The Total Synthesis of Dynemicin A Leading to Development of a Fully Contained Bioreductively Activated Enediyne Prodrug

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Abstract: The title compound has been synthesized as its racemate in 33 steps. An intramolecular Diels−Alder reaction (see Scheme 5, **24** → **25**) was used to provide control over the eventual cis C_4−C_7 relationship. The installation of another cis related ethynyl group at C_2 arose from transformation **40** → **42** (see Scheme 8) whose directionality is governed by a benzophenone ketal functioning as a temporary steric control unit. Closure of the enediyne unit was accomplished on a trimethylsilylethoxycarbonyl (TEOC) protected dihydroquinoline derivative. It involved use of a novel bis-iodoalkyne/distannylethylene interpolative coupling transformation (**61** + **58** → **63**, Scheme 12). In the terminal phase of the synthesis, a novel iminoquinone ketal **74** (Scheme 15) was condensed with homophthalic anhydride derivative **78** (Scheme 16) as indicated in Scheme 17. The final deprotection involved cleavage of a methoxymethyl ester and two methoxymethyl phenol ethers. From this work, there arose the concept and demonstration of *p*-quinone monoimines **82** and **93** (Scheme 18), as bioreductively activated enediyne prodrugs.

Introduction

In 1989, Konishi and associates disclosed the structure of dynemicin A (**1**)[1,2] which was then the newest member of the enediyne family of antibiotics.[3] This metabolite of *Micromonospora chersina* demonstrated high levels of in vitro antitumor activity comparable to those which had been registered for two other enediynes, calicheamicin (**2**)[4] and esperamicin (**3**).[4d,5] In addition, dynemicin A was described to prolong the life span of mice which had been inoculated with leukemia cell lines.[1] Unfortunately, enthusiasm for the clinical use of dynemicin A itself is attenuated by concerns surrounding its difficult accessibility as well as its insolubility and lability.

During early biological studies, it was discovered that dynemicin effects single and double stranded DNA cleavage.[6−8] This cleavage is enhanced by the addition of various cofactors including thiols, reducing agents, and even visible light.[9] The DNA cuts occasioned by **1** were not nearly as sequence specific as those observed with calicheamicin or esperamicin.[4,5] Unlike these drugs, dynemicin lacks a carbohydrate domain to provide high specificity in its DNA contacts. Although the anthraquinone section of dynemicin may well furnish drug-DNA contact through intercalation, there seems to be little or no sequence specificity associated with this effect.[10]

An important proposal concerning the mode of action of dynemicin A was advanced by Semmelhack (Scheme 2).[11] He envisioned that a sequence of transformations would be initiated by reduction of the anthraquinone system (**1** → **4**). No longer delocalized into the electron reducing quinone system, the "lone pair" nitrogen atom of **4** is now available to assist in the opening of the epoxide linkage thereby generating quinone methide **5**. Following addition of a nucleophile to **5**, a conformational

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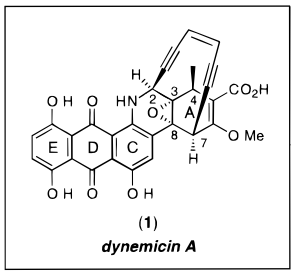
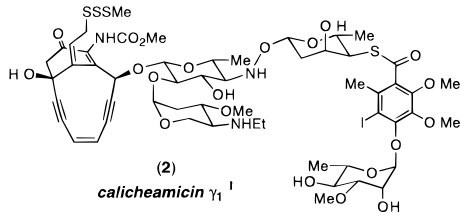
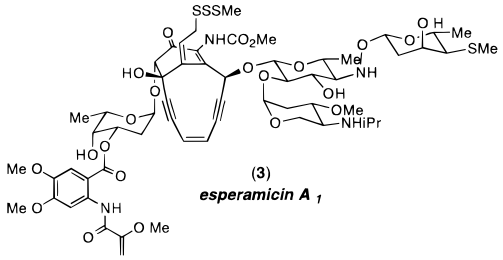
Scheme 1







restructuring of the AB ring system of **6** causes the distance between the terminii of the transannular diyne to contract, hence favoring the Bergman type cyclization wherein electronic reorganization leads to 1,4 diradical, **7**. This diyl[6] as well as related diyls from enediynes **2** and **3** have been implicated as the causative high energy intermediates in effecting single and double stranded breaks in deoxyribonucleic acid targets (via hydrogen atom abstraction).[4,5]

Owing, no doubt, to the unique mode of action of dynemicin A and to its high levels of antitumor activity, not to speak of its novel structure, interest in its synthesis began to grow.[12] Concurrently, a variety of strategies were adopted to create synthetically accessible congeners which might improve on the antitumor performance of the drug.[12a,b] The first accomplishments aimed at a dynemicin total synthesis were disclosed by Schreiber and associates.[13] These breakthroughs culminated in a route to various methylated versions of dynemicin.[14] *In early 1995, full success was realized by Myers and associates in their elegant total synthesis of (+)-dynemicin A.*[15] Early demonstrations of dynemicin inspired fully synthetic DNA cleaving agents were provided by Nicolaou.[12f]

Our laboratory began work in the dynemicin area in 1990. Two considerations drove our program. A very large impetus was the challenge associated with a total synthesis of dynemicin A. It seemed likely that this would be a challenging goal. The solution would predictably be instructive to the strategy and practice of organic synthesis.

In addition, another goal was undertaken. We hoped to generate for evaluation, functional but structurally less demanding, equivalents of dynemicin. We were of course sensitive to the Semmelhack hypothesis, wherein the active DNA cleaving (and presumably cytotoxic form) of dynemicin is incorporated in structure **4**. It is this moiety in which epoxide solvolysis is triggered, thereby initiating a cascade which leads to eventual cytotoxicity. We wondered about the possibility of generating, *in vivo*, a truncated version of **4** which would maintain the capacity for "intramolecularly assisted epoxide solvolysis," to trigger diyl formation. In our construct, we hoped to delete much of the molecular complexity associated with **4**, while retaining its capacity for DNA cleavage. One possibility for consolidation would be the napthalenediol domain. It seemed possible that this section is *per se* irrelevant to the mode of action, and that recourse to its precursor anthraquinone in the natural product arises from its being a biosynthetically accessible triggering device for *Micromonospora cherina* to employ. Another candidate area for molecular simplification would be the complex functionality found in ring E. Here are encountered a synthetically awkward combination of secondary methyl and carboxyl groups, the latter conjugated to an enol ether. Perhaps such implements could be waived in a quest for a simpler analog, where function is emphasized over optional structural frills.

Thus, we sought a hypothetical entity **9** (Scheme 3), of as yet unspecified character, which would, on suitable *in vivo* actuation, lead to a structure of the type **10**, to initiate the cytotoxic cascade. Other laboratories, notably such as that of Nicolaou and associates,[13a,b] conceived of solutions to this problem in terms of an *in vitro* cleavable urethane blocking group leading to active agent **10**. We were drawn to the possibility of a more compact type of entity, closely related to known types of drugs which might, on suitable bio-priming, lead to **10** without concurrently ejecting debris of problematic biological agendas. In other words, we sought a "fully contained" prodrug for a system of the type **10**.

In defining system **9** with greater specificity, we were not unmindful of the presumed mode of action of the mitomycins.[16] Here a cascade is initiated by *reduction of a quinone* (cf. structure **12**). This reduction event initiates a sequence leading to the active DNA damaging agent aziridinomitosene **13**. The mitomycin logic led us to propose recourse to a quinone imine as the self-contained, bioreductively activatable type of prodrug. Eventually, considerations of amenability to gram scale synthesis led us to identify quinone imine system type **14** as a prodrug. However, it was through intermediates in our total synthesis exercise that we first prepared the more complicated quinone imine (compound **82**, *vide infra*). Its promise, as established by *in vitro* and *in vivo* experiments,[17a,18,19] led us back to the still simpler target **14**. Hence, it is with the total synthesis of dynemicin[20] that our account begins.

(12) For synthesis of various dynemicin A model systems, see: (a) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908 and references cited therein. (b) Wender, P. A.; Zercher, C. K.; Beckham, S.; Haubold, E.-M. *J. Org. Chem.* **1993**, *58*, 5867 and references cited therein. (c) Nishigawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (d) Magnus, P.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 544. (e) Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1345. (f) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasildo, W. *Science* **1992**, *256*, 1172.

(13) (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898.

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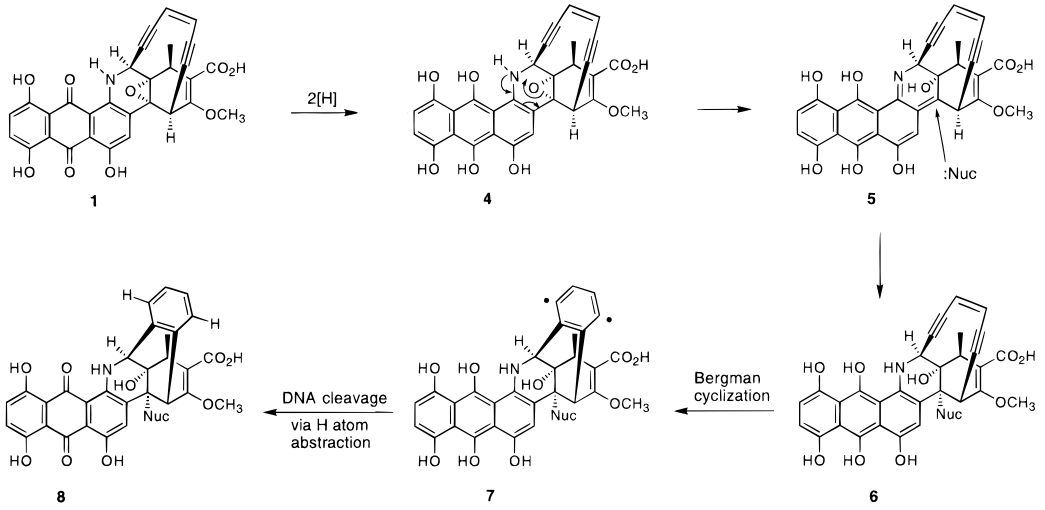
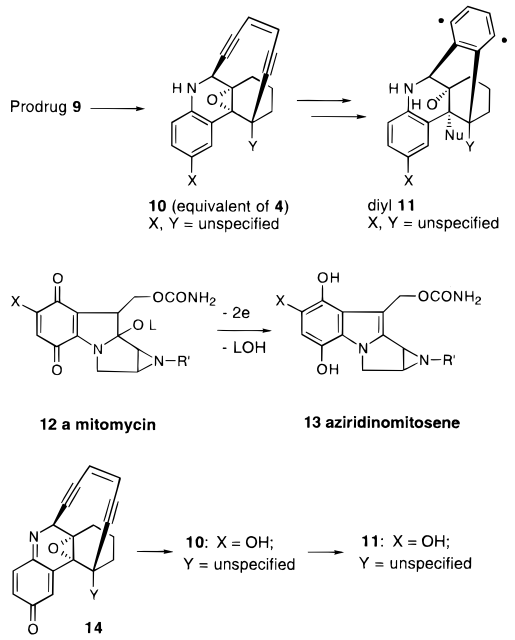
(19) Chou, D.; Shair, M. D.; Yoon, T. Y.; Zheng, Y. H.; Danishefsky, S. J. *Proc. Am. Assoc. Cancer Res.* **1995**, *36*: 384.

(20) Shair, M. D.; Yoon, T. Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1721.

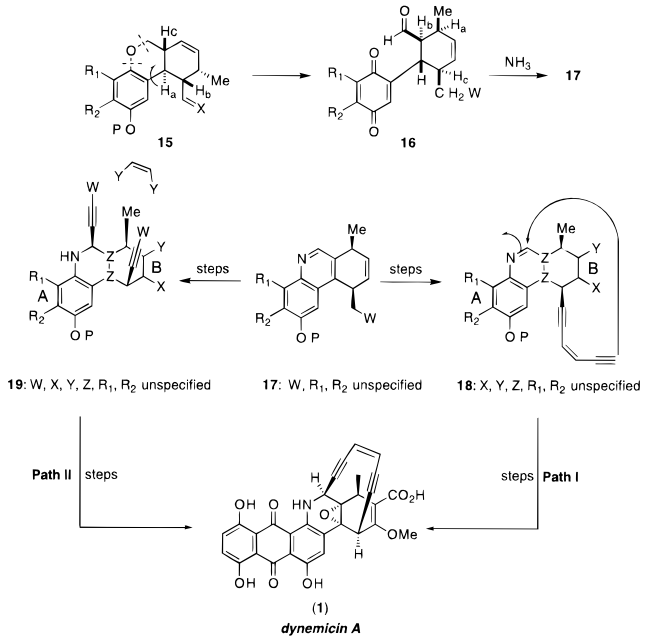
Scheme 2



Scheme 3



Scheme 4



Synthetic Strategy

We considered many prospective solutions for the installation of the enediyne bridge needed to reach dynemicin. We hoped that the challenge posed by the intriguing substructure enediyne system, and its surrounding functionality, would provide a fertile testing ground for the development of novel synthetic methodology. Two general approaches (Scheme 4) emerged among the many which were up for consideration. The first approach (see path I) focused on an intramolecular Reissert[21] coupling of an enediyne anion (or equivalent thereof) to some type of activated iminium construct (see structure **18**). At this level of the thought process, the nature of the functionality appended the A and B regions corresponding to the anthraquinone and vinylogous carbonate moieties of the goal structure were left unspecified. Correspondingly, the stage at which the epoxide linkage would be introduced was to be determined through the unfolding of events rather than via adherence to an apriori blueprint. Hence, the expression of Z in structure **18** represents uncertainty on our part at the planning level between a tetrasubstituted double bond and an α-configured epoxide. Similarly not formulated were the functions R_1 and R_2 whose nature goes to the question as to the degree to which implements for construction of the naphthoquinone domain are to be incorporated prior to fashioning the cyclic enediyne.

A second approach (see path II), which also postponed definition of these critical issues, contemplated the interpolation of a two carbon ethylene moiety unit into a suitable (syn) configured diyne construct (see structure **19**). Here again, online realities, rather than overarching doctrine would dictate the way in which the diyne functionality would be organized (see substructure unit W in structure **19**). Similarly, the specifics by which the ethylene unit (Y) would be presented for interpolation as well as the staging for introduction of the epoxide (see substructure Z) were "negotiable".

Though paths I and II represented, at this stage, rather vaguely specified perceptions, it was already discernible that the latter would be the more demanding in terms of the stereochemical relationships which would be in need of implementation. While the first program required suitable provisions for the cis connectivity of the C_4 methyl and C_7 enediyne functions to be provided (see structure **18**), the C_2 stereochemistry would be

(21) Popp, F. D. *Chem. Heterocycl. Comp.* **1982**, *32*, 353 and references cited therein.

fixed as a consequence of the cyclization. By contrast, path II required (see structure **19**) the fashioning of a cis relationship of the C_2, C_4, and C_7 substitutents before cyclization could take place.

It seemed likely that the study of both propositions (path I and II) might be possible from a common synthetic precursor of the type **17** (W unspecified). Such a construct could provide an excellent point of divergence for both plans while maintaining flexibility as to the issues raised above. It was further contemplated that **17** might arise from ammonolysis of a formal quinone aldehyde of the type **16**. The latter might conceivably become available through oxidative disconnection of generic system **15**, via either of two modalities (see alternate dotted line cleavage sites in structure **15**). It is with the pursuit of such a plan, that our journey began.

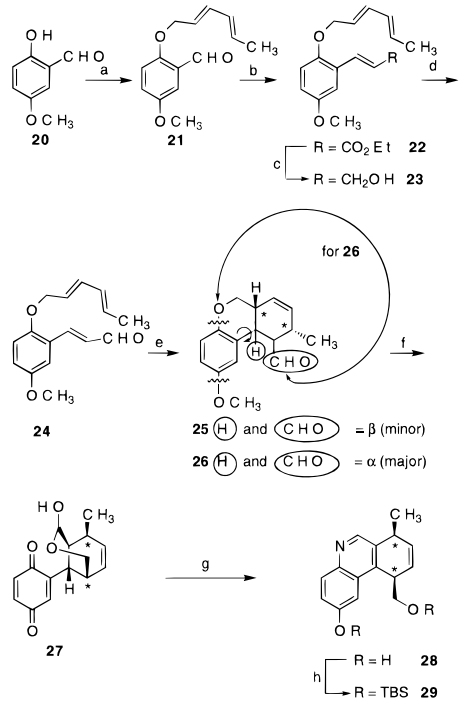
Results and Discussion

We set as a more specific goal, a tricyclic system corresponding to **17** where R_1 and R_2 are hydrogens. We had in mind several ideas for fashioning the symmetrical dihydroxynaphthaquinone moiety which, if successful, would not require prebuilt "handles" in the benzene ring. The synthesis commenced with alkylation of commercially available benzaldehyde **20**, with sorbyl bromide as shown in Scheme 5. Two carbon homologation of **21** using a Horner−Emmons procedure provided the ethyl ester **22** which was subsequently converted to triene aldehyde **24** via allylic alcohol **23**. Upon exposure of **24** to the action of $ZnCl_2$ at room temperature (Scheme 5), an endo selective intramolecular Diels−Alder reaction, leading to compound **26** took place in 60% yield. Alternatively, the Diels−Alder reaction could also be conducted by heating **24** in refluxing benzene. A 3:1 ratio of endo:exo adducts (**26** and **25**) was obtained under the thermal (uncatalyzed) conditions. Although the endo:exo ratio was *per se* of little consequence with respect to the stereochemical relationship of the emerging C_4 and C_7 centers (see starred carbons), its importance arose from the failure of the exo product **25** to survive the ensuing transformation. Accordingly, Lewis acid catalysis was used in practice. These conditions provided the endo product more cleanly albeit in a lower yield than did the strictly thermal protocol.

