 6.66 (1H, d, J = 2.9 Hz), 6.60 (1H, dd, J = 9.1, 2.9 Hz), 5.68−5.60 (1H, m), 4.47−4.39 (1H, m), 3.73 (3H, s), 3.51 (1H, dd, J = 15.8, 4.7 Hz), 3.39−3.31 (1H, m), 2.73 (1H, d, J = 15.8 Hz), 2.23 (9H, s), 1.95 (1H, d, D_2O exchangeable) 1.69 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 152.8, 134.2, 132.7, 132.0, 131.0, 128.9, 128.7, 127.9, 126.7, 124.3, 113.7, 112.5, 81.5, 66.4, 65.9, 55.4, 54.5, 41.7, 38.7, 36.2, 33.7, 31.0; HRMS (CI) calcd for $C_{28}H_{31}NO_4$ (M^+) 445.225, found 445.225.

(*E*)-Nitrile 53. A 2.5 M solution of *n*-butyllithium in hexanes (41 mL, 103 mmol, 1.05 equiv) was added dropwise to a stirred solution of diethyl (cyanomethyl)phosphonate (17 mL, 108 mmol, 1.10 equiv) in anhydrous tetrahydrofuran (0.5 mL) at 25 °C. After being stirred for 40 min at 25 °C, the colorless solution was added dropwise to a solution of **24** (43.2 mg, 98 mmol, 1.00 equiv) in tetrahydrofuran (1.5 mL) at 0 °C. The clear orange solution was stirred at 0 °C for 20 min, eluted with dichloromethane through a short column of silica gel, and evaporated to give a viscous brown oil. Purification of the crude product by chromatography over silica gel eluting with dichloromethane gave **53** as a white amorphous solid (45.6 mg, 85%): IR ($CHCl_3$) 2223, 1694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.42 (1H, m), 6.70−6.80 (2H, m), 5.91 (1H, s), 5.78 (1H, d, J = 9.4 Hz), 5.67 (1H, d, J = 9.4 Hz), 5.54 (1H, s), 4.22 (1H, X of ABX), 3.79 (3H, s), 3.56−3.38 (2H, AB of ABX), 2.17 (3H, s), 2.10 (6H, s), 1.64 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 157.0, 151.7, 129.5, 129.3, 127.2, 126.5, 121.7, 115.3, 112.4, 111.26, 100.2, 97.3, 94.0, 88.8, 83.0, 82.3, 55.4, 49.4, 41.5, 40.3, 36.0, 30.8, 24.9. HRMS (CI) calcd for $C_{30}H_{28}N_2O_3$ (M^+) 464.210, found 464.211.

Cycloaromatized Adduct 54. A solution of **53** (11.6 mg, 25 μmol) in tetrahydrofuran-d_8 (1 mL) under an argon atmosphere was heated in an oil bath at 60 °C, and aliquots were removed for ^{1}H NMR analysis. The combined aliquots were purified by PLC eluting with 10% Et_2O/dichloromethane to give **54** (5.4 mg, 47%): mp 224−225 °C (from EtOAc); IR ($CHCl_3$) 2224, 1683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.30 (2H, m), 7.21−7.10 (2H, m), 6.95 (1H, d, J = 2.8 Hz), 6.68 (1H, d, J = 2.9 Hz), 6.62 (1H, dd, J = 9.0, 2.9 Hz), 6.13 (1H, s), 5.46 (1H, s), 4.34 (1H, s), 3.74 (3H, s), 3.38 (1H, dd, J = 6.1, 4.3 Hz), 3.20 (1H, dd, J = 16.1, 2.2 Hz), 2.20 (9H, s), 1.68 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 156.5, 152.6, 134.9, 133.9, 130.9, 129.4, 129.0, 128.7, 128.6, 127.3, 125.4, 115.5, 113.2, 112.4, 91.5, 82.2, 56.3, 55.5, 43.1, 41.9, 41.1, 36.3, 31.1; HRMS (CI) $C_{30}H_{30}N_2O_3$ (M^+) calcd for 466.226, found 466.227.

