This behavior cannot be directly attributed to a K_M effect since the Michaelis constant for **2**-H is in the middle of the range of K_M's for the analogs, and rates were determined at sufficiently high concentrations of substrate to reflect maximal values. However, a steric impediment in the vicinity of C(7) could alter the orientation of the analogs in the E·S complex relative to that of tryptophan in a manner to produce an impact on k_{cat}.

Currently, little is known about the structures of prenyl transferases beyond the primary sequences of several enzymes deduced from their genes. Sequence comparisons for several different prenyl transferases reveal conserved asparate-rich regions. Ashby and Edwards[37] proposed that one of the asparate-rich motifs, which they designate domain 2, binds the allylic substrate and catalyzes rupture of the carbon–oxygen linkage to the diphosphate. This domain is conserved for a wide variety of prenyl transferases, including enzymes whose normal substrates encompass a wide variety of prenyl acceptors, and its occurrence is consistent with a common mechanism for the various prenyltransfer reactions.

Linear free energy correlations show that both FPP synthase[12] and DMAT synthase catalyze electrophilic alkylations of their respective acceptors. From the viewpoint of mechanistic organic chemistry, electrophilic alkylations are highly attractive for those prenyltransferases that alkylate weakly nucleophilic acceptors such as carbon–carbon double bonds and aromatic rings. It is, however, less clear that enzymes which alkylate the more potent hydroxyl, amino, and sulfhydryl acceptors also catalyze electrophilic additions via carbocationic species or that the mechanisms shift to a nucleophilic displacement at C(1) in the allylic substrates.

Acknowledgment. This investigation was supported by Grant GM 21328 from the National Institutes of Health.

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Design, Synthesis, and Study of Simple Monocyclic Conjugated Enediynes. The 10-Membered Ring Enediyne Moiety of the Enediyne Anticancer Antibiotics†

K. C. Nicolaou,*,‡ G. Zuccarello, C. Riemer, V. A. Estevez, and W.-M. Dai

Contribution of the Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry, University of California, San Diego, La Jolla, California 92093. *Received March 4, 1992*

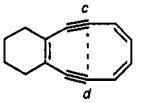
Abstract: Following the discovery of the enediyne anticancer antibiotics, investigations were initiated directed toward the design, synthesis, and study of simple monocyclic conjugated enediynes. In this article the synthesis of the parent 10-membered ring enediyne found in the enediyne natural products and its properties are described. In addition to the parent hydrocarbon **27**, the synthetic methodology developed based on the Ramberg–Bäcklund reaction delivers a series of higher ring homologs (**17–22**) and the water soluble version of the 10-membered ring compound **47**. Molecular mechanics calculations on these systems led to a number of geometrical parameters which correlated well with their tendencies to undergo the Bergman cycloaromatization reaction. Kinetic studies on the Bergman cycloaromatization of the 10-membered ring enediynes **27** and **47** led to the following thermodynamic values: **27**, energy of activation (E_a) = 23.8 kcal/mol, $\Delta G^{\ddagger}$ (37 °C) = 24.6 kcal/mol; **47**, energy of activation (E_a) = 31.5 kcal/mol, $\Delta G^{\ddagger}$ (37 °C) = 24.8 kcal/mol. The designed enediyne **47** showed potent DNA-cleaving properties becoming the first synthetic molecule to mimic the action of the naturally occurring enediynes in this regard.

Introduction

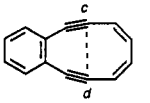
In 1987, the structures of two novel families of natural products, the calicheamicins [e.g., calicheamicin γ_1^I (**1**), Scheme I] and the esperamicins [e.g., esperamicin A_1 (**2**), Scheme I] were reported by investigators from Lederle Laboratories[1] and Bristol Myers,[2] respectively. A common and most unusual structural feature of these molecules was the 10-membered ring containing a conjugated enediyne system embedded in their skeletons. The phenomenal biological activity of these substances against bacteria and tumor cells was attributed to their ability to cause DNA cleavage. The enediyne moiety was considered crucial to their mode of action which was postulated to involve a Bergman cyclization reaction[3] leading to damaging benzenoid diradicals (Scheme II). Today, the enediyne class[4] includes, in addition to the calicheamicins and esperamicins, neocarzinostatin chromophore[5] and the dynemicins.[6]

Soon after these disclosures, and in order to test the proposed hypothesis for the mechanism of action of the naturally occurring calicheamicins and esperamicins and to probe the idea of mimicking their chemistry and biological action with simple synthetic

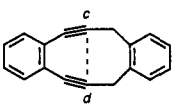
Chart I. Cyclic Conjugated Enediynes Spontaneously Undergoing Bergman Cycloaromatization at Ambient Temperature[7,8]



4a: *cd* 2.99 Å [MM2]



4b: *cd* 3.01 Å [MM2]



5: *cd* 3.03 Å [MM2]

† This work was initiated and partially carried out in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104. Partially taken from the Ph.D. Thesis of G. Zuccarello, University of Pennsylvania, 1989.

‡ The Scripps Research Institute.