Treatment of endo adduct **26** with ceric ammonium nitrate (CAN) gave rise to the quinone **27** in high yield. Several critical transformations had been accomplished in this experiment. The para dioxygenated aromatic ring had suffered oxidation to a quinone with presumed concomitant dispatch of methanol in the usual way. In addition, the hydroxymethyl function, unveiled in the same oxidation, engaged the proximal aldehyde in the form of a hemiacetal linkage. The storage of the putative aldehyde in this protective arrangement stabilized the product toward the oxidative conditions. For instance, the exo adduct (**25**), in which hemiacetal protection is not accessible, was substantially destroyed through the CAN protocol.

Exposure of compound **27** to the action of ammonium acetate in acetic acid at 100 °C afforded **28** and, following bis-silylation, **29**. Thus, was the desired quinoline structure constructed. *It will not escape the notice of the reader that the doctrine of suprafaciality in the Diels−Alder reaction (cf.* ***24*** *→* ***26****) had indeed been tapped to dictate the required syn stereochemical relationship between* C_4 *and* C_7 *of quinolines* ***28*** *and* ***29*** *(corresponding to the generalized target compound* ***17****, shown in Scheme 4).*[22]

Scheme 5[a]



[a] (a) sorbol bromide, K_2CO_3, acetone, 96% yield; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 95% yield; (c) DIBAH, CH_2Cl_2, 99% yield; (d) (COCl)2, DMSO, Et_3N, CH_2Cl_2, −78 °C; 91% yield; (e) $ZnCl_2$, CH_2Cl_2, 25 °C, 60% yield of **26**; or PhH, 80 °C, 3:1 **26**/**25**; (f) $Ce(NH_4)_2(NO_3)_6$, MeCN, H_2O, 90% yield; (g) NH_4OAc, HOAc, 100 °C, 89% yield; (h) TBSCl, IMID, CH_2Cl_2, 98% yield.

A brief account of our explorations to proceed to dynemicin via path I will be described first.[23] Since the route turned out to be unsuccessful, we present here only the highlights of these pursuits. Fuller accounts of the many initiatives to reduce this intramolecular Reissert pathway to practice have been provided elsewhere.[3a,b] Although this sequence did not lead to a total synthesis of dynemicin A, information garnered along this excursion was crucial to the success of path II and to the eventual total synthesis of dynemicin.

From compound **29**, we reached probe substrates **30** and **31** (Scheme 6).[3a,b] Unfortunately, attempted cyclization of **30** with LHMDS led primarily to elimination product **32**. Furthermore, attempted Reissert-like cyclization of **30** utilizing isopropylmagnesium bromide and methylchloroformate afforded primarily urethan **33**. These results suggested that we had in our planning exercise overlooked a serious kinetic acidity problem associated with the C_7−H bond. Given these findings, we sought to incorporate the C_7−C_8 epoxide early on. Pursuant to that reasoning, compound **29** was converted to the surprisingly stable oxirane **31**.[24] Unfortunately, several attempts to achieve palladium mediated elongation ("eneynylation") were unsuccessful. Apparently, the vinyloxirane moiety of **31** had served as an insertion site to the palladium based catalyst.

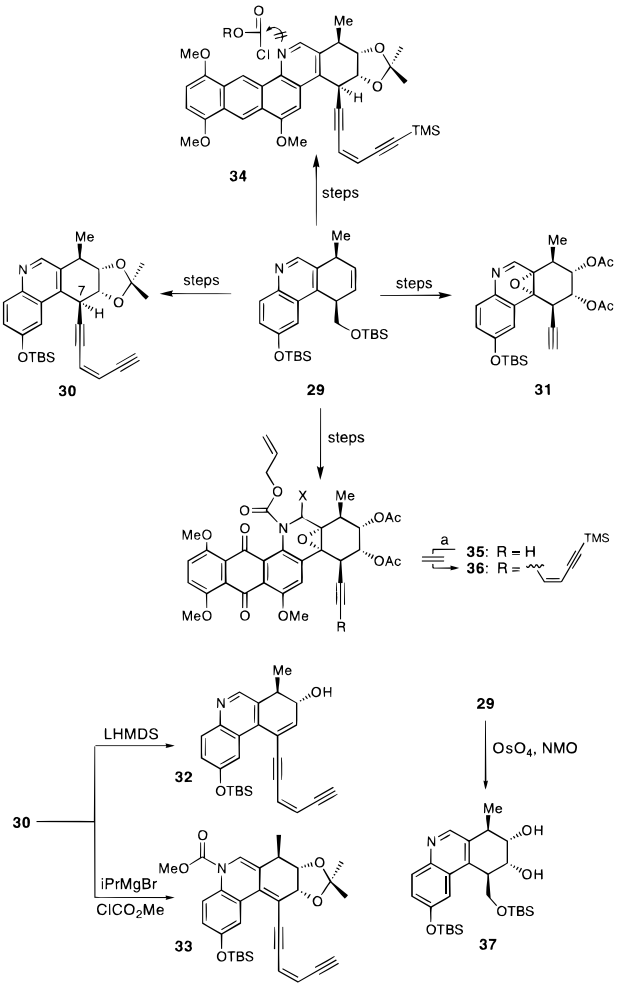
We then attempted to study the cyclization in the context of pentacyclic substrates. Toward this end, we reached substrates **34** and **35**. In the case of **34**, in which the B ring was nonquinoidal, we were unable to achieve a Reissert reaction. We attribute this impasse to difficulties associated with alkoxycarbonylation of the quinoline type nitrogen, hindered as it is

(22) Yoon, T. Y.; Shair, M. D.; Danishefsky, S. J.; Schulte, G. K. *J. Org. Chem.* **1994**, *59*, 3752.

(23) Taken in part from the following: Yoon, T. Y. Ph.D. Thesis, Yale University, 1994.

(24) Yoon, T. Y.; Shair, M. D.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 6259.

Scheme 6[a]



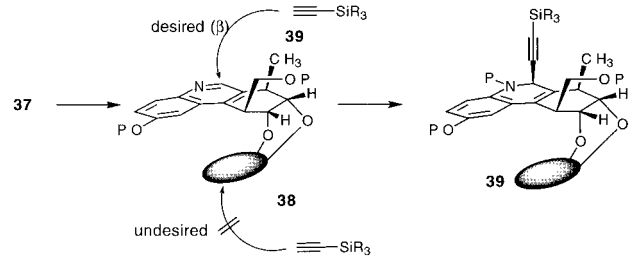
[a] (a) (Z)-Cl(H)C═C−C≡CTMS, Pd(0), many variations.

by the bay region[25] domain. In the case of intermediate **35**, we were unable to advance to the described enediyne structure **36**, apparently as a consequence of the instability of the vinyloxirane or quinone moieties to the required palladium based catalysis. It was in response to these and other setbacks that the path I program for enediyne annulation was set aside in favor of the interpolative route contemplated in path II (see Scheme 3). For this purpose, we returned to compound **29** and its derived diol **37**.

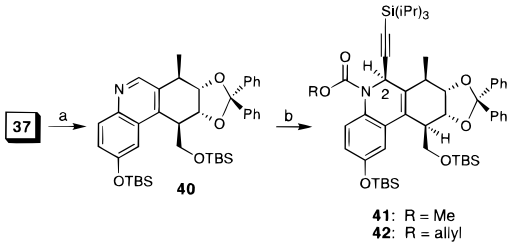
The first large challenge to testing the interpolative enediyne formation contemplated in plan II was that of arranging for the required relative stereochemistry of the various components. As noted above, it would be necessary to implement an all cis stereo relationship between carbons 2, 4, and 7. While the 4,7 relationship had already been secured, via compound **28** through the Diels−Alder based strategy (Scheme 5) we now had to squarely face the problem of introducing an ethynyl group on the β face of C_2, cis to the already existing β disposed functions at carbons 4 and 7. The problem to be contended with was that *intermolecular* Reissert reaction, resulting in placement of an alkoxycarbonyl group at the nitrogen and an ethynyl equivalent at C_2, would most likely occur from the α face of the system, thereby avoiding abutments with the already existing β face functionality.

It was for the purpose of maneuvering around this very serious problem, that we were drawn to the possibility of using the

Scheme 7



Scheme 8[a]



[a] (a) (i) $Ph_2C(OMe)_2$, H_2SO_4, CH_2Cl_2, 40 °C, (ii) TBSCl, imidazole 83% yield (i and ii); (b) (triisopropylsilyl)ethynyl magnesium bromide, $ClCO_2R$, THF, −20 °C, 80% yield, R = Me (**41**) or allyl (**42**).

α-disposed vicinal diol at carbons 5 and 6 of compound **37** in a creative way. *The hope was to engage these alcohols in a protective device which would, in fact, render the* α *face of the total ensemble more hindered than the* β *face.* If that could be accomplished, an ethynyl equivalent might be directed to the β face. We attempt to capture this concept in Scheme 7 wherein the goal becomes the conversion of diol **37** to the unspecified construct **38**, whose α face would be so shielded as to direct a nucleophile (possibly an ethynyl silyl anion as shown) to the β face (see formation of construct **39**). Needless to say, this temporary steric control unit must eventually give way to the vinylogous carbonate functionality of the natural system.

The 1,2 diol linkage of **37** was engaged as *a benzophenone ketal* (see compound **40**) under the carefully maintained conditions specified in Scheme 8. Following previous studies, and in response to insights provided by molecular modeling, a theory arose to the effect that one of the diastereotopic phenyl rings of the ketal might lie beneath the face of the C_2 carbon. Were this the case, a putative nucleophile could well attack from its β-face.

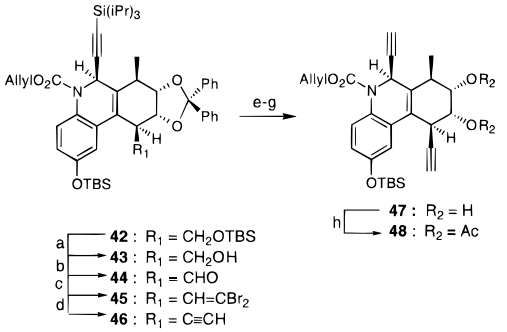
In the event, when compound **40** was exposed to the action of methylchloroformate in the presence of the Grignard anion of triisopropylsilyl acetylene at −20 °C, a 9:1 ratio of diastereomeric products favoring the desired β addition product **41** was isolated in excellent yield.[23] Our configurational assignment was confirmed by X-ray crystallographic analysis. Although this chemistry was originally developed with the methyl carbamate, the use of an allyl carbamate (see compound **42**) proved to be a critical advance for the total synthesis effort (*vide infra*). Thus, an important hurdle had been surmounted. The problem of required syn stereochemical connectivity issues relating carbons 2, 4, and 7 had been solved. Construction of the C_7 alkyne unit and conversion of adducts **41** and **42** to an enediyne cyclization precursor now awaited investigation.

Experiments directed toward this end in the case of compound **42** commenced (Scheme 9) with selective cleavage of the primary silyl linkage. Under strictly defined acidic conditions, alcohol **43** became accessible. Oxidation[26] of compound **43** and exposure of the labile aldehyde to the Corey−Fuchs

(25) Lakshman, M. K.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1991**, *113*, 6589.

(26) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

Scheme 9[a]



[a] (a) concentrated HCl, THF, 86% yield; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) PPh_3, CBr_4, CH_2Cl_2, −78 °C, 84% yield; (d) ^{n}Buli, $PhCH_3$, −78 °C, 74% yield; (e) TBAF, THF, 0 °C; (f) conc. HCl, MeOH, 25 °C, 74% yield (two steps); (g) NaH, TBSCl, THF, 85% yield; (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95% yield.

protocol[27] unveiled the terminal acetylene **46**. At this stage, both the alkynyl and phenolic functional groups were liberated by treatment of **46** with TBAF. Additionally, the benzophenone ketal linkage was cleaved under acidic conditions to afford a triol which, following selective silylation of the phenolic oxygen, was smoothly converted to diol **47**. Following acylation, diyne **48** was obtained.

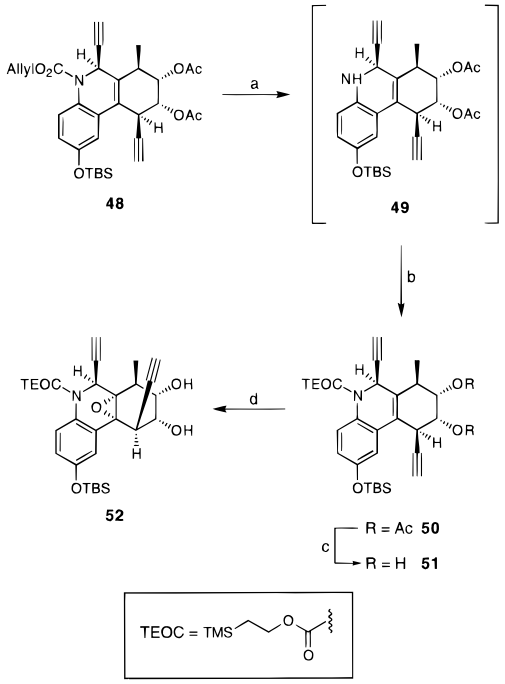
In anticipation of the conditions which were to be employed in the interpolative enediyne construction (i.e., palladium), it proved advantageous to exchange the carbamate protecting group to avoid interference with the allyl carbamate. Thus, a trimethylsilylethoxycarbonyl (TEOC) group was selected to replace the "alloc" linkage. Unfortunately, the TEOC group could not be employed from the start of our sequence due to the requirement of fluoride induced deprotection maneuvers.

Removal of the alloc group from **48** was accomplished through the action of $Pd(PPh_3)_4$ in combination with morpholine (Scheme 10).[28] In situ acylation of **49** with TEOCCl under basic conditions delivered the carbamate exchanged product **50** in 90% yield. Cleavage of the two acetates with ammonia afforded compound **51** which, upon stereospecific epoxidation of the resultant diol with mCPBA, gave rise to epoxide **52**. With this substance in hand, we could initiate an investigation to explore the feasibility to interpose the cis ethylene unit as discussed earlier in Scheme 3 under plan II.

The first attempts to accomplish such an insertion involved a projected Sonogashira variant of the Castro−Stephens reaction in the methyl carbamate series (Scheme 11).[29] The epoxydiyne **53** (synthesized in a manner analogous to the above described TEOC carbamate series) was exposed to the action of Pd(0)/Cu(I) conditions in the presence of *cis*-1,2-dichloroethylene (**54**). Unfortunately, even after numerous attempts, none of the desired cyclic enediyne **55** was observed.[30]

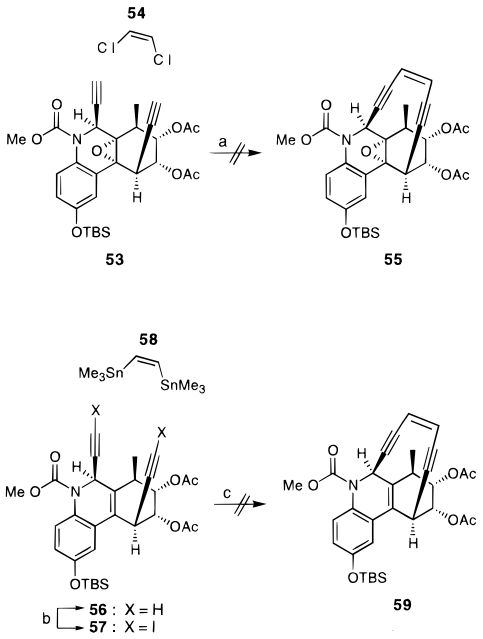
Our attentions then turned to more powerful cross-coupling conditions. Stille had previously described highly efficient Pd-catalyzed cross coupling conditions which employed stannyl acetylide and vinyl iodide.[31] However, the prospects of using the parent *cis*-1,2-diiodoethylene, a compound reputed to be thermally and photolytically unstable,[31] were not reassuring. Additionally, stannyl acetylides are known to be quite sensitive functionalities. Therefore, we decided to pursue a coupling

Scheme 10[a]



[a] (a) $Pd(PPh_3)_4$, morpholine, THF, 0 °C; (b) TEOCCl, NaH, DMAP, THF, 0−25 °C; (c) NH_3, MeOH, 90% (three steps); (d) mCPBA, CH_2Cl_2, 87% yield.

Scheme 11[a]



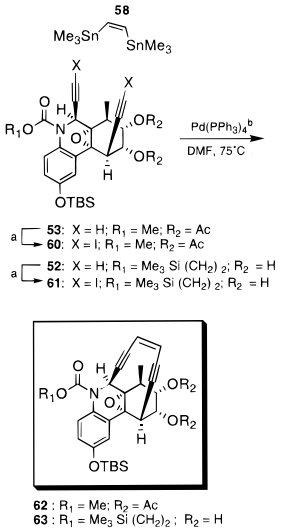
[a] (a) $Pd(PPh_3)_4$, CuI, $nBuNH_2$, PhH. (b) (catalyst) $AgNO_3$, NIS, THF; (c) **57**, $Pd(PPh_3)_4$, DMF, 60 °C, slow addition.

reaction between *cis*-1,2-distannyl ethylene and a bis-iodoalkyne. There had been a reported coupling of this type by Liebeskind and co-workers between an iodoalkyne and a stannyl cyclobutenedione.[32] A conceptually related interpolative ring closure, though using totally different chemistry, was described by Nicolaou and associates in their total synthesis of rapamycin.[33]

The possibility was first probed in the case of compound **56**. This substance had been prepared *en route* to **53** starting with

(27) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(28) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825.
(29) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
(30) For the only example of this type of construction to produce a cyclic enediyne in the context of an annulene synthesis, see: Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337.
(31) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138.
(32) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.
(33) Nicolaou, K. C.; Chakraborty, T. Y.; Piscopio, A. D.; Monowa, N; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115* 4419.