Cycloaromatized Adduct 55. To a solution of **48** (23.8 mg, 53.7 μmol) in dichloromethane (1 mL) was added *m*-chloroperoxybenzoic acid (18.5 mg, 53.7 mmol), and the mixture stirred at 25 °C for 1.5 h. Saturated aqueous $NaHCO_3$ (2 mL) was added, and the mixture extracted with dichloromethane (3 × 10 mL), dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by PLC eluting with 1:1 pentane/Et_2O to give **55** (14.5 mg, 59%): mp 193−195 °C (from EtOAc); IR ($CHCl_3$) 1746, 1709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, s), 7.29−7.14 (3H, m), 7.08−6.98 (2H, m), 6.64 (1H, dd, J = 8.9, 2.8 Hz), 6.58 (1H, d, J = 2.8 Hz), 4.38 (1H, X of ABX), 3.76 (3H, s), 3.72 (1H, A of ABX), 3.16 (1H, B of ABX), 2.20 (9H, s), 1.69 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 157.5, 152.5, 134.9, 131.7, 130.4, 129.6, 129.2, 129.0, 126.8, 113.0, 112.8, 85.3, 83.0, 55.4,

52.2, 41.3, 39.2, 36.1, 30.9, two aromatic resonances not detected; HRMS (CI) calcd for $C_{28}H_{29}NO_5$ (M^+) 459.205, found 459.204.

Lactone 56. To a solution of **24** (45.9 mg, 104 μmol) in dichloromethane (4 mL) was added *m*-chloroperoxybenzoic acid (71.8 mg, 416 μmol), and the mixture stirred at 25 °C for 20 h. Workup as for **55** gave **56** (39.2 mg, 82%): IR ($CHCl_3$) 3200, 1757, 1721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 (1H, d, J = 8.6 Hz), 6.81 (1H, d, J = 2.4 Hz), 6.78 (1H, dd, J = 8.6, 2.4 Hz), 5.76 (1H, d, J = 10.1 Hz), 5.66 (1H, d, J = 10.1 Hz), 4.10−4.03 (1H, X of ABX), 3.74 (3H, s), 3.26−3.16 (1H, B of ABX,), 3.13−2.95 (1H, A of ABX), 2.09 (3H, s), 2.07 (6H, s), 1.57 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$, 323K) δ 173.4, 160.8, 152.8, 152.6, 136.3, 131.5, 130.9, 126.8, 118.2, 114.6, 114.1, 98.6, 91.9, 89.2, 85.6, 80.9, 55.6, 44.6, 41.2, 36.1, 31.1, 23.7; MS (FAB) base peak 135, no M + 1 detected.

Indole 57. A solution of **56** (38.0 mg, 80.2 μmol) in 3,6-dihydrotoluene (8 mL) was heated in a sealed tube at 140 °C for 20 h. The mixture was evaporated *in vacuo* and the residue purified by chromatography over silica gel eluting with dichloromethane to give **57** (5.0 mg, 15%): mp 206−207 °C (from dichloromethane/Et_2O); IR ($CHCl_3$) 1786, 1762, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, d, J = 8.9 Hz), 7.79 (1H, d, J = 7.7 Hz), 7.72−7.65 (1H, m), 7.58 (1H, d, J = 7.6 Hz), 7.50−7.41 (1H, m), 6.83 (1H, dd, J = 9.0, 2.7 Hz), 6.43 (1H, d, J = 2.7 Hz), 3.85 (1H, B of AB, J = 17.4 Hz), 3.70 (3H, s), 3.41 (1H, A of AB, J = 17.4 Hz), 2.26 (6H, s), 2.22 (3H, s), 1.69 (6H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 173.2, 157.1, 153.5, 148.4, 135.9, 134.4, 134.2, 129.9, 128.4, 126.5, 125.7, 116.6, 113.6, 108.4, 84.5, 55.7, 41.4, 38.7, 36.1, 31.0; HRMS (CI) calcd for $C_{27}H_{27}NO_3$ (M^+) 413.200, found 413.199.