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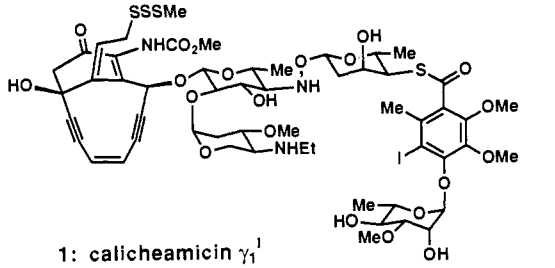
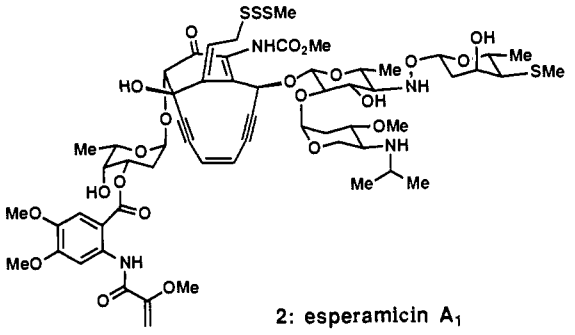
Scheme I. Structures of the Enediyne Antibiotics Calicheamicin γ_1^I (1) and Esperamicin A_1 (2)

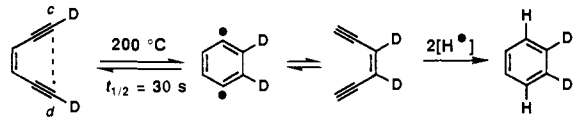


1: calicheamicin γ_1^I



2: esperamicin A_1

Scheme II. The Bergman Cyclization Reaction (1972)



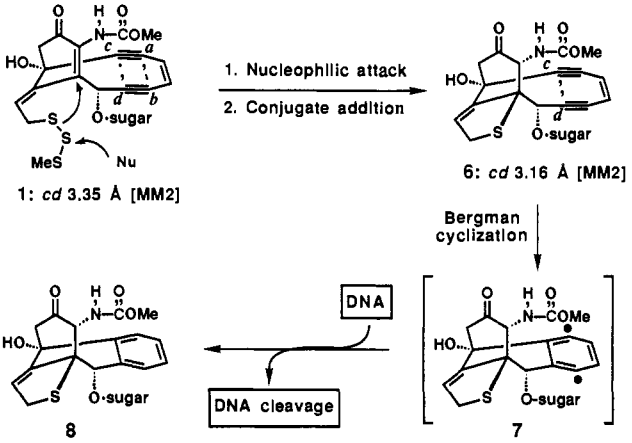
3: *cd* 4.12 Å [MM2]

enediynes, we initiated a series of studies directed toward the design, synthesis, and investigation of such systems. In this article we described our results in this area that culminated in the first designed enediynes which mimic the three important properties of the natural enediyne anticancer antibiotics, namely (a) Bergman cycloaromatization at ambient temperatures, (b) DNA cleaving action, and (c) cytotoxic activity.

The Bergman Reaction and the Mechanism of Action of the Calicheamicin/Esperamicin Enediyne Anticancer Antibiotics

In 1972 Bergman[3] reported his elegant designed studies involving cycloaromatization of acyclic (*Z*)-enediynes via 1,4-benzenoid diradicals (Scheme II). This reaction, now known as the Bergman cyclization reaction, is precisely the process used by nature to generate the reactive species that damage the genetic material. Several other observations[7-9] made with cyclic conjugated enediynes prior and subsequent to 1972 further demonstrated the generality and scope of this reaction (Chart I).

Scheme III. Mechanism of DNA-Cleaving Action of Calicheamicin γ_1^I (1)



The mechanism of action of calicheamicin γ_1^I (1), shown in Scheme III, postulates DNA binding via the oligosaccharide moiety within the minor groove of DNA, preferentially along TCCT and TCTC sites and by orienting the tail of the oligosaccharide toward the 3′ ends of DNA fragments.[10] The scenario then envisions nucleophilic attack (e.g., by glutathione) at the central sulfur atom of the trisulfide trigger which leads to the formation of a highly nucleophilic thiol or its corresponding thiolate. Finding itself in a suitable position, this internal nucleophile proceeds to attack the α,β-unsaturated ketone within the adjacent six-membered ring, leading to compound **6**. This transformation, converting the trigonal point of attack to a tetragonal center opens the way for a Bergman reaction leading to the benzenoid diradical **7**. It is quite interesting to note that the distance between carbon atoms c and d (cd distance, acetylenic carbons remote from double bond of the enediyne, see Scheme III) is significantly shortened in going from the stable calicheamicin γ_1^I (1) [cd = 3.35 Å, MM2] to the highly strained intermediate **6** [cd = 3.16 Å, MM2].[11] The highly reactive diradical species **7** is capable and well positioned to abstract hydrogen atoms mainly from the C-5′ (but also from the C-4′) positions of ribose at opposite strands.[10,12] The DNA radicals so generated then proceed to react with molecular oxygen leading finally to double strand cleavages. Experiments carried out subsequent to the mechanistic proposals led to the observation of the proposed intermediate **6** (estimated half-life at 37 °C ~4.5 s).[13] Other experiments[14] demonstrated the requirements of thiols for the high potency of calicheamicin γ_1^I (1) in DNA cleavage and the crucial role of the ethylamino group on the terminal carbohydrate unit.