Scheme 12[a]



[a] (a) $AgNO_3$ (catalyst), NIS, THF, 25 °C, 60: 98%, 61: 91%. (b) 5 mol% $Pd(PPh_3)_4$, 0.023 M, 75 °C, **62**: (78% yield), **63**: (81% yield).

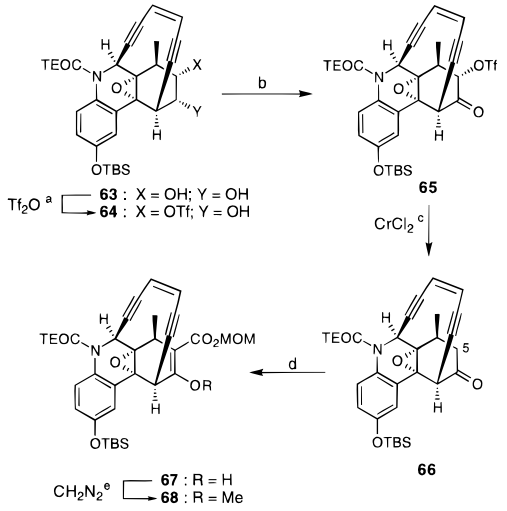
methylcarbamate **41**, via much the same chemistry employed in reaching the alloc urethane **48**. The two ethynyl linkages of **56** were iodinated with NIS in the presence of silver nitrate to afford bis-iodo-alkyne **57**.[34a] Exposure of this compound to the action of Pd(0) and *Z*-1,2-bis-(trimethylstannyl)ethylene (**58**)[34b] failed to bring about formation of any of the desired cyclic enediyne (**59**). Although rapid cross-coupling had occurred, only the product of two intermolecular couplings was isolated.

Though the interpolation of the ethylene unit into **56** or **57** was unsuccessful, *it was hoped that cyclization could be accomplished if the epoxide were in place. The C_8-C_9 epoxide might serve to shorten the approach of the two ethynyl units while providing some relief from the projected strain in the cyclization product.* To study this possibility, we returned to the previously mentioned epoxide **53**. Bis-iodination proceeded smoothly, as described for **56**, to provide the bis-iodide **60** in 98% yield. Following extensive experimentation and optimization, treatment of **60** with bis-stannyl ethylene reagent **58** and catalytic $Pd(PPh_3)_4$ under medium dilution conditions, a 78% yield of the long sought after cyclic enediyne **62** was obtained![35] As anticipated, conduct of the cyclization reaction in the presence of the central epoxide was critical to the successful double coupling.

With this success, we returned to the TEOC series, focusing on the epoxydiol **52**. This compound was converted to bis-iodide **61** in high yield. *The transformation which was to be the hallmark of our total synthesis involved exposure of compound **61** to $Pd(PPh_3)_4$ and synthon **58** to afford the crucial cyclic enediyne **63** in 81% isolated yield.* With access to cyclic enediyne **63** accomplished, exploration of chemistry which would eventually lead to a total synthesis of dynemicin A would now be taken up in full earnest.

The first stage of the progression of **63** to dynemicin A involved the further development of the C_5-C_6 vinylogous carbonate region. A crucial requirement in this regard would be the ability to differentiate the vicinal hydroxyl groups. This subgoal was indeed realized through selective triflation of the equatorial C_5 hydroxyl with Tf_2O as shown in Scheme 13. Oxidation of the resultant C_6 hydroxyl of **64** with Dess−Martin

Scheme 13[a]



[a] (a) Tf_2O, Pyr, CH_2Cl_2, −20 °C, 95%; (b) Dess−Martin periodinate, CH_2Cl_2, 95% yield; (c) $CrCl_2$, THF, 75% yield; (d) $MgBr_2$, CO_2, Et_3N, MeCN then MOMCl, iPr_2NEt, THF, 61% yield (two steps); (e) CH_2N_2, MeOH, 0 °C, 70% yield.

periodinane[36] afforded the labile keto-triflate **65**. Reductive excision of the trifloxy function was accomplished via the action of $CrCl_2$ to provide ketone **66**.[37] With the intention of installing the C_5 carboxyl function, several attempts to generate a "stoichiometric" enolate of the ketone in **66** were undertaken. These initiatives were uniformly unsuccessful. Decomposition products whose structures were not readily formulated were produced.

Accordingly, we turned to the use of the mild conditions for α-carboxylation developed by Rathke.[38] In the event, ketone **66** was treated with $MgBr_2$ and Et_3N under an atmosphere of CO_2. This protocol produced a highly labile β-keto acid. It was not isolated as such, but rather immediately treated with MOMCl, as shown, to afford enol **67**. After careful optimization of this sequence, a reliable 61% yield could be attained over the two steps (**66** → **67**). Finally, methylation of enol **67** with diazomethane in methanol produced the MOM protected vinylogous carbonate **68**. This compound represents a suitably protected but fully functionalized version of the ABC ring system of **1**.

Due to the lack of natural material available to us, survey of a variety of feasible conditions for removal of protecting groups using probe structures derived from dynemicin would not be possible. In this context, successful cleavage of the MOM group from advanced ABC ring systems bolstered our confidence that this way of containing the vinylogous carbonate and the eventual anthraquinone hydroxyl functions (*vide infra*) would service our needs. Having developed a synthetic route to the fully functionalized ABC core system of **1**, we entered what we hoped would be the final phase of our total synthesis journey. We now had to deal with the attachment of the D and E rings to form the trihydroxyanthraquinone moiety via a deprotectable precursor of dynemicin A.[39]

Any DE + ABC annulation scheme which was to be accomplished, must take note of vulnerabilities which might result in cleavage of the epoxide linkage. *Any intermediate which lacked nitrogen stabilization would certainly be at serious*

(34) (a) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int Ed. Engl.* **1984**, *23*, 727. (b) Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. J. *Organomet. Chem.* **1986**, *304*, 257.

(35) Shair, M. D.; Yoon, T. Y.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.

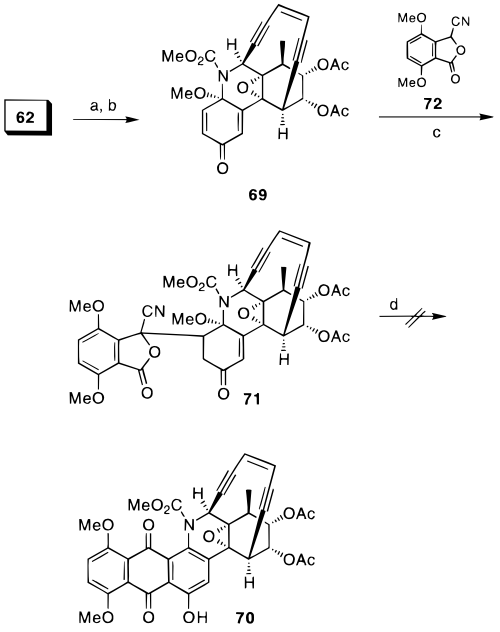
(36) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(37) Hanson, J. R. *Synthesis* **1974**, 1.

(38) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877.

(39) For an excellent survey of methods to construct anthraquinone constructs, see: Krohn, K. *Angew.Chem., Int. Ed. Engl.* **1986**, *25*, 790.

Scheme 14[a]



[a] (a) TBAF, AcOH, THF, 0 °C; (b) $PhI(OAc)_2$, MeOH, 0 °C, 65% (two steps); (c) **72**, LDA, THF, 0 °C; (d) various bases and Lewis acids.

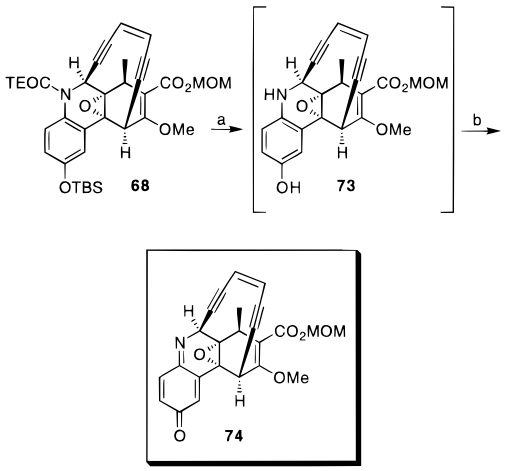
risk with respect to epoxide solvolysis culminating in Bergman cyclization as discussed earlier in Scheme 2. The resolution of this problem would require the implementation of delicate chemical transformations under the most exacting of conditions.

Our first tendencies were to utilize chemistry which we had developed earlier in the synthesis of a pentacyclic anthraquinone system in reaching compound **35** discussed earlier. To apply these lessons to the case at hand, we returned to model compound **62**. In order to fashion a quinone aminal bearing the cyclic enediyne, the phenolic silyl linkage of **62** was cleaved (Scheme 14), and the resulting free phenol was oxidized with $PhI(OAc)_2$ in methanol to afford quinone aminal **69** as a single diastereomer. Treatment of **69** with the anion of cyanophthalide **72** was undertaken. Unfortunately, in the case at hand, this reaction did not lead to desired anthraquinone **70**. Instead, seco product **71** was isolated. Apparently, a Michael addition had indeed occurred. However, the hoped for cyclization by addition of the resulting enolate to the lactone had not materialized. Numerous attempts to coax the cyclization of **71** were unsuccessful. Additionally, quinone aminal **69** appeared to be unresponsive as a potential dienophile in any type of Diels–Alder process.

Having failed to bring about the needed attachment of the DE ring system using tested quinone aminal technology, we hoped to generate a system with increased reactivity through reduced steric encumberance in the environment of the nitrogen center. We were concerned that the presence of a carbamate, or other protective linkage, might inhibit a cyclization event by placing the N-resident group on the inside contour of the "bay region". Previously (Scheme 6, compound **34**) we had rationalized that access to the nitrogen of pentacyclic systems was thwarted by the steric limits of this concave molecular surface. The target system we chose, which would deal with the criteria posed above, was a *quinone imine*.

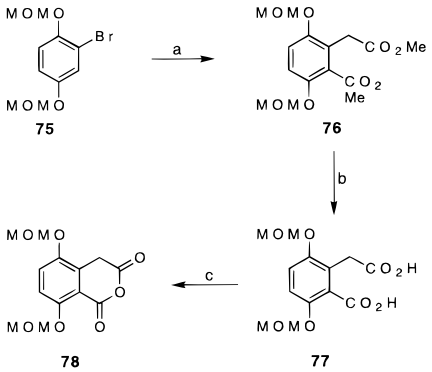
It was not without some trepidation that we undertook (TBAF) the removal of the TEOC and TBS groups of compound **68** since the resulting product was to be **73** wherein the integrity of the epoxide linkage could well be threatened. Fortunately, in situ oxidation $PhI(OAc)_2$ of **73** thus generated led to the

Scheme 15[a]



[a] (a) TBAF, THF, 0 °C; (b) $PhI(OAc)_2$, 0 °C, 60% yield (two steps).

Scheme 16[a]



[a] (a) $LiCH(CO_2Me)_2$, LiTMP, THF, −78 °C, 71% yield; (b) KOH, MeOH, H_2O, 95% yield; (c) (trimethylsilyl)ethynyl ether, CH_2Cl_2, 0 °C, quant.

formation of quinone imine **74**. Although intermediates similar to **73** had been observed spectroscopically,[12f] this was the first instance where a chemical reaction had been conducted on this unstable system. The quinone imine construct served to stabilize the epoxide linkage by attenuating the potential nucleophilicity of the nitrogen from the epoxide linkage. *We note in passing that through recourse to quinone imines, our total synthesis and prodrug design efforts had been joined. We shall return to this subject shortly*.

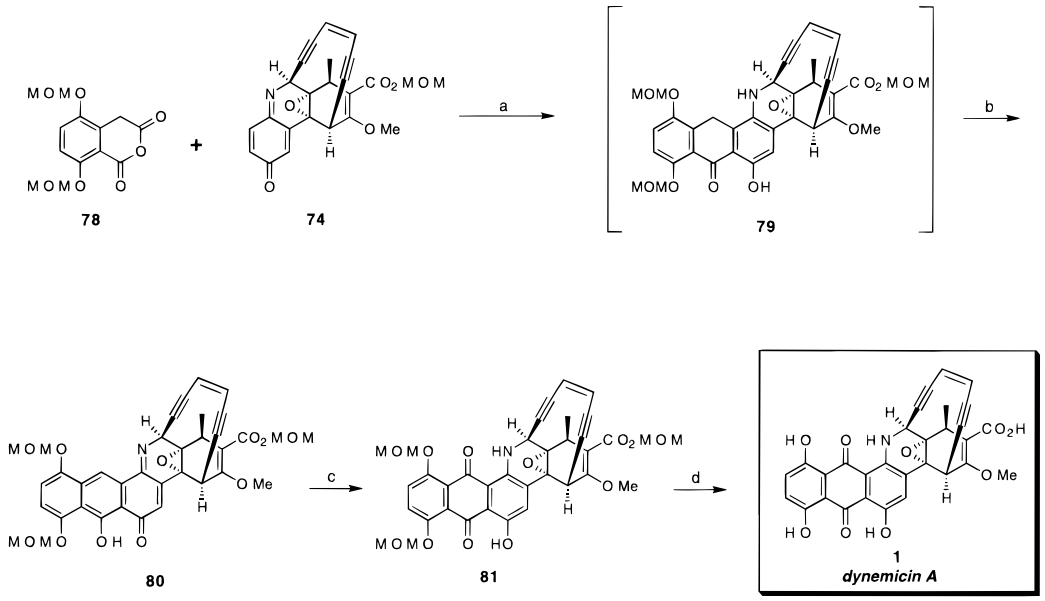
At this juncture, we turned to the application of homophthalic anhydride (HPA) methodology which had been developed by Tamura and associates as a means of delivering a naphthoquinone ring system in a mild and versatile way.[40] Notwithstanding the numerous examples of HPA systems which had been previously synthesized, the substitution pattern which was required for dynemicin had not been reported. The synthesis of a suitably protected and oxygenated HPA construct is detailed in Scheme 16.

In a not widely precedented transformation, the bromoarene **75** was condensed with the anion of dimethylmalonate in the presence of lithium tetramethylpiperidide at low temperature.[41] The homophthalic ester **76** was isolated in 71% yield. Presumably, the product ester arises via the intermediacy of a benzyne which has been intercepted by the malonate anion. Although a related transformation had been previously described, the reported yield was quite low (10%), and the desired reaction

(40) Tamura, Y.; Fukata, F.; Sasho, M.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 2273 and references cited therein.

(41) Guyot, M.; Molho, D. *Tetrahedron Lett.* **1973**, *14*, 3433.

Scheme 17[a]



[a] (a) LHMDS, **78**, THF, 0 °C, then **74**; (b) $PhI(OCOCF_3)_2$, THF, 0 °C, 5 min; (c) air, daylight, THF, high concentration; (d) $MgBr_2$, Et_2O, 15% yield (four steps).

was accompanied by the formation of numerous side products. Our optimization of this reaction should prove quite applicable to the general synthesis of highly substituted homophthalic esters and related compounds from easily accessible bromo arenes. Saponification of diester **76** yielded diacid **77** which underwent cyclodehydration via the action of (trimethylsilyl)ethynyl ether[42] thereby affording the target homophthalic anhydride **78**.

The successful amalgamation of the DE region of dynemicin, as homophthalic anhydride **78**, and the ABC region, as quinone imine **74**, paving the way for the synthesis to the naturally occurring product (**1**) is depicted in Scheme 17. Deprotonation of **78** with LHMDS generated a bright yellow entity to which was added quinone imine **74**. A product, presumed to be the highly unstable and unisolable anthrone **79** quickly formed and was immediately oxidized with $PhI(OCOCF_3)_2$ to deliver anthracenol **80**.[43] Following the screening of numerous unsuccessful oxidation protocols, it was discovered that exposure of **80** to daylight under aerobic conditions brought about an oxidation which afforded the long sought after protected goal structure **81**.[44] *In the concluding step of the synthesis, treatment of **81** with $MgBr_2$ in ether, following purification on a sephadex column, yielded a pure sample of (±)-dynemicin A (**1**). Comparison of spectral data recorded for synthetic (**1**) with literature data and data recorded on a trace specimen supplied by the Bristol-Myers pharmaceutical company confirmed that the total synthesis of (**1**) had indeed been accomplished.* The overall yield of the sequence from **74** to isolated homogenous **1** (four steps) was only 15%. The disappointing efficiency of the transformations is attributable to the instability of the intermediates, and the difficulty associated with the isolation and purification of **1**, rather than to failings in the chemical reactions *per se*. In fact, the difficulties in the management of the intermediates in our synthesis due to their marginal stability cannot be overemphasized. Notwithstanding these problems, a total synthesis of the enediyne antibiotic dynemicin A (**1**) has been achieved.