[2-[*N*-(Adamantoxycarbonyl)amino]phenyl]-1,2,3,4-tetrahydro-1-oxo-4,8-bis(3,5-dimethylphenyl)thio]naphthalene (58). A slurry of NaH (4 equiv) in tetrahydrofuran (10 mL) was treated with 3,5-dimethylthiophenol (3 0 equiv). The mixture was stirred for 15 min at 0 °C, followed by dropwise addition of **23** (0.60 g) in tetrahydrofuran (5 mL). After 10 min, the cooling bath was removed and the mixture was stirred for 4 h. The mixture was quenched with water (10 mL) and extracted with EtOAc (3 × 10 mL). The extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude mixture was purified by chromatography over silica gel to give **58** (0.73 g, 73%): IR ($CHCl_3$) δ 3413, 2916, 1712, 1663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (1H, d, J = 7.7 Hz), 7.57 (1H, br d, J = 7.7 Hz), 7.31−7.00 (8H, m), 6.90 (1H, s), 6.80 (2H, m), 4.75 (1H, m), 4.05 (1H, X of ABX), 2.82−2.63 (2H, AB of ABX), 2.32 (6H, s), 2.29 (6H, s), 2.11 (9H, br s), 1.64 (6H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 153.6, 146.5, 144.7, 139.3, 138.7, 136.5, 133.4, 133.3, 132.5, 131.7, 131.1, 130.7, 129.9, 129.4, 129.3, 127.9, 127.6, 126.4, 126.2, 125.3, 124.0, 80.0, 79.8, 48.5, 48.0, 41.4, 36.0, 30.7, 21.1, 21.0; HRMS (CI) calcd for $C_{43}H_{46}NO_3S_2$ (M^+ + 1) 688.290, found 688.292.

1-[(3,5-Dimethylphenyl)thio]-11*H*-benzo[*a*]carbazole (59). A solution of **58** (650 mg, 1.18 mmol) in dichloromethane (10.0 mL) was treated with trifluoroacetic acid (5.18 mL, 59.1 mmol) at 25 °C. The mixture was stirred for 1.5 h, quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc (3 × 5 mL). The extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by chromatography over silica gel eluting with dichloromethane to give **59** (100 mg, 24%): IR ($CHCl_3$) 3397, 2921, 1601 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 11.53 (1H, br s), 8.31 (1H, d, J = 8.5 Hz), 8.19 (1H, dd, J = 8.1 Hz), 8.16 (1H, dd, J = 8.1, 1.1 Hz), 7.84 (1H, dd, J = 7.2, 1.1 Hz), 7.77 (1H, d, J = 8.5 Hz), 7.76 (1H, dd, J = 8.1 Hz), 7.56 (1H, dd, J = 8.1 Hz), 7.40 (1H, dt), 7.25 (1H, dt), 6.88 (2H, br s), 6.77 (1H, s), 2.12 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 137.9, 137.0, 136.3, 134.6, 134.2, 131.0, 128.3, 126.5, 125.3, 125.0, 124.8, 124.7, 123.1, 122.7, 120.6, 120.1, 119.9, 119.6, 111.3, 21.2; HRMS (CI) calcd for $C_{24}H_{19}NS$ (M^+) 353.123, found 353.124.

[2-[*N*-(Adamantoxycarbonyl)amino]phenyl]-1-hydroxy-8-[(3,5-dimethylphenyl)thio]naphthalene (60). To a slurry of NaH (9.0 mg, 0.364 mmol) in tetrahydrofuran (3 mL) was added a solution of **58** (20 mg, 0.036 mmol) in tetrahydrofuran (3 mL). The mixture was stirred for 5 h followed by the addition of water (3 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with 20% Et_2O/pentane to give **60** (11.4 mg, 72%) as a yellow solid: IR ($CDCl_3$) 3424, 3188, 2915, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.7 (1H, s), 8.00 (1H, bd, J = 7.5 Hz), 7.94 (1H, dd, J = 8.0, 1.2 Hz), 7.72 (1H, dd, J = 7.4, 1.2 Hz), 7.53 (1H, d, J = 8.4 Hz), 7.47 (1H, dd, J = 8.0, 7.4 Hz), 7.38 (1H, d, J = 8.4 Hz), 7.36 (1H, dt, J = 7.5, 2.0 Hz), 7.24 (1H, dd, 7.7, 2.0 Hz), 7.12 (1H, dt, J = 7.7, 1.3 Hz), 6.79 (2H, s), 6.74 (1H, s), 2.19 (6H, s), 2.11 (3H, s), 2.03 (6H, s), 1.61 (6H, s); HRMS (CI) calcd for $C_{35}H_{35}NO_3S$ 549.233, found 549.234. **23a** is missing signals at δ 7.72 and 7.53 in the ^1H NMR spectrum.