Synthesis and Biological Evaluation of Enediyne Containing Quinone Imine Systems

The logic of the emergence of the quinone imine linkage suitably arranged such that its reduction product might initiate a sequence leading to diyl formation (see structure **11**) was discussed earlier. Surely, we were drawn to such a system by analogy to the paradigm for bioreductive activation of mitomycins (see structures **12** and **13**).[16] The recognition that this type of arrangement could be central to our total synthesis helped to augment interest in this class of compounds. The first compound examined was compound **82**[17a] (Scheme 18). This compound had been prepared, as previously described, through a shunt in our total synthesis effort.[17a] The promising biological activity of compound **82**, as regards DNA cutting, as well as *in vitro* cytoxicity and *in vivo* experiments in mice have been described elsewhere.[17,18,19] It seemed unlikely that the C_4-methyl group and the C_5 and C_6 acetoxyl groups were playing a role at the mechanistic level in fostering the dynemicin like activity. We were not unmindful of the synthetic complications involved in incorporating this apparently noncritical functionality in the prodrug. Accordingly, we set out to examine a system which would be more readily synthesized. We defined as our goal structure compound **93**. From a strictly biomechanistic point of view, there was no *a priori* reason to include the C_7 hydroxyl group (R_3 = OH). In this instance, inclusion of such an additional group would be likely to simplify the synthesis.

Our route to quinone imine **93** is shown in Scheme 18. It follows from the enediyne cyclization chemistry used in our synthesis of calicheamicin and from chemistry developed by Nicolaou in connection with a prodrug in the dynemicin series based on a cleavable urethane blocking group.[45] Diacetate **84** was prepared from phenolic acetate **83** via a Polonovski reaction. A C_2 acetylenic unit was then installed by treatment of **84** with ethynylmagnesium bromide and (trimethylsilyl)ethoxy carbo-

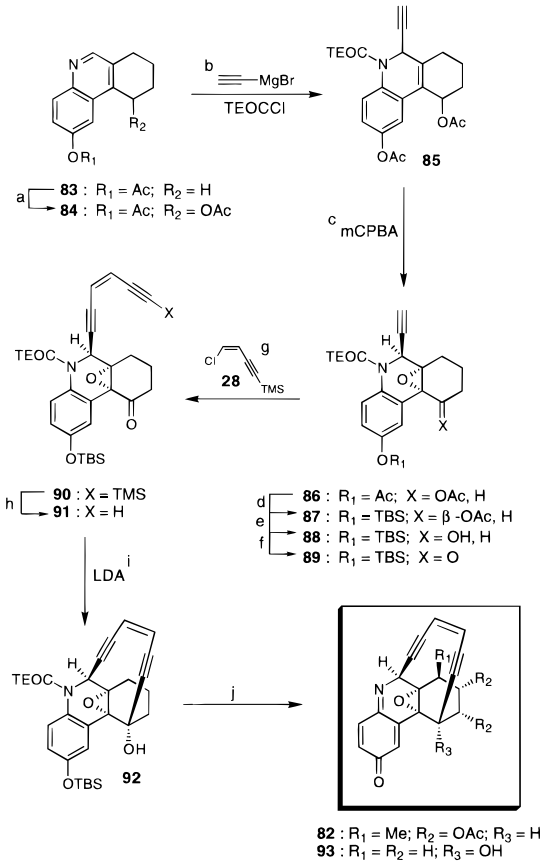
(42) Kita, Y.; Akai, S.; Ajimura, N.; Yoshigi, M.; Yasuda, H.; Tamura, Y. *J. Org. Chem.* **1986**, *51*, 4150.

(43) Although anthracenol **98** could not be purified and hence fully characterized due to its lability, analysis of its ^1H NMR spectrum matched well with a related model system.

(44) For the conversion of anthracenols to anthraquinones in the presence of ground state oxygen and light, see: (a) Cameron, D. W.; Schultz, P. E. *J. Chem. Soc. (C)* **1967**, 2121. (b) Julian, P. L.; Cole, G. *J. Am. Chem. Soc.* **1945**, *67*, 1721.

(45) Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendeborn, W. V.; Dai, W.-M.; Chadha, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8890.

Scheme 18[a]



[a] (a) mCPBA, CH_2Cl_2, then Ac_2O, 70 °C, 84% yield; (b) THF, −78 °C; (c) mCPBA, CH_2Cl_2, $NaHCO_3$, 42% yield (two steps); (d) (i) KCN, MeOH, (ii) TBSCl, imidazole, CH_2Cl_2, 69% yield (two steps); (e) DIBAH, CH_2Cl_2, −78 °C; (f) PCC, CH_2Cl_2, 25 °C, 46% yield (two steps); (g) $Pd(PPh_3)_4$, CuI, $nBuNH_2$, PhH, 75% yield; (h) $AgNO_3$, EtOH−THF, 90% yield; (i) LDA, $PhCH_3$, −78 °C, 71% yield (j) i) TBAF, THF, 0 °C, (ii) $PhI(OAc)_2$, THF, 0 °C, 49% yield (two steps).

nylchloride to give **85** as a moderately unstable compound. Stereoselective epoxidation of **85** was accomplished with mCPBA to furnish **86** in 42% overall yield. The phenolic ester linkage was then cleaved selectively with KCN in methanol, and the free phenol was subsequently silylated with TBSCl to deliver silyl ether **87**. It was then necessary to unveil the C_7 hydroxyl group without cleaving the hydrolytically labile phenolic silyl unit. This was efficiently accomplished by exposure of **87** to DIBAH at −78 °C which furnished alcohol **88**. Ketone **89** was accessed by PCC oxidation of **88** under standard conditions.

At this juncture, we elected to install the enediyne unit through a Sonogashira type coupling of **89** with (*Z*)-1-trimethylsilyl-4-chloro-but-3-en-1-yne. The intended reaction proceeded smoothly, and enediyne **90** was in hand.

In order to induce cyclization, the alkynyl bound silyl group of **90** was cleaved through Ag(I) catalysis, providing **91**. Exposure of this compound to the action of lithium diisopropylamide at −78 °C induced a rapid cyclization which afforded the cyclic enediyne system **92** in 71% yield. In close analogy to the chemistry which had been developed during our dynemicin A total synthesis effort, compound **92** was treated with TBAF. The resultant unstable product was then treated immediately with $PhI(OAc)_2$ to produce the goal quinone imine structure **93** in 49% yield over the two-step procedure.

Our first investigation into the antitumor potential of quinone imine **93** involved evaluation of its *in vitro* performance with respect to several cancer cell lines. The results are recorded in Table 1 which also provides an IC_{50} comparison of the clinically prescribed anticancer agent mitomycin C. Compound **93** exhibited *in vitro* activity between 7 and 43 times greater potency than mitomycin C.

Table 1. In Vitro Cytotoxicity of **93** and Mitomycin C versus Various Cancer Cell Lines

	IC_{50} (μM)				
compd	HL-60	MT-2	MT-4	833K	SK-Br-3
93	0.012	0.015	0.0035	0.020	0.015
mitomycin C	0.08	0.10	0.15	0.30	0.30

Table 2. In Vivo Anticancer Activity of **105** and Mitomycin C (MMC) in B2D6F1 Mice Bearing Lewis Lung Adenocarcinoma

	dose	AWC		ATV	
compd	(mg/kg)	day 7	day 10	day 7	day 10
control	0	+0.4	+1.0	1.00	1.00
93	0.5	−1.2	−1.7		
93	1.0	−3.9	−4.8	0.15	0.18
MMC	0.5	−1.5	−0.1	0.53	0.71
MMC	1.0	−0.8	−0.9	0.38	0.45

We turned to a more critical *in vivo* evaluation of compound **93** versus clinically prescribed mitomycin C. Listed in Table 2 are the relative life prolongation performances of compound **93** versus mitomycin C with respect to mice bearing subcutaneously implanted Lewis lung adenocarcinoma.

As in the *in vitro* study, compound **93** has also outperformed mitomycin C in this screen. After ten days of treatment with a dosage of 0.5 mg/kg of compound **93** a 50% reduction in tumor mass resulted. In comparison, mitomycin C treatment has resulted in a 29% reduction in tumor volume in the same screen. While more searching preclinical investigations are required and are, indeed, in progress, the biorationale involved in leading us to such quinoneimine enediyne prodrugs has been vindicated.

Summary

A total synthesis of the enediyne natural product dynemicin A (**1**) has been accomplished in 33 chemical steps. Several notable transformations were employed in this expedition. The suprafaciality of the Diels−Alder reaction was utilized to control the stereochemical relationship between the C_4 and C_7 appendages of (**1**). Additionally, a novel method for the insertion of an ethylene unit between a cis diyne system was developed for the synthesis of the strained enediyne bridge. This method has already found use in another laboratory.[12e] Additionally, recourse to the highly sensitive **73** (Scheme 15) *en route* to the critical quinone imine linkage had been successfully navigated. A homophthalic anhydride annulation partner for the construction of the anthraquinone moiety was efficiently constructed (see compound **78**).

As a consequence of the access to enediyne quinone imines occasioned by these studies, we investigated the use of this reductively activatible linkage for triggering diyl formation. The synthesis of two such agents (**82** and **93**) was accomplished, and their biological profiles both *in vitro* and *in vivo* are suggestive of the emergence of a novel enediyne prodrug, drawing from the lessons of the mitomycin and dynemicin parent drugs.

Experimental Section

General Procedures. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-400. Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR. Optical rotations were measured on a Jasco DIP-370 polarimeter. Mass spectra were obtained on a JOEL JMS-

DX-303 HF mass spectrometer. Analytical chromatography was performed on E. Merck silical gel 60 F_{254} plates (0.25 mm). Flash chromatography was performed on Mallinckrodt silica gel 60 (230−400 mesh). Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile, benzene (PhH), triethylamine, and pyridine were distilled from calcium hydride. *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich in sure seal containers. All other commercially obtained reagents were used as received.

2-(2,4-Hexadienoxy)-5-methoxybenzaldehyde (21). To a solution of 5-methoxysalicyl aldehyde **20** (28 g, 0.18 mol) in 300 mL of acetone was added 100 g (0.72 mol) of finely ground K_2CO_3. To the yellow suspension was added crude sorbyl bromide (prepared from sorbol (37 mL, 0.33 mol) and PBr_3 (15 mL, 0.16 mol) in ice-cold ether), and the mixture was refluxed for 30 min when the fluorescent yellow color disappeared. The mixture was allowed to cool to room temperature and filtered, and the filtrate was concentrated and redissolved in ether. The ethereal solution was washed twice with 1 N NaOH and once with saturated brine, dried (Na_2SO_4), and concentrated to a small volume. Treatment with hexane gave rise to formation of white crystalline solid which was filtered and dried to give 29 g of **21**. The mother liquor was concentrated and chromatographed on silica to give additional 12 g of the product (96%, combined): mp 74−75 °C (Et_2O−hexane); IR (neat) ν_{max} 2900, 1679, 1669, 1494, 1275, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1 H, C*H*O), 7.32 (d, J = 3.2 Hz, 1 H, H6), 7.10 (dd, J = 9.0, 3.2 Hz, 1 H, H4), 6.93 (d, J = 9.0 Hz, 1 H, H3), 6.32 (dd, J = 15.3, 10.4 Hz, 1 H, diene), 6.08 (dd, J = 15.3, 10.4 Hz, 1 H, diene), 5.8−5.7 (m, 2 H, diene), 4.63 (d, J = 6.0 Hz, 2 H, CH_2-OAr), 3.79 (s, 3 H, OCH_3), 1.77 (d, J = 6.6 Hz, 3 H, methyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 156.0, 153.8, 134.3, 131.4, 130.4, 125.5, 124.2, 123.6, 115.2, 110.2, 69.9, 55.9, 18.2; MS (20 eV EI) *m/e* (rel intensity) 232 (M^+, 3), 152 (100), 137 (9), 81 (83); HRMS (FAB) for $C_{14}H_{16}O_3$, calcd 232.1100, found 232.1098. Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.95. Found: C, 72.34; H, 6.94.

2-(2,4-Hexadienoxy)-5-methoxycinnamaldehyde (24). To a flame-dried 500 mL flask was placed NaH (60% in mineral oil, 4 g, 0.10 mol). The mineral oil was removed by washing with pentane and decanting under N_2 atmosphere. Charged with 150 mL of anhydrous THF, to the stirred suspension at 0 °C was added triethyl phosphonoacetate (18.2 mL, 0.092 mol) slowly dropwise. After the addition was complete, the mixture was further stirred at room temperature for 30 min to give clear solution, to which was added a solution of **21** (19.5 g, 0.084 mol) in 70 mL THF via a dropping funnel slowly dropwise over a 30 min period. Further stirred at room temperature for another 30 min, THF was removed by rotary evaporation. The residue was diluted by saturated $NaHCO_3$ and extracted 3 times with Et_2O. Combined ether layer was washed with saturated brine, dried ($MgSO_4$), and concentrated to give crude cinnamate **22** as a yellowish oil which was pure enough to be used directly: IR (neat) ν_{max} 2936, 1710, 1632, 1496, 1215, 1171, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 16.2 Hz, 1 H, H2), 7.03 (d, J = 2.7 Hz, 1 H, H6′), 6.84 (AB of ABX, $\Delta\nu$ = 4.3 Hz, J_{AB} = 9.0 Hz, J_{BX} = 2.7 Hz, 2 H, H3′ and 4′), 6.48 (d, 16.2 Hz, 1 H, H1), 6.30 (dd, J = 15.2, 10.4 Hz, 1 H, diene), 6.08 (dd, J = 16.2, 10.4 Hz, 1 H, diene), 5.8−5.7 (m, 2 H, diene), 4.55 (d, J = 5.9 Hz, 2 H, CH_2OAr), 4.25 (q, J = 7.1 Hz, OCH_2-CH_3), 3.77 (s, 3 H, OCH_3), 1.76 (d, J = 6.6 Hz, 3 H, methyl), 1.33 (t, J = 7.1 Hz, 3 H, OCH$_2$CH_3).

To a solution of the crude **22** from above in 300 mL of anhydrous CH_2Cl_2 at −78 °C was added 1.5 M DiBAL (in toluene, 144 mL, 0.22 mol). Stirred at −78 °C for 1 h, the reaction was quenched by cautious addition of 5 mL of MeOH before allowed to warm to room temperature. The mixture was poured into 300 mL of ice−water and acidified by concentrated HCl with vigorous stirring with external cooling. The organic layer separated, the aqueous phase was extracted again with CH_2Cl_2, and the combined organic was dried ($MgSO_4$) and concentrated to ca. 75 mL, which was then diluted with an equal volume of hexane, and resulting slurry was filtered to collect 13.5 g of the alcohol **23** as a white crystalline solid. Silica gel column chromatography of the concentrated mother liquor gave an additional 7 g of the product (94%, combined): mp 82−84 °C (toluene−hexane); IR ($CDCl_3$) ν_{max} 3610, 2938, 1493, 1212, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, J = 2.9 Hz, 1 H, H6′), 6.93 (d, J = 16.0 Hz, 1 H, H3), 6.78 (AB of ABX, $\Delta\nu$ = 9.7 Hz, J_{AB} = 8.9 Hz, J_{BX} = 2.9 Hz, 2 H, H3′ and 4′), 6.37 (dt, J = 16.0, 5.9 Hz, 1 H, H2), 6.3−6.0 (m, 2 H, diene), 5.8−5.7 (m, 2 H, diene), 4.51 (d, J = 6.0 Hz, 2 H, CH_2OAr), 4.33 (d, J = 5.9 Hz, 2 H, H1), 3.78 (s, 3H, OCH_3), 1.77 (d, J = 6.7 Hz, 3H, methyl).

To a stirred solution of oxalyl chloride (5.0 mL, 58 mmol) in 200 mL of anhydrous CH_2Cl_2 at −78 °C was slowly added DMSO (9.4 mL, 130 mmol). As soon as gas evolution subsided, a solution of the above alcohol (12.5 g, 48 mmol) in 30 mL of CH_2Cl_2 was added *via* a dropping funnel slowly dropwise over a 30 min period. Further stirred for 30 min at −78 °C, triethylamine (33 mL, 240 mmol) was added, and the mixture was allowed to warm to ambient temperature over 15 min before quenched by 300 mL of HCl. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated to ca. 50 mL by rotary evaporation. Resulting suspension was diluted by an equal volume of hexane to precipitate out the product which was collected and dried to give 9.4 g of **24** as a yellow crystalline solid. The mother liquor was concentrated and chromatographed on silica to give an additional 2 g of **24** (92%, combined): mp 82−84 °C (CH_2Cl_2−hexane); IR ($CDCl_3$) ν_{max} 2915, 2836, 1672, 1620, 1494, 1285, 1210, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, J = 7.8 Hz, 1 H, C*H*O), 7.85 (d, J = 16.1 Hz, 1 H, H3), 7.06 (d, J = 2.9 Hz, 1 H, H6′), 7.10 (dd, J = 9.0, 2.9 Hz, 1 H, H4′), 6.87 (d, J = 9.0 Hz, 1 H, H3′), 6.73 (dd, J = 16.1, 7.8 Hz, 1 H, H2), 6.31 (dd, J = 15.2, 10.5 Hz, 1 H, diene), 6.10 (dd, J = 15.2, 10.5 Hz, 1 H, diene), 5.8−5.7 (m, 2 H, diene), 4.58 (d, J = 4.1 Hz, 2 H, CH_2OAr), 3.79 (s, 3 H, OCH_3), 1.77 (d, J = 6.7 Hz, 3 H, methyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 153.6, 151.9, 147.9, 134.3, 131.4, 130.5, 129.0, 124.5, 123.9, 118.6, 114.3, 112.6, 69.8, 55.8, 18.2; HRMS (FAB) for $C_{16}H_{18}O_3$, calcd 258.1256, found 258.1259. Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.14; H, 7.05.