1,4-Dihydro-1,4-epoxy-2-(methoxycarbonyl)-3-(3-methylpyrid-2-yl)-5,8-dimethoxynaphthalene (63). A mixture of 4,7-dimethoxyisobenzofuran (0.99 g, 5.50 mmol) and **62** (1.02 g, 5.80 mmol) in benzene (30 mL) was heated at reflux for 18 h. The mixture was cooled to room temperature and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel eluting with EtOAc to give **63** (1.95 g, 100%): IR ($CHCl_3$) 2954, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, d, J = 4.4 Hz), 7.48 (1H, d, J = 7.7 Hz), 7.13 (1H, dd, J = 7.7, 4.4 Hz), 6.62 (2H, s), 6.31 (1H, d, J = 1.0 Hz), 6.06 (1H, d, J = 1.0 Hz), 3.86 (3H, s), 3.72 (3H, s), 3.62 (3H, s), 2.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 151.7, 148.6, 148.4, 146.7, 142.6, 137.5, 135.5, 135.0, 132.0, 122.9, 113.67, 113.4, 85.7, 82.0, 56.7, 56.8, 51.6, 18.2; HRMS (CI) calcd for $C_{20}H_{20}NO_5$ (M^+ + 1) 354.134, found 354.133.

2-(Methoxycarbonyl)-3-(3-methylpyrid-2-yl)-4-[(*tert*-butyldimethylsilyl)oxy]-5,8-dimethoxynaphthalene (64). To a mixture of 2,6-lutidine (0.66 mL, 5.66 mmol) and **63** (0.10 g, 0.28 mmol) in dichloromethane (10 mL) at −78 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.325 mL, 1.42 mmol). The mixture was stirred at room temperature for 18 h, quenched with water (10 mL), and extracted with dichloromethane (3 × 5 mL). The extracts were dried ($MgSO_4$), concentrated *in vacuo*, and purified by chromatography over silica eluting with EtOAc to give **64** (0.132 g, 99.6%) as a pale yellow foam: IR ($CHCl_3$) 2955, 2898, 1723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, s), 8.44 (1H, d, J = 4.7 Hz), 7.50 (1H, d, J = 7.5 Hz), 7.13 (1H, dd, J = 7.5, 4.7 Hz), 6.75 (2H, q, J = 8.5 Hz), 3.95 (3H, s), 3.80 (3H, s), 3.60 (3H, s), 2.33 (3H, s), 0.75 (9H, s), −0.23 (3H, s), −0.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 158.8, 150.7, 149.8, 149.2, 145.9, 136.9, 133.9, 130.6, 128.6, 127.4, 122.1, 121.9, 118.5, 107.6, 104.7, 55.8, 55.7, 51.9, 25.9, 19.2, 18.3, −3.9, −4.3; HRMS (CI) calcd for $C_{26}H_{33}NO_5Si$ (M^+) 467.213, found 467.214.

8,11-Dimethoxy-12-hydroxy-6-[(*tert*-butylcarbonyl)oxy]naphtho-[2,3-*h*]quinoline (65). A solution of tetrahydrofuran (2 mL) and diisopropylamine (0.18 mL, 1.28 mmol) was cooled to 0 °C followed by addition of *n*-BuLi (2.5 M, 0.43 mL, 1.07 mmol). After 30 min, **64** (0.10 g, 0.21 mmol) in tetrahydrofuran (3 mL) was added. The mixture was warmed to room temperature for 2 h and quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer extracted with dichloromethane (3 × 5 mL). The extracts were dried ($MgSO_4$), concentrated *in vacuo*, and dissolved in dichloromethane (10 mL) containing pyridine (0.70 mL, 8.56 mmol) and pivaloyl chloride (0.52 mL, 4.28 mmol). The mixture was stirred overnight, concentrated *in vacuo*, and purified by chromatography over silica gel eluting with EtOAc to give **65** (0.62 g, 72%) as a pale yellow powder: IR ($CHCl_3$) 2935, 1752, 1624, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, dd, J = 4.8, 1.4 Hz), 8.20 (1H, s), 8.14 (1H, dd, J = 7.9, 1.4 Hz), 7.52 (1H, dd, J = 7.9, 4.8 Hz), 7.30 (1H, s), 6.85 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 8.5 Hz), 4.07 (3H, s), 4.00 (3H, s), 1.57 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.7, 152.4, 149.3, 148.5, 147.4, 143.1, 135.7, 128.5, 126.6, 126.0, 120.8, 115.9, 115.2, 111.2, 104.8, 104.5, 104.2, 56.8, 56.0, 40.3, 27.4; HRMS (CI) calcd for $C_{24}H_{23}NO_5$ (M^+) 405.158, found 405.158.

8,11-Dimethoxy-7,12-dioxo-6-[(*tert*-butylcarbonyl)oxy]naphtho-[2,3-*h*]quinoline (66). To a slurry (sonicated for 5 min) of $Ag^{II}O$ (12.2 mg, 98.8 mmol), **65** (10.0 mg, 24.7 mmol), and dioxane (0.75 mL, freshly distilled over sodium) was added 6 M HNO_3 (0.05 mL). The mixture rapidly changed from a green-yellow color to an intense red color. The mixture was stirred for 3 min and quenched with a mixture of chloroform and water (4:1, 5 mL). The aqueous layer was extracted with chloroform (3 × 5 mL), and the extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by preparative plate chromatography eluting with EtOAc to give **66** (7.5 mg, 72%) as an orange-yellow solid: IR ($CHCl_3$) 2934, 1752, 1685, 1602 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.22 (1H, dd, J = 4.2, 1.0 Hz), 8.12 (1H, dd, J = 8.3, 1.0 Hz), 7.65 (1H, s), 7.51 (1H,

dd, $J = 8.3, 4.2$ Hz), 7.20 (1H, d, $J = 9.3$ Hz), 7.17 (1H, d, $J = 9.3$ Hz), 3.95 (3H, s), 3.89 (3H, s), 1.47 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 182.7, 177.3, 153.0, 151.9, 151.8, 144.9, 142.6, 135.4, 134.4, 131.2, 131.0, 125.4, 125.2, 124.1, 123.1, 118.9, 118.7, 57.1, 56.3, 39.25, 27.1; HRMS (CI) calcd for $C_{24}H_{21}NO_6$ (M^+) 419.137, found 419.137.

6,8,11-Triacetoxy-7,12-dioxonaphtho[2,3-*h*]quinoline (68). A solution of **66** (20.0 mg, 47.7 mmol) in 5:1 aqueous hydrogen bromide (48%)/glacial acetic acid was heated at reflux for 4 h. The mixture was concentrated to dryness *in vacuo* followed by addition of acetic anhydride (3 mL) and pyridine (2 mL). The reaction mixture was stirred for 12 h and concentrated to dryness *in vacuo*. The product was purified by preparative plate chromatography eluting with EtOAc to give **68** (14.1 mg, 68%) as an orange-yellow solid: mp >175 °C dec; IR ($CDCl_3$) 2985, 1771, 1686, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (1H, dd, $J = 4.8, 2.3$ Hz), 8.16 (1H, dd, $J = 8.0, 2.3$ Hz), 7.77 (1H, s), 7.55 (1H, dd, $J = 8.0, 4.8$ Hz), 7.38 (1H, d, $J = 8.2$ Hz), 7.33 (1H, d, $J = 8.2$ Hz), 2.51 (3H, s), 2.46 (3H, s), 2.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 183.6 169.6, 169.1, 169.1, 157.6, 153.6, 146.5, 146.1, 143.3, 135.6, 131.9, 131.3, 130.3, 129.3, 128.4, 127.2, 126.4, 125.2, 121.7, 21.2, 21.0, 21.0; HRMS (CI) calcd for $C_{23}H_{16}NO_8$ ($M^+ + 1$) 434.088, found 434.089.