6-Methoxy-3-methyl-3,4,4a,9,10,10a-hexahydro-9-oxaphenanthrene-4-carbaldehyde (26). (A) Thermal Reaction. A solution of **24** (10.0 g, 38.7 mmol) in 250 mL of anhydrous toluene was heated to 80 °C for 5 days. After cooling to room temperature, the solvent was removed by rotary-evaporation, and the residue was chromatographed on silica to give 9.3 g of **25** + **26** (inseparable mixture of endo:exo = ca. 3:1 by NMR) as a yellowish oil (93%). **(B) $ZnCl_2$-Catalyzed Reaction.** To a solution of **24** (150 mg; 0.58 mmol) in 3 mL of anhydrous CH_2Cl_2 was added 1 M $ZnCl_2$ (in ether, 0.60 mL, 0.60 mmol). The mixture was stirred at room temperature for 3 days, diluted by aqueous NH_4Cl, and extracted twice with CH_2Cl_2. Combined organic was dried (Na_2SO_4), concentrated, and chromatographed on silica to give 88 mg of **25** + **26** (endo:exo = ca. 20:1 by ^1H NMR) as a yellowish oil (59%): IR (neat) ν_{max} 2963, 2721, 1720, 1495, 1210, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (d, J = 4.3 Hz, 1 H, C*H*O), 6.72 (AB of ABX, $\Delta\nu$ = 13.3 Hz, J_{AB} = 8.8 Hz, J_{BX} = 2.7 Hz, 2 H, H12,13), 6.42 (d, J = 2.7 Hz, 1 H, H10), 5.85 (ddd, J = 9.8, 4.3, 2.7 Hz, 1 H, H4 or 5), 5.59 (dt, J = 9.8, 1.8 Hz, 1 H, H4 or 5), 4.41 (dd, J = 10.1, 5.0 Hz, 1 H, H2), 3.96 (dd, J = 12.2, 10.1 Hz, 1 H, H2), 3.70 (s, 3 H, OCH_3), 3.12 (app t, J = 10.9 Hz, 1 H, H8), 2.91 (ddd, J = 10.9, 6.7, 4.3 Hz, 1 H, H7), 2.78 (m, 1 H, H3), 2.44 (m, 1 H, H6), 1.14 (d, J = 7.2 Hz, 3 H, 6-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 153.4, 148.7, 134.0, 126.9, 124.5, 117.2, 113.1, 111.4, 71.1, 55.8, 52.2, 36.9, 34.3, 32.2, 16.9; HRMS (FAB) for $C_{16}H_{18}O_3$, calcd 258.1256, found 258.1238. Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.60; H, 6.89.

9-(1,4-Benzoquinonyl)-2-hydroxy-8-methyl-3-oxabicyclo[3.3.1]-non-6-ene (27). To a solution of **25** + **26** (11.0 g, 42.6 mmol, ca. 3:1 diastereomeric mixture) in 100 mL of MeCN at 0 °C was added aqueous solution of ammonium cerium nitrate (60 g, 109 mmol) in 200 mL of H_2O rapidly dropwise. The initially black solution became orange as yellow solid precipitated at the end of the addition. Stirred at 0 °C for 30 min, the solid was collected by filtration and air-dried to give 6.9 g of **27** as a yellow solid (62%): mp >176 °C (dec); IR ($CDCl_3$) ν_{max} 3601, 2964, 1657, 1602, 1287, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1 H, H3), 6.73 (AB of ABX, $\Delta\nu$ = 18.6 Hz, J_{AB} = 10.1 Hz, J_{BX} = 2.2 Hz, 2 H, H5, 6), 5.73 (AB of ABX, $\Delta\nu$ = 30.3 Hz, J_{AB} = 10.1 Hz, J_{AX} = 5.3 Hz, 2 H, H4′, 5′), 5.39 (s, 1 H, acetal), 4.22 (dd, J = 10.6, 1.3 Hz, 1 H, −CH_2O−), 3.73 (s, 1 H, H1′), 3.45 (dd, J = 10.6, 1.5 Hz, 1 H, −CH_2O−), 2.74 (br s, 1 H, -O*H*), 2.25−2.10 (m, 3

H, H2′, 3′, 6′), 1.08 (d, J = 7.2 Hz, 3 H, 3′-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 187.3, 148.9, 137.4, 135.9, 134.4, 132.6, 123.6, 91.9, 63.8, 41.1, 33.6, 32.8, 30.2, 17.2. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.84; H, 6.05.

2-(*tert*-Butyldimethylsilyl)oxy-10-[(*tert*-butyldimethylsilyl)oxy]-methyl-7-methyl-7-10-dihydrophenanthridine (29). To a suspension of **27** (5.8 g, 22.3 mmol) in 20 mL of AcOH was added a solution of NH_4OAc (12 g, 156 mmol) in 20 mL of water. The mixture was heated to 100 °C with stirring under N_2 atmosphere for 1 h. Resulting dark solution was cooled to 0 °C and neutralized by NH_4OH until basic under continuous stream of nitrogen. After further stirring for 1 h at 0 °C with the N_2 stream maintained, the precipitate was filtered, washed 3 times with water, and air-dried to give 5 g of greenish tan powder (**28**), which was dissolved in 10 mL of DMF, cooled to 0 °C, and 7.1 g of imidazole (91 mmol) and 7.8 g of TBSCl (49 mmol) were added. After having been stirred for 2 h, diluted by water, and extracted 3 times with Et_2O, the ether layer was washed with saturated brine, dried (Na_2SO_4), concentrated, and chromatographed to give 9.0 g of **29** as a slightly tan viscous oil (86%) : IR (neat) ν_{max} 2950, 1617, 1503, 1254, 1101, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1 H, H2), 7.96 (d, J = 8.9 Hz, 1 H, H13), 7.38 (d, J = 2.5 Hz, 1 H, H10), 7.23 (dd, J = 8.9, 2.5 Hz, 1 H, H12), 6.18 (dd, J = 9.8, 4.4 Hz, 1 H, H6), 6.08 (dd, J = 9.8, 4.5 Hz, 1 H, H5), 4.2−4.0 (m, 2 H, H7, one of CH_2OTBS), 3.7−3.5 (m, 2 H, H4, one of CH_2OTBS), 1.41 (d, J = 7.2 Hz, 3 H, 4-CH_3), 1.03 (s, 9 H), 0.85 (s, 9 H), 0.27 (s, 6 H), −0.1 (s, 3 H), −0.3 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 149.2, 142.8, 137.8, 133.8, 131.4, 131.1, 127.5, 127.1, 123.9, 110.8, 69.4, 39.2, 33.5, 26.0, 25.8, 25.2, 18.5, 18.3, −4.2, −5.3; HRMS (FAB) for $C_{27}H_{44}NO_2Si_2$ (M + H), calcd 470.2911, found 470.2913. Anal. Calcd for $C_{27}H_{43}NO_2Si_2$: C, 69.03; H, 9.23; N, 2.98. Found: C, 68.08; H, 9.49; N, 3.00.

2-(*tert*-Butyldimethylsilyl)oxy-10-[(*tert*-butyldimethylsilyl)oxy]-methyl-8,9-dihydroxy-7-methyl-7,8,9,10-tetrahydrophenanthridine (37). To a solution of **29** (9.0 g, 19 mmol) in 30 mL of THF and 12 mL of *t*-BuOH was added 0.2 M OsO_4 (in THF, 0.5 mL, 0.1 mmol) and 60% aqueous NMO (5 mL, 48 mmol). The mixture was stirred at room temperature for 4 h, concentrated to a small volume (ca. 5 mL), and diluted by 5 mL of 10% $NaHSO_3$ and 50 mL of saturated $NaHCO_3$. Resulting precipitate was collected, washed thoroughly with water, air-dried, and finally washed with hexane to give 8.93 g of **37** as a slightly tan powder (90%) which was pure enough to be used in subsequent reactions. An analytical sample was prepared by recrystallization from hexane−ethyl acetate: mp 206−209 °C (hexane−EtOAc); IR (neat) ν_{max} 3600, 2931, 1617, 1505, 1260, 1238, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (s, 1 H, H2), 7.94 (d, J = 8.9 Hz, 1 H, H13), 7.28 (d, J = 2.5 Hz, 1 H, H10), 7.21 (dd, J = 9.0, 2.4 Hz, 1 H, H12), 4.49 (app t, J = 2.8 Hz, 1 H, H6), 4.13 (dd, J = 8.9, 2.5 Hz, 1 H, CH_2OTBS), 3.99 (dd, J = 7.2, 2.5 Hz, 1 H, H5), 3.72 (app dt, J = 8.9, 2.8 Hz, 1 H, H7), 3.65 (app t, J = 8.9 Hz, 1 H, CH_2OTBS), 3.10 (app quint, J = 7.2 Hz, 1 H, H4), 1.55 (d, J = 7.2 Hz, 3 H, 4-CH_3), 1.02 (s, 9 H), 0.83 (s, 9 H), 0.25 (s, 6 H), −0.02 (s, 3 H), −0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 148.5, 142.7, 136.2, 132.6, 131.4, 127.9, 127.1, 124.1, 110.5, 72.4, 70.9, 65.3, 45.6, 36.0, 25.9, 25.8, 18.5, 18.3, −4.2, −5.4; MS (20 eV EI) *m/e* (rel intensity) 446 (40, M-^{t}Bu), 428 (39), 336 (23), 324 (25), 312 (100); HRMS (FAB) for $C_{27}H_{46}NO_4Si_2$ (M + H), calcd 504.2965, found 504.2979. Anal. Calcd for $C_{27}H_{45}NO_4Si_2$: C, 64.37; H, 9.00; N, 2.78. Found: C, 64.18; H, 9.01; N, 2.64.

Quinoline (40). The diol **37** (20 g, 39.8 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (300 mL) and cooled to 0 °C. To this solution was added $Ph_2C(OMe)_2$ (23 g, 99 mmol, 2.5 equiv) and concentrated H_2SO_4 (3.3 mL, 59.7 mmol, 1.5 equiv), and the reaction was then allowed to warm to 25 °C followed by warming to 40 °C. After 2 h at 40 °C, the reaction was allowed to cool to 25 °C, diluted with Et_2O (750 mL), washed with saturated $NaHCO_3$ (2 × 150 mL), and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude ketal was then resubjected to silylative conditions by dissolving in CH_2Cl_2 (150 mL), followed by addition of imidazole (3.25 g, 48 mmol, 1.2 equiv) and TBSCl (6.0 g, 40 mmol, 1.0 equiv) after 30 min, and the reaction was diluted with EtOAc (600 mL) and washed with H_2O (250 mL) and saturated brine (200 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 20:1 → 10:1 → 4:1 hexane/EtOAc) yielded 22 g (83%) of the ketal **40** as a sticky white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.62 (m, 2H), 7.36 (m, 4H), 7.27 (d, J = 2.5 Hz, 1H), 7.24 (dd, J = 9.0, 2.5 Hz, 1H), 7.03 (m, 2H), 6.94 (m, 2H), 4.98 (d, J = 6.9 Hz, 1H), 4.48 (dd, J = 6.9, 1.4 Hz, 1H), 3.95 (dd, J = 11.5, 2.1 Hz, 1H), 3.87 (dd, J = 11.4, 2.1 Hz, 1H), 3.65 (t, J = 11.4 Hz, 1H), 3.54 (q, J = 7.8, 1.3 Hz, 1H), 1.35 (d, J = 7.8 Hz, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.29 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.1, 149.7, 143.3, 141.6, 141.2, 136.9, 132.4, 131.4, 128.1, 128.0, 127.9, 127.6, 126.6, 126.4, 123.9, 110.1, 108.8, 108.1, 78.3, 75.1, 64.8, 42.9, 35.7, 25.7, 25.6, 22.3, 18.1, −4.3, −4.4, −5.4, −5.5; FTIR ($CDCl_3$) ν 2930 (s), 2858 (s), 2247 (m), 1617 (s), 1504 (s), 1449 (s) cm^{-1}; HRFABMS calcd for $C_{39}H_{53}NO_4Si_2$ 655.3513, found 655.3510.

Alkyne (41). To a solution of (triisopropylsilyl)acetylene (6.35 mL, 28.32 mmol, 3.5 equiv) in THF (100 mL) at 0 °C was added a 3 M solution of ethylmagnesium bromide (8.09 mL, 24.7 mmol, 3.0 equiv) in ether. The reaction was allowed to warm to room temperature and stir for 3 h. After which time, the reaction was cooled to −78 °C, and a THF (50 mL) solution of quinoline **40** (5.3 g, 8.09 mmol, 1.0 equiv) was added followed by the slow dropwise addition of methylchloroformate (3.12 mL, 40.5 mmol, 5.0 equiv) by syringe pump. After complete addition of the chloroformate, the reaction was allowed to slowly warm to −30 °C over 1.5 h and stir at −30 °C for an additional 15 h. The reaction was quenched by the addition of methanol (5 mL) and allowed to warm to room temperature. The reaction was poured into a mixture of EtOAc (400 mL) and H_2O (100 mL). The layers were separated, and the organic layer was washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 25:1 → 10:1 hexane/EtOAc) gave 26.9 g (73%) of the alkyne **41** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 3H), 7.37 (m, 4H), 7.10 (m, 4H), 6.80 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.6 2.5 Hz, 1H), 5.50 (br s, 1 H), 4.70 (d, J = 7.0 Hz, 1H), 4.22 (d, J = 7.0 Hz, 1H), 3.84 (m, 1H), 3.80 (s, 3H), 3.43 (t, J = 10.5 Hz, 1H), 3.26 (dd, J = 10.5, 3.0 Hz, 1H), 2.81 (br s, 1.0 H), 1.34 (d, J = 8.1 Hz, 3H), 1.05 (s, 9H), 0.99 (s, 9H), 0.85 (m, 21 H), 0.20 (s, 6H), 0.07 (s, 3H), 0.03 (s, 3H); FTIR ($CDCl_3$) ν 2955 (s), 2930 (s), 2890 (m), 2246 (w), 1698 (s), 1494 (s), 1445 (m), 1257 (s) cm^{-1}; LRMS (CI, NH_3) *m/z* 926 ([M + H + NH_3] 100%); Anal. Calcd for $C_{53}H_{77}NO_6Si_3$: C, 70.12; H, 8.56. Found: C, 70.22; 8.59.

Alkyne (42). To a solution of (triisopropylsilyl)acetylene (14.8 mL, 66 mmol, 2.0 equiv) in THF (220 mL) at 0 °C was added a 3 M solution of ethylmagnesium bromide (22 mL, 66 mmol, 2.0 equiv) in ether. The reaction was allowed to warm to room temperature and stir for 3 h. After which time, the reaction was cooled to −78 °C, and a THF (50 mL) solution of quinoline **40** (22 g, 32.98 mmol, 1.0 equiv) was added followed by the slow dropwise addition of allylchloroformate (10.83 mL, 102 mmol, 3.1 equiv) via syringe pump. After complete addition of the chloroformate, the reaction was allowed to slowly warm to −30 °C over 1.5 h and stir at −30 °C for an additional 15 h. The reaction was quenched by the addition of methanol (10 mL) and allowed to warm to room temperature. The reaction was poured into a mixture of EtOAc (500 mL) and H_2O (200 mL). The layers were separated, and the organic layer was washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 25:1 → 10:1 hexane/EtOAc) gave 26.9 g (80%) of the alkyne **42** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) (330 K) δ 7.82 (d, J = 5.3 Hz, 2H), 7.51−7.62 (m, 2H), 7.47 (t, J = 5.3 Hz, 2H), 7.41−7.35 (m, 2H), 7.14−7.07 (m, 2H), 6.82 (d, J = 2.6 Hz, 1H), 6.72 (dd, J = 6.7, 2.6 Hz, 1H), 5.94 (m, 1H), 5.55 (br s, 1H), 5.35 (dd, J = 17.1, 1.4 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 4.73 (d, J = 7.0 Hz, 1H), 4.70 (br s, 2H), 4.23 (d, J = 7.0 Hz, 1H), 3.84 (dd, J = 10.7, 3.8 Hz, 1H), 3.44 (t, J = 10.7 Hz, 1H), 3.27 (dd, J = 10.7, 3.8 Hz, 1H), 2.84 (br s, 1H), 1.36 (d, J = 7.7 Hz, 3H), 1.00 (s, 9H), 0.91 (s, 9H), 0.88 (s, 18H), 0.22 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.4, 141.4, 137.4, 132.2, 132.1, 129.9, 129.4, 128.1, 128.0, 127.9, 127.6, 126.9, 126.7, 124.8, 118.2, 117.6, 113.9, 108.2, 104.7, 84.7, 78.7, 75.2, 66.5, 64.2, 49.7, 42.7, 39.9, 25.7, 25.6, 20.2, 18.3, 18.2, 18.1, 18.0, 11.0, 10.8, 10.5, −4.5, −5.3, −5.6; IR ($CDCl_3$) ν 2955 (s), 2247 (w), 1697 (s), 1657 (m), 1448 (s), 1279 (s), 1258 (s) cm^{-1}; HRFABMS calcd for $C_{52}H_{79}NO_6Si_3$ 897.5215, found 897.5210.

Alcohol (43). The alkyne **42** (26.9 g, 28.3 mmol, 1 equiv) was dissolved in THF (200 mL) and cooled to 0 °C. Concentrated HCl (5.1 mL) was added dropwise, and the reaction was allowed to warm to room temperature. After stirring 1.2 h, the reaction was quenched by the addition of saturated $NaHCO_3$ (200 mL) and diluted with EtOAc (200 mL). The organic layer was separated and washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 25:1 → 15:1 → 8:1 hexane/EtOAc) provided the alcohol **43**, 20 g (86%) as a white foam: mp = 72−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (330 K) δ 7.57 (dd, J = 8, 1.4 Hz, 2H), 7.39 (m, 3H), 7.16 (m, 5H), 6.84 (d, J = 2.6 Hz, 1H), 6.75 (dd, J = 8.7, 2.6 Hz, 1H), 5.95 (m, 1H), 5.61 (br s, 1H), 5.35 (d, J = 17.2, 1.4 Hz, 1H), 5.21 (d, 10.4 Hz), 4.72 (br s, 1H), 4.64 (d, J = 6.7 Hz, 1H), 4.31 (d, J = 6.7 Hz), 3.86 (d, J = 11.1 Hz, 1H), 3.68 (m, 1H), 3.31 (d, J = 5.1 Hz, 1H), 2.80 (br s, 1H), 1.39 (d, J = 7.6 Hz), 1.07 (s, 3H), 1.02 (s, 9H), 0.89 (s, 18H), 0.23 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.4, 141.7, 141.6, 132.1, 129.2, 128.9, 128.0, 127.9, 127.6, 126.7, 126.6, 125.5, 125.2, 124.1, 118.5, 117.6, 113.8, 108.2, 104.7, 84.7, 78.9, 76.0, 66.6, 63.9, 49.5, 42.3, 40.2, 25.6, 25.5, 19.9, 18.3, 18.2, 18.1, 17.6, 12.2, 11.1, 10.9, 10.8, 10.5, −3.7, −4.5, −4.5; FTIR ($CDCl_3$) ν 3670 (m), 3619 (m), 2943 (s), 2248 (m), 1698 (s), 1493 (s), 1281 (s) cm^{-1}; HRFABMS calcd for $C_{46}H_{65}NO_6Si_2$ 783.4350, found 819.4354.

Acetylene (46). The dibromoolefin **45** (20 g, 20.51 mmol, 1.0 equiv) was dissolved in toluene (450 mL) and cooled to −78 °C. Then, ^{n}-Buli (17.23 mL, 43.07 mmol, 2.1 equiv) was added dropwise via syringe pump. Following addition, the reaction was stirred at −78 °C for 4.5 h and then quenched at −78 °C by the addition of AcOH (3 mL). The reaction was allowed to warm to room temperature and then diluted with EtOAc (500 mL) and H_2O (300 mL). The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 20:1 hexane/EtOAc) yielded 12.3 g (74%) of the acetylene **46** as a white foam: mp = 121−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0, 1.4 Hz, 2H), 7.42 (m, 3H), 7.09 (m, 6H), 6.94 (d, J = 2.6 Hz, 1H), 6.73 (d, J = 7.3 Hz, 1H), 5.94 (m, 1H), 5.70 (br s, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 5.19 Hz, 1H), 4.71 (br s, 1H), 4.70 (d, J = 7.2 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 3.90 (s, 1H), 2.92 (br s, 1H), 2.13 (d, J = 2.8 Hz, 1H), 1.49 (d, J = 7.6 Hz, 3H), 1.00 (s, 9H), 0.89 (s, 21H), 0.23 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.5, 140.5, 132.2, 129.9, 128.4, 127.9, 127.6, 126.9, 126.3, 118.7, 117.6, 114.0, 108.5, 103.7, 85.6, 83.2, 78.6, 77.5, 77.2, 76.9, 76.6, 70.9, 66.6, 50.2, 39.1, 30.1, 25.6, 18.3, 18.2, 18.2, 17.5, 10.7, −4.5, −4.7; IR ($CDCl_3$) 3306 (m), 2943 (s), 1698 (s), 1495 (s), 1449 (s), 1281 (s) cm^{-1}; HRFABMS calcd for $C_{47}H_{63}NO_5Si_2$ 777.4244, found 777.4241.

Diacetate (48). The triol (2.44 g, 6.404 mmol, 1.0 equiv) was azeotroped from benzene (3 × 10 mL) and dissolved in THF (35 mL). A 60% dispersion of NaH (307 mg, 7.69 mmol, 1.2 equiv) was added at once to this solution. After 5 min, TBSCl (1.17 g, 8.00 mmol, 1.25 mmol) was added at once as a solid. After an additional 15 min, the reaction was quenched by the addition of H_2O (100 mL) and EtOAc (500 mL). Separation of the layers was followed by washing the organic layer with saturated brine (100 mL), drying (MgSO4), filtering, and concentration. The crude product was directly acylated by dissolving the diol in CH_2Cl_2 (40 mL) and adding Et_3N (4.5 mL, 32 mmol, 5.0 equiv) and Ac_2O (3.0 mL, 32 mmol, 5.0 equiv) followed by DMAP (50 mg). After 12 h of being stirred, the reaction was diluted with EtOAc (500 mL) and washed with H_2O (150 mL) and saturated brine (100 mL). The product was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 5:1 → 3:1 hexane/EtOAc) provided 3.15 g (83%, two steps) of the diacetate **48** as a white foam, mp 72−77 °C: ^{1}H NMR (400 MHz, $CDCl_3$) (330 K) δ 7.45 (br s, 1H), 7.21 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 8.8, 2.7 Hz, 1H), 5.95 (m, 1H), 5.72 (br s, 1H), 5.50 (t, J = 2.4 Hz, 1H), 5.30 (m, 3H), 4.76 (dd, J = 6.7, 2.5 Hz, 1H), 4.64 (br s, 1H), 3.51 (s, 1H), 2.79 (m, 1H), 2.46 (d, J = 2.6 Hz, 1H), 2.14 (d, J = 2.5 Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.30 (d, J = 7.0 Hz, 1H), 0.98 (s, 9H), 0.22 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 170.1, 152.5, 131.9, 128.5, 119.2, 117.9, 114.5, 80.54, 79.8, 73.3, 72.3, 71.7, 70.1, 66.9, 45.4, 34.4, 33.4, 25.5, 20.9, 20.8, 18.0, 14.2, −4.5, −4.6; IR ($CDCl_3$) ν 3306 (s), 2956 (s), 2258 (m), 2248 (m), 1744 (s), 1699 (s), 1497 (s), 1393 (s), 1245 (s) cm^{-1}; HRFABMS calcd for $C_{32}H_{39}NO_7Si$ 577.2496, found 577.2498.

Diol (51). The allylcarbamate **48** (2.40 g, 4.03 mmol, 1.0 equiv) was dissolved in THF (60 mL) and cooled to 0 °C. To this solution was added $Pd(PPh_3)_4$ (140 mg, 0.121 mmol, 0.03 equiv) followed by morpholine (843 μL, 9.67 mmol, 2.4 equiv) dropwise, and the reaction was allowed to stir at 0 °C for 2 h. Then, the reaction was warmed to 25 °C for 30 min and cooled back to 0 °C. To the reaction was added a 60% dispersion of NaH (806 mg, 20.13 mmol, 5.0 equiv) and TeocCl (3.5 mL, 20.13 mmol, 5.0 equiv), and the reaction was allowed to warm to 25 °C and stir for 13 h. At which point, the reaction was quenched by the addition of H_2O (50 mL) and diluted with EtOAc (300 mL). The layers were separated, and the organic layer washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. The crude diacetate **50** was then dissolved in dry MeOH (30 mL), and 7 M NH_3 (20 mL, 20 equiv) was added. After 20 h, the reaction was concentrated to a small volume and purified by column chromatography (SiO_2, 3:2 hexane/EtOAc) to yield 2.02 g (90%) of the diol **51** as a white foam: mp 127−130 °C.; ^{1}H NMR (400 MHz, $CDCl_3$) (330 K) δ 7.45 (br s, 1H), 7.21 (d, J = 2.7 Hz, 1H), 6.74 (dd, J = 8.8, 2.7 Hz, 1H), 5.68 (br s, 1H), 4.30 (m, 2H), 4.21 (s, 1H), 3.91 (t, J = 7.2 Hz, 1H), 3.53 (s, 1H), 2.50 (m, 1H), 2.33 (d, J = 2.6Hz, 1H), 2.15 (d, J = 4.5Hz, 1H), 2.11 (d, J = 2.3 Hz, 1 H), 2.05 (d, J = 2.3 Hz, 1H), 1.42 (J = 7.0 Hz, 3H), 1.06 (t, J = 7.5 Hz, 2H), 0.98 (s, 9H), 0.22 (s, 6H), 0.03 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.2, 128.8, 124.9, 122.3, 118.9, 114.3, 82.2, 80.3, 72.4, 72.3, 72.2, 71.2, 64.8, 45.5, 37.2, 35.5, 25.5, 18.0, 17.5, 14.7, −1.65, −4.6; FTIR ($CDCl_3$) ν 3614 (m), 3577 (m), 3306 (s), 2956 (s), 2249 (m), 1691 (s), 1495 (s), 1202 (s) cm^{-1}; HRFABMS calcd for $C_{30}H_{43}NO_5Si_2$ 553.2680, found 553.2677.

Epoxide (52). The diol **51** (1.5 g, 2.75 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL). To this solution was added 95% mCPBA (2.11 g, 11.01 mmol, 4.0 equiv) at once as a solid. The reaction was allowed to stir for 8.5 h at 25 °C. After which time, saturated $NaHCO_3$ (50 mL) was added to the reaction followed by the addition of Me_2S (710 μL). After stirring for 20 min, the reaction was diluted with EtOAc (300 mL), and the layers were separated. The organic layer was washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 2:1 hexane/EtOAc) provided 1.31 g (87%) of the epoxide **52** as a white foam: mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 2.7 Hz, 1H), 7.18 (br s, 1H), 6.83 (dd, J = 8.7, 2.7 Hz, 1H), 5.66 (br s, 1H), 4.26 (m, 1H), 4.18 (br s, 1H), 4.12 (dt, J = 12.1, 3.1 Hz, 1H), 3.85 (t, J = 3.7 Hz, 1H), 3.78 (ddd, J = 10.5, 3.1 Hz, 1H), 3.43 (d, J = 12.1 Hz, 1H), 2.35 (m, buried, 1H), 2.35 (d, J = 2.5 Hz, 1H), 2.20 (d, J = 10.7 Hz, 1H), 2.13 (s, 1H), 1.58 (d, J = 7.3 Hz, 3 H), 0.99 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), −0.02 (br s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.7, 130.2, 120.03, 118.9, 79.7, 79.00, 74.8, 73.8, 73.5, 72.7, 70.8, 64.6, 62.2, 45.5, 37.9, 32.9, 25.4, 17.9, 17.3, 15.6, −2.1, −4.8, −4.9; FTIR ($CDCl_3$) ν 3562 (w), 3307 (m), 2956 (s), 2257 (m), 1697 (s), 1501 (s), 1252 (s), 1208 (s) cm^{-1}; HRFABMS calcd for $C_{30}H_{43}NO_6Si_2$ 569.2629, found 569.2633.

Bisiodide (60). The epoxide **53** (150 mg, 0.268 mmol, 1.0 equiv) was dissolved in THF (4.0 mL). To this solution was added $AgNO_3$ (4.6 mg, 0.027 mmol, 0.1 equiv) followed by *N*-iodosuccinimide (150 mg, 0.67 mmol, 2.5 equiv), and the reaction was stirred in the dark for 3.5 h. After which time, the reaction was diluted with H_2O (50 mL) and EtOAc (150 mL). The layers were separated, and the organic layer was washed saturated brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 2.5:1 hexane/EtOAc) provided 215 mg (98%) of the bis-iodoalkyne **60** as a very pale yellow glass: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 2.6 Hz, 1H), 7.11 (br s, 1H), 6.79 (dd, J = 8.7, 2.6 Hz, 1H), 5.78 (br s, 1H), 5.36 (t, J = 2.8 Hz, 1H), 5.23 (dd, J = 11, 2.8 Hz, 1H), 3.95 (d, J = 2.8 Hz, 1H), 3.72 (s, 1H), 2.70 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 1.39 (d, J = 7.3 Hz, 3H), 1.00 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H); FTIR ($CDCl_3$) ν 2956 (s), 2257 (m), 2190 (w), 1741 (s), 1703 (s), 1502 (s), 1373 (s), 1246 (s), 1151 (m) cm^{-1}; LRMS (CI, NH_3) 838 ([M + NH_3 + H] 73%), 837 ([M + NH_3] 90%), 818, ([M + H] 12%). Anal. Calcd for $C_{30}H_{35}I_2NO_8Si$: C, 44.06; H, 4.28. Found: C, 43.96; H, 4.12.

Enediyne (62). The diiodide **60** (197 mg, 0.241 mmol, 1.0 equiv) was dissolved in DMF (22 mL), and dry argon was passed through the

solution for 20 min. The reaction was then heated to 75 °C, at which temperature $Pd(PPh_3)_4$ (14 mg, 0.012 mmol, 0.05 equiv) was added under a stream of argon. A 0.023 M solution of cis-1,2-bis-(trimethylstannyl)ethylene (12.0 mL, 0.277 mmol, 1.15 equiv) in degassed DMF was then added dropwise to the reaction via syringe pump over 1.2 h. After complete addition, the yellow-tan reaction mixture was allowed to warm to room temperature and then poured into H_2O (100 mL) and Et_2O (250 mL). The layers were separated, and the organic layer was washed with H_2O (5 × 30 mL). The organic layer was then washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 4:1 EtOAc/hexane) gave 111 mg (78%) of the enediyne **62** as an off-white foam: mp 77−78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (br s, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.75 (dd, J = 8.0, 2.0 Hz, 1H), 5.77 (dd, J = 10.1, 1.0 Hz, 1H), 5.69 (dd, J = 10.1, 1.0 Hz, 1H), 5.49 (t, J = 3 Hz, 1H), 5.32 (dd, J = 11.0, 3.0 Hz, 1H), 3.99 (d, J = 3.0 Hz, 1H), 3.76 (s, 3H), 2.80 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.40 (d, J = 8.0 Hz, 3H), 0.96 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); FTIR ($CDCl_3$) 2959 (s), 1743 (s), 1701 (s), 1492 (s), 1223 (w); LRMS (EI) m/z 591 ([M^+] 100). Anal. Calcd for $C_{32}H_{37}NO_8Si$: C, 64.97; H, 6.26. Found: C, 65.09; H, 6.31.

Bisiodide (61). The epoxide **52** (560 mg, 1.005 mmol, 1.0 equiv) was dissolved in THF (20 mL). To this solution was added $AgNO_3$ (18 mg, 0.10 mmol, 0.1 equiv) followed by *N*-iodosuccinimide (610 mg, 2.71 mmol, 2.7 equiv), and the reaction was stirred in the dark for 3.5 h. After which time, the reaction was diluted with H_2O (100 mL) and EtOAc (300 mL). The layers were separated, and the organic layer was washed saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 2:1 hexane/EtOAc) provided the bis-iodoalkyne **61** 740 mg (91%) as a very pale yellow glass: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 2.6 Hz, 1H), 7.18 (br s, 1H), 6.84 (dd, J = 8.7, 2.4 Hz, 1H), 5.72 (s, 1H), 4.35 (m, 1H), 4.16 (br s, 1H), 4.06 (dt, J = 12.1, 3.2 Hz, 1H), 3.95 (d, J = 3.0 Hz, 1H), 3.76 (m, 1H), 3.41 (d, J = 12.1 Hz, 1H), 2.45 (m, 1H), 2.22 (d, J = 10.4 Hz, 1H), 1.55 (d, J = 7.3 Hz, 3H), 1.00 (s, 9H), 0.26 (s, 3H), 0.24 (s, 3H), −0.02 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.5, 130.1, 120.1, 118.8, 79.5, 79.0, 74.3, 73.3, 73.1, 73.0, 72.5, 71.1, 65.9, 62.0, 51.1, 45.5, 37.8, 34.1, 25.3, 17.8, 15.2, −2.0, −4.8, −4.9; FTIR ($CDCl_3$) ν 3560 (w), 3301 (m), 2953 (s), 2261 (m), 1699 (s), 1501 (s), 1251 (s) cm^{-1}; HRFABMS calcd for $C_{30}H_{41}I_2NO_6Si_2$ 821.0565, found 821.0559.