2,5-Dimethoxyphthalide (70). To a stirred solution of **69** (8.86 g, 52.72 mmol) in dry tetrahydrofuran (180 mL) at −78 °C was added dropwise a solution of 2.5 M *n*-butyllithium in hexanes (42 mL, 105.55 mmol). The mixture was slowly warmed to 70 °C, allowed to stir for 2.0 h, and then cooled to 0 °C. Dry carbon dioxide was bubbled through the solution for 0.25 h, followed by addition of an excess of 2 M hydrochloric acid. Phthalide **70** precipitated as a colorless crystalline solid (4.32 g, 42%) which was collected *via* vacuum filtration, and rinsed with hexanes. The mother liquors were extracted with chloroform (3 × 100 mL). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. Purification by chromatography over silica gel eluting with petroleum ether/EtOAc (4:1) gave a further quantity of **70** (3.87 g, 38%), total yield 80%: mp 167−168 °C (from EtOAc/hexanes); IR (thin film) 1762, 1606 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (1H, d, $J = 8.77$ Hz), 6.84 (1H, d, $J = 8.77$ Hz), 5.16 (2H, s), 3.91 (3H, s), 3.83 (3H, s); HRMS (CI) calcd for $C_{10}H_{11}O_4$ ($M^+ + 1$) 195.066, found 195.066.

2α-Carbethoxy-3β-(3-methylpyrid-2-yl)-4β-hydroxy-5,8-dimethoxy-3,4-dihydro-1(2*H*)-naphthenone (71). To a stirred solution of diisopropylamine (2.09 g, 20.62 mmol) in dry tetrahydrofuran (80 mL) at −60 °C was added *n*-butyllithium (1.32 g, 20.62 mmol) in hexanes (6.31 mL). After 0.75 h, **70** (2.00 g, 10.31 mmol) was added to the mixture, and the mixture was allowed to stir for 1 h. Ethyl 3-(3-methylpyrid-2-yl)propenoate (1.97 g, 10.31 mmol) was added to the mixture, and after 0.5 h at −78 °C the mixture was quenched with saturated aqueous NH_4Cl (20 mL) and diluted with distilled water (100 mL), and the resulting solution extracted with chloroform (3 × 100 mL). The combined extracts were washed with water (3 × 50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give **71** as a colorless solid (3.80 g, 96%) and a mixture of diastereomers: IR (thin film) 3292, 2965, 1715, 1684 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (1H, d, $J = 3.9$ Hz), 7.50 (1H, d, $J = 6.9$ Hz), 7.11−7.15 (2H, m), 7.11−7.15 (2H, m), 6.96−6.99 (1H, d, $J = 9.02$ Hz), 6.30−6.38 (1H, br s, −OH), 5.40 (1H, d, $J = 1.9$ Hz), 4.60 (1H, d, $J = 12.5$ Hz), 3.87−4.07 (2H, m), 3.84 (3H, s), 3.81 (3H, s), 2.37 (3H, s), 1.06 (3H, t, $J = 7.2$ Hz); HRMS (CI) calcd for $C_{21}H_{24}NO_6$ ($M^+ + 1$) 386.160, found 386.160.

Ethyl 1-(Pivaloyloxy)-3-(3-methylpyrid-2-yl)-5,8-dimethoxy-2-naphthoate (72). To a stirred solution of **71** (7.50 g, 19.48 mmol) in chloroform (500 mL) at 40 °C was added *p*-toluenesulfonic acid monohydrate (20.00 g), and the mixture was allowed to stir for 15.0 h. The mixture was made basic with saturated aqueous $NaHCO_3$ (500 mL), and the chloroform layer separated. The aqueous phase was extracted with chloroform (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a moderately stable colorless solid (6.90 g, 96%): IR ($CHCl_3$) 3340, 2941, 1733, 1612, 1369, 1254 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.30 (1H, s), 8.43 (1H, d, $J = 4.3$ Hz), 8.43 (1H, d, $J = 4.3$ Hz), 7.62 (1H, s), 7.52 (1H, d, $J = 7.5$ Hz), 7.15 (1H, dd, $J = 4.8, 7.5$ Hz), 6.77 (2H, s), 3.89−4.05 (5H, m), 3.87 (3H, s), 2.19 (3H, s), 0.84 (3H, t, $J = 7.1$ Hz). To a stirred solution of the above compound (1.88 g, 5.12 mmol) in dry dichloromethane (20 mL) at 26 °C was added Et_3N (5.18 g 51.23 mmol) followed by a catalytic amount of 4-(dimethylamino)pyridine. Pivaloyl chloride (3.71 g, 30.74 mmol) was added over 0.5 h. After an additional 1.0 h, the dichloromethane and excess pivaloyl chloride were removed *in vacuo*. The resulting residue was chromatographed over silica gel eluting with EtOAc/petroleum ether (2:3). The product **72** (2.10 g, 87%) was crystallized from hexanes/EtOAc to give needles: mp 123−125 °C; IR (thin film) 2981, 2936, 1756, 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (1H, d, $J = 4.6$ Hz), 8.14 (1H, s), 7.55 (1H, d, $J = 7.6$ Hz), 7.16 (1H, dd, $J = 4.8, 7.6$ Hz), 6.77 (2H, s), 3.95 (2H, q, $J = 7.1$ Hz), 3.89 (3H, s), 3.85 (3H, s), 2.27 (3H, s), 1.38 (9H, s), 0.86 (3H, t, $J = 7.1$ Hz); HRMS (CI) calcd for $C_{26}H_{30}NO_6$ ($M^+ + 1$) 452.206, found 452.207.