Enediyne (63). The diiodide **61** (480 mg, 0.592 mmol, 1.0 equiv) was dissolved in DMF (56 mL) and dry argon was passed through the solution for 20 min. The reaction was then heated to 75 °C, at which temperature $Pd(PPh_3)_4$ (34 mg, 0.0296 mmol, 0.05 equiv) was added under a stream of argon. A 0.023 M solution of *cis*-1,2-bis-(trimethylstannyl)ethylene (33 mL, 0.769 mmol, 1.3 equiv) in degassed DMF was then added dropwise to the reaction via syringe pump over 1.2 h. After complete addition, the yellow-tan reaction mixture was allowed to warm to room temperature and then poured into H_2O (100 mL) and Et_2O (250 mL). The layers were separated, and the organic layer was washed with H_2O (5 × 60 mL). The organic layer was then washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 3:1 EtOAc/hexane) gave 284 mg (81%) of the enediyne **63** as an off-white foam: mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) (330 K) δ 7.20 (br s, 1H), 7.00 (d, J = 2.6 Hz, 1H), 6.79 (dd, J = 8.7, 2.5 Hz, 1H), 5.75 (br s, buried, 1H), 5.74 (dd, J = 9.9, 1.4 Hz, 1H), 6.67 (dd, J = 9.9, 1.4 Hz, 1H), 4.29 (m, 1H), 4.22 (br s, 1H), 4.09 (dt, J = 12.5, 3.7 Hz, 1H), 4.03 (d, J = 2.9 Hz, 1H), 3.79 (dt, J = 12.5, 3.7 Hz, 1H), 3.34 (d, J = 12.1 Hz, 1H), 2.47 (m, 1H), 2.27 (d, J = 12.5 Hz, 1H), 1.54 (d, J = 6.5 Hz, 1H), 1.02 (bt, buried, 3H), 0.97 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H), 0.00 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 152.6, 129.4, 128.6, 127.4, 124.0, 122.8, 120.3, 118.4, 97.4, 94.2, 92.2, 90.5, 73.0, 71.9, 71.7, 65.1, 63.4, 46.6, 38.5, 34.4, 25.6, 25.5, 18.1, 17.4, 15.0, -1.6, −4.4, −4.6; FTIR ($CDCl_3$) ν 3559 (m), 3491 (m), 2956 (s), 2255 (m), 1697 (s), 1502 (s), 1395 (s), 1314 (s) cm^{-1}; HRFABMS calcd for $C_{32}H_{43}NO_6Si_2$ 593.2629, found 593.2631.

Triflate (64). The diol **63** (200 mg, 0.341 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (15 mL) and subsequently cooled to −78 °C. Anhydrous pyridine (1.11 mL, 13.64 mmol, 40.0 equiv) was then added, followed by Tf_2O (103 μL, 0.613 mmol, 1.80 mmol). The reaction was then warmed to −20 °C (CCl_4/CO_2) and stirred for 1.5 h. After which time, the reaction was diluted with H_2O (30 mL) and EtOAc (100 mL). The organic layer was washed with 1.0 N HCl (1 × 20 mL), saturated $NaHCO_3$ (1 × 20 mL), and saturated brine (1 × 20 mL). The organics were then dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 6:1 hexanes/EtOAc) yielded 232 mg (95%) of the triflate **64** as an amorphous white solid: mp 71−75 °C dec; ^{1}H NMR (400 MHz, C_6D_6) (330 K) δ 7.30 (br s, 1H), 7.04 (d, 2.6 Hz, 1H), 6.79 (dd, J = 8.7, 2.5 Hz, 1H), 6.15 (br s, 1H), 5.30 (d, J = 7.1 Hz, 1H), 5.02 (s, 2H), 4.35(m, 1H), 4.25 (m, 1H), 3.64 (d, J = 4.2 Hz, 1H), 3.38 (d, J = 12.6 Hz, 1H), 2.41 (br s, 1H), 1.28 (d, J = 6.4 Hz, 3H), 1.02 (s, 9H), 0.89 (t, J = 5.8 Hz, 2H), 0.15 (s, 3H), 0.14 (s, 3H), −0.31 (br s, 9H); ^{13}C NMR (C_6D_6) δ 152.7, 129.9, 128.4, 127.7, 123.5, 122.8, 120.2, 118.6, 117.0, 96.6, 94.2, 92.6, 90.7, 89.9, 72.6, 69.6, 64.8, 63.0, 46.6, 34.7, 34.2, 25.4, 25.3, 17.9, 17.3, 13.9, −2.12, −4.7, −4.9; FTIR (C_6D_6) ν 3502 (s), 3300 (w), 2956 (s), 1702 (s), 1502 (s), 1411 (s), 1314 (s)1251 (s) cm^{-1}; HRFABMS calcd for $C_{33}H_{42}F_3NO_8SSi_2$ 725.2121, found 725.2126.

Keto-Triflate (65). The triflate **64** (232 mg, 0.326 mmol, 1 equiv) was dissolved in CH_2Cl_2 (12 mL), and Dess−Martin periodinane (415 mg, 0.978 mmol, 3.0 equiv) was added. After 3 h, the reaction was diluted with saturated $NaHCO_3$ (30 mL) and EtOAc (100 mL) and stirred vigorously until the layers became clear. The layers were then separated, and the organic layer was washed with saturated brine, dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (SiO_2, 10:1 hexanes/EtOAc) yielded 220 mg (95%) of the keto-triflate **65** as a yellow foam. The instability of **65** required that the compound be stored frozen in benzene for prolonged intervals, and extensive characterization was not accomplished: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 2.5 Hz, 1H), 5.90 (dd, J = 9.1, 1.1 Hz, 1H), 5.83 (dd, J = 9.0, 1.1 Hz, 1H), 5.55 (d, J = 7.5 Hz, 1H), 4.42 (s, 1H), 4.25 (m, 2H), 3.10 (q, J = 7.5, 2.1 Hz, 1H), 1.69 (d, J = 7.5 Hz, 1H), 0.95 (s, 9H), 0.19 (s, 6H), 0.00 (br s, 9H); CI (NH_3) m/z = 724 [M + H] (45%).

Ketone (66). A dry flask was charged with anhydrous $CrCl_2$ (206 mg, 1.69 mmol, 6.0 equiv) and THF (5 mL). To this suspension was added keto-triflate **65** (200 mg, 0.281 mmol, 1 equiv) dropwise as a solution in THF (10 mL). The reaction turned from green to a dark green-grey color, and after 2 h, the reaction was poured into a vigorously stirring solution of saturated NH_4Cl (10 mL) and Et_2O (70 mL). After 5 min, the reaction layers were separated, and the organic layer was washed with saturated NH_4Cl (10 mL), H_2O (2 × 20 mL), saturated brine (10 mL), then dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (SiO_2, 12:1 hexane/EtOAc) yielded 121 mg (75%) of the ketone **66** as an amorphous solid: mp 70−72 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (d, J = 2.6 Hz, 1H), 6.78 (dd, J = 8.8, 2.6 Hz, 1H), 5.75 (dd, J = 9.7, 1.3 Hz, 1H), 5.69 (dd, J = 9.7, 1.4 Hz, 1H), 5.68 (br s, buried, 1H), 4.25 (m, 1H), 4.19 (s, 1H), 3.14 (m, 1H), 2.84 (dd, J = 11.1, 6.5 Hz, 1H), 2.48 (dd, J = 11.1, 3.0 Hz, 1H), 1.50 (d, J = 6.6 Hz, 1H), 1.03 (bt, buried, 1H), 0.97 (s, 9H), 0.18 (s, 3H), 0.16 (s, 1H), 0.00 (br s, 3H); FTIR (C_6D_6) ν 2957 (s), 1700 (s), 1611 (m), 1501 (s), 1313 (s), 1250 (s) cm^{-1}; HRFABMS calcd for $C_{32}H_{41}NO_5Si_2$ 575.2523, found 575.2518.

Enol (67). A recovery flask was charged with anhydrous $MgBr_2$ (114 mg) and anhydrous CH_3CN (2 mL). Then, the flask was charged with ketone **66** (64 mg, 0.113 mmol, 1 equiv) in CH_3CN. The reaction was purged with dry CO_2 for 15 min, then, under an atmosphere of CO_2, Et_3N (473 μL, 3.39 mmol, 30.0 equiv) was added at once. The reaction was stirred under an atmosphere of dry CO_2 for 2.5 h and concentrated in vacuo. The crude β-keto acid product was diluted with Et_2O (40 mL) and 1 N HCl (15 mL), the layers were separated, and the organic layer was washed with H_2O (1 × 20 mL) and saturated brine (1 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude acid was azetroped from benzene (3×) and dissolved in THF (7 mL). To the reaction was added ^{i}PrNEt$_2$ (1.72 mL, 22.6 mmol, 200 equiv) followed by MOMCl (200 mL, 1.13 mmol, 10 equiv) dropwise slowly. After 3 min, TLC indicated that the starting material acid was fully consumed, and the reaction was diluted with saturated $NaHCO_3$ (30 mL) and EtOAc (100 mL). The layers were separated, and the organic layer was washed with saturated brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (12:1 hexane/EtOAc) yielded 45 mg (61%) of the β-keto ester **67** as

an amorphous solid: mp 71−75 °C dec; ^{1}H NMR (400 MHz, C_6D_6) δ 12.86 (br s, 1H), 7.34 (br s, 1H), 7.09 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.7, 2.6 Hz, 1H), 6.18 (br s, 1H), 5.12 (d, J = 5.9 Hz, 1H), 5.09 (dd, J = 6.0, 1.1 Hz, 1H), 5.06 (dd, J = 6.0, 1.1 Hz, 1H), 4.77 (d, J = 5.9 Hz, 1H), 4.27 (s, 1H), 4.18 (m, 2H), 3.77 (br s, 1H), 2.96 (s, 3H), 1.41 (br s, 3H), 0.96 (s, 9H), 0.82 (t, J = 8.0 Hz, 2H), 0.10 (s, 3H), 0.09 (s, 3H), -0.21 (br s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 171.3, 165.6, 152.8, 130.8, 128.3, 123.5, 123.2, 119.7, 118.2, 102.0, 98.1, 96.0, 91.1, 90.6, 89.3, 71.6, 64.6, 63.2, 56.9, 47.8, 35.3, 33.8, 25.5, 18.7, 18.0, 17.2, −2.1, −4.7, −4.9; FTIR (C_6D_6) ν 2957 (s), 1699 (s), 1666 (s), 1613 (m), 1500 (s), 1391 (s), 1278 (s) cm^{-1}; HRFABMS calcd for $C_{35}H_{45}NO_8Si_2$ 663.2684, found 663.2690.

Vinylogous Carbonate (68). The enol **67** (47 mg, 0.0718 mmol, 1 equiv) was dissolved in dry MeOH (5 mL) and cooled to 0 °C. To this solution was added CH_2N_2 (0.35 M in Et_2O) until the yellow color persisted for 1.2 h. After 1.2 h, the excess CH_2N_2 was quenched with a few drops of an AcOH/Et_2O solution, and the reaction was concentrated. Purification by column chromatography (SiO_2, 7:1 → 4:1 hexane/EtOAc) yielded 34 mg (70%) of the vinylogous carbonate **68** as an amorphous solid, mp 70−71 °C. ^{1}H NMR (400 MHz, C_6D_6) δ 7.35 (br s, 1H), 7.16 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.7, 2.4 Hz, 1H), 6.17 (br s, 1H), 5.24 (J = 5.9 Hz, 1H), 5.12 (dd, J = 10.1, 1.0 Hz, 1H), 5.07 (dd, J = 10.0, 1.1 Hz, 1H), 5.07 (br s, buried, 1H), 4.19 (m, 2H), 4.10 (s, 1H), 3.95 (br s, 1H), 3.42 (s, 3H), 3.10 (s, 3H), 1.47 (br s, 3H), 0.96 (s, 9H), 0.81 (t, J = 8.4 Hz, 2H), 0.13 (s, 3H), 0.12 (s, 3H), −0.19 (br s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 165.1, 155.9, 152.6, 130.8, 128.3, 123.4, 123.1, 119.5, 118.2, 115.2, 98.8, 96.0, 90.9, 90.2, 89.6, 71.3, 64.6, 63.6, 58.3, 56.8, 47.6, 36.5, 33.7, 25.5, 18.4, 18.0, 17.2, −2.1, −4.6, −4.8; FTIR (C_6D_6) ν 2934 (s), 1703 (s), 1500 (s), 1277 (s); HRFABMS calcd for $C_{36}H_{47}NO_8Si_2$ 677.2840, found 677.2835.

Quinone Aminal (69). The enediyne **62** (66 mg, 0.112 mmol, 1.0 equiv) was dissolved in THF (3 mL) and cooled to 0 °C. To this solution was added HOAc (223 μL, 0.223 mmol, 2.0 equiv) as a 1.0 M solution in THF. Then, 1.0 M TBAF in THF (123 μL, 0.123 mmol, 1.1 equiv) was added dropwise. After 20 min, the reaction was poured into EtOAc and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude phenol was then diluted in dry MeOH (4 mL) and cooled to 0 °C, and $PhI(OAc)_2$ (43 mg, 0.134 mmol, 1.2 equiv) was added. After 30 min, the reaction was poured into EtOAc and H_2O, the organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 1:1 EtOAc/hexane) provided 37 mg (65%) of the quinone aminal **69** as a clear glass. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 1.9 Hz, 1H), 6.32 (dd, J = 10.1, 1.9 Hz, 1H), 5.87 (d, J = 9.8 Hz, 1H), 5.79 (d, J = 9.8 Hz), 5.42 (t, J = 3.4 Hz, 1H), 5.28 (dd, J = 10.0, 3.4 Hz, 1H), 3.82 (s, 3H), 3.71 (d, J = 3.5 Hz, 1H), 3.07 (s, 3H), 2.77 (m, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 1.33 (d, J = 7.3 Hz, 1H); FTIR (film) ν 2931 (m), 1742 (s), 1714 (s), 1673 (s), 1641 (s), 1247 (s) cm^{-1}; EI [M$^+$] = 509 (100%).

Ketone (71). The cyanophthalide **72** (58 mg, 0.266 mmol, 4.1 equiv) was dissolved in THF (4 mL) and cooled to 0 °C. Then, 0.3 M LDA (850 μL, 0.26 mmol, 4.0 equiv) was added dropwise. To the yellow solution was added quinone aminal **69** (33 mg, 0.65 mmol, 1.0 equiv) as a solid at once. After 3 h at room temperature, the reaction was poured into EtOAc and H_2O, and the organic layer washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 1:1 EtOAc/hexane) provided 12 mg (35%) of the adduct **71** as a clear oil. The product was isolated as an inseperable mixture of diastereomers. The ^{1}H NMR spectra is shown in the supporting information. EI [M$^+$] = 539 (55%).

Quinone Imine (74). The vinylogous carbonate **68** (41 mg, 0.0613 mmol, 1.0 equiv) was dissolved in THF (4 mL) and cooled to 0 °C. Then, 1.0 M TBAF (171 mL, 0.171 mmol, 3.0 equiv) was added dropwise. After 3.5 h at 0 °C, $PhI(OAc)_2$ (102 mg, 0.319 mmol, 5.2 equiv) was added as a solid at once. After an additional 30 min at 0 °C, the reaction was poured into saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (SiO_2, 2:1 hexane/EtOAc) provided 15.5 mg (60%) of the quinone imine **74** as a pale yellow powder: mp 75−78 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, J = 10.0 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.04 (dd, J = 10.0, 2.0 Hz, 1H), 5.31 (d, J = 5.9 Hz, 1H), 5.15 (m, 3H), 5.04 (s, 1H), 3.81 (q, J = 7.3, 2.5 Hz, 1H), 3.61 (s, 1H), 3.48 (s, 3H), 3.20 (s, 3H), 1.38 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 185.3, 165.2, 161.0, 154.7, 140.7, 136.8, 131.3, 128.3, 127.5, 127.0, 126.7, 123.5, 122.8, 115.5, 108.5, 96.9, 90.5, 88.1, 63.5, 58.2, 56.8, 35.99, 31.5, 18.5; FTIR ($CDCl_3$) ν 1703 (s), 1652 (s), 1450 (m) cm^{-1}; HRFABMS calcd for $C_{24}H_{19}NO_6$ 417.1212, found 417.1218.

Homophthalic Ester (76). A solution of 2,2,6,6-tetramethylpiperidine (8.78 mL, 52.0 mmol, 2.45 equiv) in THF (200 mL) was cooled to −78 °C. To this solution was added 2.48 M nBuLi (21 mL, 51.1 mmol, 2.4 equiv) dropwise. After 10 min, dimethylmalonate (2.91 mL, 25.5 mmol, 1.2 equiv) was added slowly dropwise. After 10 min, the bromoarene **75** (5.9 g, 21.3 mmol, 1.0 equiv) was added dropwise via syringe pump as a solution in THF (100 mL). The reaction took on a purple color as the bromide was added. After complete addition of the bromide and an additional 10 min at −78 °C, the reaction was quenched by the addition of H_2O (100 mL) and the reaction was diluted with EtOAc (700 mL). The layers were separated, and the organic layer was washed with saturated brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 3:1 → 2:1 hexane/EtOAc) provided 4.96 g (71%) of the homophthalic ester **76** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 5.08 (d, J = 5.8 Hz, 4H), 3.85 (s, 3H), 3.64 (s, 2H), 3.63 (s, 3H), 3.42 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.9, 167.3, 150.1, 148.7, 126.0, 122.5, 116.4, 115.5, 95.4, 94.8, 55.8, 52.0, 38.4, 32.8, 31.1; FTIR ($CDCl_3$) ν 2953 (s), 2256 (s), 1728 (s), 1599 (s), 1481 (s) cm^{-1}; HRFABMS calcd for $C_{15}H_{20}O_8$ 328.1158, found 328.1159.

Homophthalic Acid (77). The homophthalic ester **76** (2.80 g, 10.45 mmol, 1 equiv) was dissolved in MeOH (100 mL), and to this was added solid KOH (13.80 g, 209 mmol, 20 equiv) and H_2O (50 mL). The reaction was warmed to reflux for 2 h. After which time, the reaction was allowed to cool to room temperature and concentrated. The resulting oil was partitioned between Et_2O (200 mL) and H_2O (200 mL), and the pH was adjusted to 1 by addition of 1 N HCl. The layers were separated, and the aqueous layer was extracted again with Et_2O (100 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The homophthalic acid **77** precipitated from Et_2O as a white powder to provide 2.6 g (99%) mp = 116 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.08 (d, J = 8.7 Hz, 1H), 7.02 (d, J = 8.7 Hz, 1H), 5.11 (s, 2H), 5.09 (s, 2H), 3.66 (s, 2H), 3.39 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100.6 MHz, acetone-d_6) δ 175.8, 172.4, 155.5, 153.5, 128.0, 121.0, 120.3, 100.4, 99.9, 60.4, 60.2, 37.38; FTIR (KBr) ν 3150 (s), 1705 (s), 1485 (s) cm^{-1}; HRFABMS calcd for $C_{13}H_{16}O_8$ 300.0845, found 300.0841.

Homophthalic Anhydride (78). The homophthalic acid **77** (313 mg, 1.05 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5 mL), and to this solution was added (trimethylsilyl)ethoxyacetylene (208 mL, 1.47 mmol, 1.4 equiv). After having been stirred for 2 h, the reaction was concentrated to yield 294 mg (100%) of the anhydride **78** as a white solid: mp = 70−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 4.01 (s, 2H), 3.53 (s, 3H), 3.47 (s, 3H); FTIR (CH_2Cl_2) ν 3060 (s), 2960 (s), 1799 (s), 1759 (s), 1592 (m), 1487 (s), 1092 (s) cm^{-1}; HRFABMS calcd for $C_{13}H_{14}O_7$ 282.0739, found 282.0743.

Dynemicin A (1). The homophthalic anhydride **78** (49 mg, 0.173 mmol, 6.0 equiv) was dissolved in THF (2.5 mL) and cooled to 0 °C. Then, a 1.0 M solution of LHMDS (171 μL, 0.171 mmol, 5.9 equiv) was added dropwise, and the solution immediately became bright yellow. After 35 min, the quinone imine **74** (12 mg, 0.029 mmol, 1.0 equiv) was added as a solution in THF (1 mL). The reaction slowly became a dark red-brown color, and, after 35 min, TLC indicated that no starting material remained. At this time, $PhI(OCOCF_3)_2$ (93 mg, 0.218 mmol, 7.5 equiv) was added as a solid at once. Upon addition, the reaction turned a red-violet color, and, after 5 min, the reaction was poured into saturated $NaHCO_3$ (15 mL) and EtOAc (30 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (15 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude napthalenol **80** was dissolved in THF (6 drops) and exposed to daylight and air. After 20 h, TLC indicated that no napthalenol was present, and a new more polar spot had appeared. At this time, the

protected anthraquinone **81** was dried over Na_2SO_4, filtered, and concentrated. The crude violet-red colored product was then dissolved in Et_2O (3 mL) and cooled to 0 °C. A 0.3 M solution of $MgBr_2$ (96 μL, 0.29 mmol, 10 equiv) was added dropwise. The reaction became a deep blue color after 2 h, and the reaction was allowed to warm to room temperature for 10 h. After which time, the reaction was poured into EtOAc (100 mL) and H_2O (20 mL), and the aqueous layer was extracted (3×) with EtOAc (20 mL). The organic layer was washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (Sephadex LH-20 20% CH_3-CN/MeOH) yielded 2.3 mg (15%) of (±)-dynemicin A (**1**) as a deep blue-violet solid, mp = 212−215 °C (dec): ^{1}H NMR (400 MHz, d_6 DMSO) δ 13.12 (s, 1H, aryl O**H**), 12.71 (br s, 1H, aryl O**H**), 12.15 (br s, 1H, aryl O**H**), 9.85 (s, 1H, H-1, N**H**), 8.04 (s, 1H, H-10, aryl **H**), 7.39 (d, J = 9.2 Hz, 1H, H-16 or 17, aryl **H**), 7.34 (d, J = 9.2 Hz, 1H, H-16 or 17, aryl **H**), 6.08 (d, J = 9.9 Hz, 1H, H-25 or 26, C≡C−C**H**═C), 6.06 (d, J = 9.9 Hz, 1H, H-25 or 26, C≡C−C**H**═C), 5.08 (d, J = 3.6 Hz, 1H, H-2, NC**H**), 4.89 (s, 1H, H-7, C≡C−C**H**), 3.81 (s, 3H, OC**H**$_3$), 3.57 (q, J = 7.3 Hz, 1H, H-4, C**H**CH$_3$), 1.25 (d, J = 7.1 Hz, 3H, H-29, CHC**H**$_3$); FTIR (neat) ν 3683−2733 (br, m-s), 3415 (m), 2926 (w), 1663 (s), 1628 (s), 1470 (s), 1270 (s), 1038 (m); HRFABMS calcd for $C_{30}H_{19}NO_9$ 537.1058, found 537.1060; R_f (0.45) (vis) 10% MeOH/CH_2Cl_2.

Diacetate (**84**). A recovery flask was charged with the acetate **83**[45] (4.36 mmol, 1.0 g) in CH_2Cl_2 (20 mL). The solution was cooled to 0 °C, and mCPBA (42%) (6.1 mmol, 2.51 g) was added. The solution was stirred for 3 h under Ar and was slowly warmed to room temperature. Upon completion of the reaction $(CH_3)_2S$ (0.4 mL) was added, and the resulting solution was stirred for 30 min. $NaHCO_3$ was then added, and the organic layer was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. The *N*-oxide was obtained as a crude oil.

The *N*-oxide was then subjected to the action of Ac_2O (5 mL), and this solution was stirred at 70 °C for 1 h. The reaction was cooled to room temperature and was redissolved in CH_2Cl_2. Saturated $NaHCO_3$ was added, and the organic layer was separated. The solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (SiO_2, 1:1 EtOAc/hexanes) provided the diacetate **84** as a yellow solid (1.32 g, 84%): mp 95.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.09 (d, 1H, J = 9.0 Hz), 7.46 (d, 1H, J = 2.4 Hz), 7.39 (d, 1H, J = 2.4 Hz, 9.0 Hz), 6.48 (d, 1H, J = 3.5 Hz), 2.8−3.2 (m, 2H), 2.0−2.3 (m, 4H), 2.36 (s, 3H), 2.08 (s, 3H); FTIR (CDCl3) ν 2951 (m), 1760 (s), 1730 (s), 1507 (s), 1370 (s) 1014 (s) cm^{-1}; HRFABMS calcd for $C_{17}H_{17}NO_4$ 200.1157, found 200.1013.

Epoxide (86). A recovery flask was charged with a solution of the diacetate **84** (6.5 mmol, 2.0 g) in THF (30 mL). The solution was cooled to −78 °C and was treated with ethynylmagnesium bromide (0.5 M in THF, 6.5 mmol, 13.0 mL). The solution was stirred for 30 min after which time TeocCl (7.8 mmol, 1.38 mL) was added at −78 °C, and the solution was gradually warmed to 0 °C. An additional 5 equiv of ethynylmagnesium bromide and an additional 2 equiv of TeocCl were added over the course of 5 h until the reaction was completed. Water and saturated $NaHCO_3$ were then added, and the organic layer was extracted with EtOAc, separated, dried (Na_2SO_4), filtered, and concentrated to yield a crude yellow oil.

This crude acetylide **85** was redissolved in CH_2Cl_2 (15 mL) and was treated with mCPBA (95%, 18.5 mmol, 3.36 g) and was stirred for 2−3 days at room temperature, monitoring the reaction periodically by ^{1}H NMR. Upon completion, $(CH_3)_2S$ (0.8 mL) was added, and the solution was stirred for 30 min. Saturated $NaHCO_3$ was added, and the organic layer was extracted with CH_2Cl_2, dried, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 5:1 hexanes/EtOAc) yielded the amber colored epoxide **86** as an oil (1.24 g, 42% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 1H), 7.05 (dd, 1H), 7.05 (buried d, 1H), 5.75 (dd, 1H, J = 6.1 Hz, 9.0 Hz), 5.55 (br s, 1H), 4.25 (m, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 1.4−2.1 (m, 6H), 0.0 (br s, 3H); FTIR (CH2Cl2) ν 3450 (m), 2955 (s), 1738 (s), 1508 (s), 1426 (s), 1398 (s), 1315 (s), 1287 (s), 1234 (s), 1188 (s), 934 (s), 861 (s), 839 (s) cm^{-1}; HRFABMS calcd for $C_{23}H_{31}NO_7Si$ 461.1869, found 461.1799.

Acetate (87). To a solution of the epoxide **86** (14.0 mmol, 6.8 g) in freshly distilled MeOH (100 mL) at −78 °C was added dry KCN (14.0 mmol, 0.91 g). The solution was stirred initially at −78 °C and was then gradually warmed to 0 °C continuing to stir for 2 h. H_2O was then added, and the product was extracted with EtOAc, separated, dried (Na_2SO_4), filtered, concentrated, and azeotroped (3×) from benzene. Column chromatography (SiO_2, 10:1 hexanes/EtOAc) yielded the phenolic alcohol as an oily residue.

The phenolic alcohol was immediately redissolved in dry CH_2Cl_2 (100 mL), and TBSCl (70 mmol, 10.5 g) and imidazole (70 mmol, 4.76 g) were added, and the reaction was stirred at room temperature for 1 h. Upon completion of the reaction H_2O and EtOAc were added, the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The resulting oil was azeotroped (3×) from benzene and was subsequently chromatographed (SiO_2, 10:1 hexanes/EtOAc) to yield the siloxy-acetate **87** as a yellow foam (5.2 g, 69% over two steps): ^{1}H NMR ($CDCl_3$) δ 7.18 (br s, 1H), 6.78 (d, 1H, J = 8.8 Hz), 6.75 (d, 1H, J = 2.5 Hz), 5.76 (dd, 1H, J = 6.01 Hz, 8.6 Hz), 5.56 (br s, 1H), 4.26 (t, 2H, 8.3 Hz), 2.10 (s, 3H), 1.6−2.75 (m, 6H), 1.0 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.0 (s, 9H); FTIR (CH2Cl$_2$) ν 3299 (w), 2955 (s), 1732 (s), 1658 (sh), 1500 (s), 1372 (s), 1315 (s), 1287 (s), 1234 (s), 1180 (s), 1064 (s), 1045 (s), 934 (s), 861 (s) cm^{-1}; HRFABMS calcd for $C_{27}H_{43}NO_6Si_2$ 533.2628, found 533.2645.

Ketone (89). To a solution of the siloxy acetate **87** (7.7 mmol, 15.4 mL) in CH_2Cl_2 (100 mL) at −78 °C was added a solution of DIBAL-H (15.4 mmol, 15.4 mL). The solution was stirred at −78 °C for 2 h, and MeOH was then added dropwise at −78 °C until the bubbling had stopped. The solution was then warmed to 25 °C, and ether and Rochelle's salt were added. The solution was stirred for 30 min until the layers became clear. The organic layer was separated, washed with brine (2×), dried (Na_2SO_4), filtered, concentrated, and azeotroped (3×) from benzene to yield the oily yellow secondary alcohol **88**.

The crude oil **88** was redissolved immediately in CH_2Cl_2 (100 mL), and 4Å dry molecular sieves (3.4 g) and pyridinium chlorochromate (20.4 mmol, 4.4 g) were added. The solution was then stirred under Ar at 25 °C for 3 h. The solution was then diluted with ether and filtered through Celite and SiO_2, flushing with generous amounts of ether. The solution was concentrated to a dark oil and chromatographed (SiO_2 10:1 hexanes/EtOAc) to yield the yellow siloxy ketone **89** as a foam (1.78 g, 46% over two steps). ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 1H, J = 2.5 Hz), 7.25 (1H), 7.16 (br s, 1H), 6.81 (d, 1H, J = 2.5 Hz, 8.6 Hz), 5.65 (br s, 1H), 4.24 (t, 2H, J = 8.3 Hz), 2.6−2.7 (m, 1H), 2.51−2.58 (m, 1H), 2.21−2.29 (m, 2H), 1.88−2.04 (m, 2H), 1.0 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H), 0.0 (s, 9H); FTIR (CH_2Cl_2) ν 3300 (m), 2956 (s), 2931 (m), 2879 (m), 2858 (m), 1715 (s), 1494 (s), 1313 (s), 1288 (s), 1247 (s) cm^{-1}; HRFABMS calcd for $C_{26}H_{39}NO_5Si_2$ 501.2366, found 501.2371.

Enediyne (90). In a 25 mL recovery flask was placed $Pd(PPh_3)_4$ (0.0095 mmol, 0.010 g) in dry degassed (3 h) benzene (1 mL). $nBuNH_2$ (0.76 mmol, 0.076 mL) was then added followed by the chloroenyne (0.62 mmol, 0.098 mL). A solution of the acetylene **89** (0.19 mmol, 0.10 g) in benzene (3 mL) was then added to the solution followed by freshly purified CuI (0.038 mmol, 0.0072 g), and the solution was stirred at 25 °C overnight. The solution was then poured into saturated $NaHCO_3$ and was extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and concentrated. Column chromatography (SiO_2, 100% hexanes, 20:1 hexanes/EtOAc, 15:1 hexanes/EtOAc) yielded the foamy yellow solid **90** (0.090 g, 75%): ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, J = 2.74 Hz), 7.15 (br s, 1H), 6.80 (d, 1H, J = 6.14 Hz), 5.78 (d, 1H, J = 11.1 Hz), 5.63 (d, 1H, J = 11.1 Hz), 4.24 (t, 2H, J = 8.3 Hz), 2.6−2.7 (m, 2H), 2.2−2.3 (m, 2H), 1.8−2.0 (m, 2H), 1.02 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.21 (s, 9H), 0.0 (s, 9H); FTIR (CH_2Cl_2) ν 2957 (s), 2931 (s), 2897 (s), 2144 (w), 1696 (s), 1609 (m), 1578 (m), 1495 (s), 1391 (s), 1117 (s), 938 (s), 860 (s) cm^{-1}; HRFABMS calcd for $C_{34}H_{49}NO_5Si_3$ 636.0298, found 636.0289.

Cyclic Enediyne (92). In a 100 mL recovery flask was placed **90** (2.2 mmol, 1.4 g) in 1:1:1 THF/EtOH/H_2O (50 mL). $AgNO_3$ (1.1 mmol, 0.19 g) was then added, and the reaction was stirred for 2 h at 25 °C. H_2O was then added, and the solution was extracted with ether. The organic layer was dried (Na_2SO_4), filtered, concentrated, and chromatographed to yield the yellow oil **91** (1.24 g, 90%).

The deprotected enediyne **91** (1.96 mmol, 1.11 g) was then dissolved immediately in freshly distilled toluene (200 mL), and the solution was cooled to −78 °C. Freshly prepared LDA (2.9 mmol, 4.99 mL) was

then added slowly dropwise. The reaction was stirred under Ar at -78 °C for 1 h. NH_4Cl was then added, the solution was warmed to room temperature, and H_2O was added. The solution was extracted with EtOAc, and the organic layer was separated, dried, and concentrated. Column chromatography (SiO_2, 10:1 hexanes/EtOAc) yielded the cyclic enediyne **92** as a yellow oil (0.78 g, 71%): *^{1}H NMR* ($CDCl_3$) δ 8.10 (d, 1H, J = 2.7 Hz), 6.75 (dd, 1H, J = 2.7 Hz, 8.7 Hz), 5.80 (d, 1H, J = 10 Hz), 5.65 (dd, 1H, J = 1.6 Hz, 10 Hz), 4.25 (t, 2H, J = 8.1 Hz), 2.27 (m 1H), 2.15 (m, 3H), 1.88 (m, 1H), 1.73 (m, 1H), 0.96 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.0 (s, 9H); FTIR (CH_2Cl_2) ν 3574 (w), 2957 (m), 2927 (m), 2872 (w), 1798 (m), 1650 (s), 1271 (s), 1106 (m) cm^{-1}; HRFABMS calcd for $C_{31}H_{41}NO_5Si_2$ 563.8471, found 563.8475.

Quinone Imine (93). To a solution of the cyclic enediyne **92** (0.35 mmol, 0.20 g) in THF (10 mL) cooled to 0 °C was added TBAF (1.0 M, 1.76 mmol, 1.76 mL). Immediately the color of the solution changed from light yellow to bright red. The solution was then stirred at O °C for 2 h. After removal of the Teoc and TBS groups had been completed as monitored by thin layer chromatography, $PhI(OAc)_2$ (2.47 mmol, 0.796 g) was added, and the solution was stirred at 0 °C for 1 h. A solution of saturated $NaHCO_3$ was then added, and the solution was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (SiO_2 4:1 hexanes/EtOAc, 3:2 EtOAc/hexanes) yielded the quinone imine as a yellow oil. Recrystallization from ether/hexanes yielded the quinone imine **93** as a powdery yellow solid (0.49 g, 49%), mp >125 C: ^{1}H NMR ($CDCl_3$) δ 7.69 (d, 1H, J = 2.0 Hz), 7.12 (d, 1H, J = 10.0 Hz), 6.51 (dd, 1H, J = 2.0 Hz, 10.0 Hz), 5.94 (d, 1H, J = 10.0 Hz), 5.88 (d, 1H, J = 10.0 Hz), 5.13 (s, 1H), 1.3-2.2 (m, 6H); FTIR (CH_2Cl_2) ν 3577 (w), 2966 (s), 2930 (m), 2858 (w), 1698 (s), 1496 (s), 1471 (m), 1392 (s), 1314 (s), 1289 (s), 1249 (s) 1199 (s) cm^{-1}; HRFABMS calcd for $C_{19}H_{13}NO_2$ 287.3209, found 287.3210.

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