6-Ethoxy-7-hydroxy-8,11-dimethoxynaphtho[2,3-*h*]quinoline (73). To a stirred solution of diisopropylamine (0.225 g, 2.22 mmol) in dry tetrahydrofuran (8 mL) at −78 °C was added dropwise a solution of *n*-butyllithium (0.142 g, 2.22 mmol) in dry hexanes (0.734 mL). After 0.75 h, **72** (0.200 g, 0.443 mmol) was added to the solution. The mixture was warmed to 26 °C, after 0.5 h, saturated aqueous NH_4Cl (5 mL) was added to the mixture, and the resulting solution was extracted with chloroform (3 × 50 mL). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. Chromatography over silica gel eluting with EtOAc/hexanes (2:3) gave **73** as a yellow solid (0.143 g, 95%): mp 205−210 °C (from hexanes/EtOAc, yellow needles); IR (thin film) 3333, 2966, 1621 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.01 (1H, s), 9.67 (1H, s), 8.81 (1H, dd, $J = 1.5, 4.4$ Hz), 7.89 (1H, dd, $J = 1.5, 7.9$ Hz), 7.40 (1H, d, $J = 4.4, 7.9$ Hz), 6.73−6.75 (2H, m), 6.69 (1H, s), 4.39 (2H, q, $J = 6.9$ Hz), 4.04 (3H, s), 4.03 (3H, s), 1.65 (3H, t, $J = 6.9$ Hz); HRMS (CI) calcd for $C_{21}H_{20}NO_4$ ($M^+ + 1$) 350.138, found 350.139.

6-Ethoxy-7,12-dioxo-8,11-dimethoxynaphtho[2,3-*h*]quinoline (74). To a stirred solution of **73** (1.65 g, 4.876 mmol) in acetonitrile (150 mL) at −10 °C was added dropwise a solution of ceric ammonium nitrate (5.33 g, 9.734 mmol) in distilled water (10 mL) over 0.25 h. After 1.0 h, the mixture was filtered through a short plug of silica gel eluting with EtOAc to give **74** (1.3 g, 74%): mp softens at 248 °C and decomposed at 281 °C (from hexanes/EtOAc, dark orange needles); IR (Nujol) 1685, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (1H, dd, $J = 1.4, 3.6$ Hz), 8.00 (1H, dd, $J = 1.5, 8.5$ Hz), 7.42 (1H, dd, $J = 3.8, 8.6$ Hz), 7.23 (1H, s), 7.15 (2H, s), 4.28 (2H, q, $J = 6.8$ Hz), 3.94 (3H, s), 3.93 (3H, s), 1.60 (3H, t, $J = 7.2$ Hz); HRMS (CI) calcd for $C_{21}H_{18}NO_5$ ($M^+ + 1$) 364.119, found 364.118.

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Supporting Information Available: Complete experimental details and spectral information for compounds **8**−**12**, **12b**, **12c**, **12d**, **12**, **23e**, **28**, **29**, **34**−**36**, **41**, **43**−**47**, **62**, and ethyl 3-(3-methylpyrid-2-yl)propenoate and X-ray spectral data for structure **54** (33 pages). See any current masthead page for ordering and Internet access instructions.

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