Cyclodeca-1,5-diyn-3-ene (27): The Parent "Warhead" of the Enediyne Anticancer Antibiotics

Intrigued by the fascinating mode of action of the enediyne anticancer antibiotics, particularly the role of the enediyne "warhead", and driven by the potential of the Bergman cyclization reaction[3] in biology and medicine, we set out to explore the underlying principles governing the reactivity of these systems. Our initial goals were (a) to design simple enediynes and define the ring size necessary for spontaneous Bergman cyclization, (b) to develop viable synthetic routes to these compounds, (c) to study

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the fundamental chemistry, particularly the Bergman cycloaromatization of these simple ring systems, and (d) to demonstrate the ability of simple monocyclic conjugated enediynes to cleave DNA and mimic the biological action of the naturally occurring compounds.

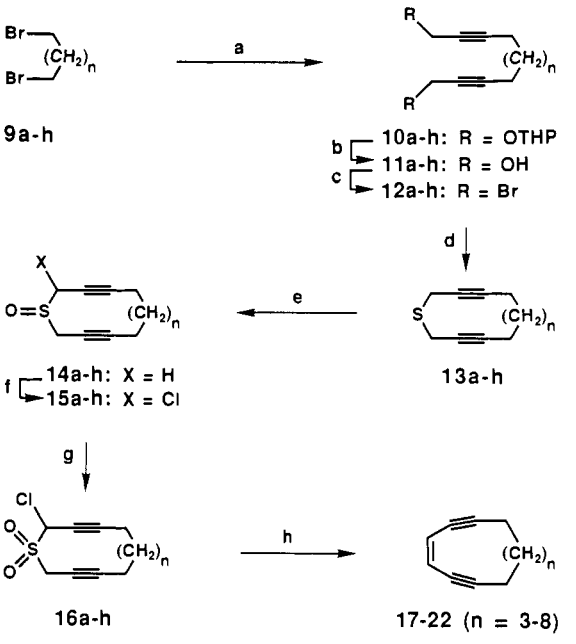
Crucial for the reaction cascade of Scheme III is the geometrical change in going from structure **1** to **6**. Specifically, it was hypothesized that saturation of the double bond in **1** ought to result in shortening of the distance between the acetylenic carbons (Scheme III, ab and cd distances). Molecular mechanics calculations (MacroModel,[15] MM2) on the aglycon skeletons of **1** and its cyclic product **6** (entries 6 and 7, Table I) confirmed that the distances ab and cd shortened considerably in going from structures of type **1** to structures of type **6**. Of particular interest was the distance cd which determines the degree of p orbital overlap leading to bond formation during Bergman cyclization. In the case at hand, this distance changed from 3.35 to 3.16 Å which apparently is sufficiently close for spontaneous ring closure to take place pending energy considerations (vide infra). Table I includes a number of other known systems and their calculated cd distances. Inspection of these values led to the realization of a trend and to the conclusion that the crucial turning point from stability ("locked" enediyne structure) to spontaneous cyclization ("unlocked" enediyne structure) must be in the cd range of 3.31–3.20 Å. Thus, examples of compounds with lower than 3.20 Å cd values have been claimed as transient intermediates, suffering spontaneous cyclization to benzenoid systems, whereas compounds with higher than 3.31 Å cd values are known as stable compounds at 25 °C (e.g. entries 8–10).[16] A number of designed model systems are also included in Table I (entries 4, 5, 11–18) together with calculated cd values and predictions regarding their stability profiles at 25 °C. Thus, the compounds of entries 4 and 11 with a calculated cd value below 3.20 Å should undergo spontaneous ring closure, whereas the compounds of entries 5 and 13–18 with cd values higher than 3.31 Å ought to be stable toward cyclization at ambient temperatures. The parent, 10-membered ring system of entry 12 (Table I) whose cd distance of 3.25 Å falls right in the middle of the critical range (3.31–3.20 Å) was considered to be of particular interest, particularly with regards to its behavior at ambient temperatures. Using the value of the cd distance as a tool to predict reactivity in conjugated enediynes should not be taken as a universal rule. It is only proposed to serve as a rough guide, to be used only with caution, particularly in polycyclic frameworks where other factors such as the effect of ring fusion, substitution, and strain energies of starting materials, transition states, and products should be taken into account before any prediction can safely be made. It is not, therefore, surprising that several "exceptions" to the rule are already known.[17]

Synthesis of Monocyclic Conjugated Enediynes

The synthesis of the 10-membered ring enediyne and its homologs was the initial focus of this program due to their centrality to the mode of action of the naturally occurring enediynes. After several abortive attempts to construct the ring system via the palladium-catalyzed coupling of terminal acetylenes with vinyl halides, our efforts focused on the Ramberg–Bäcklund reaction[18] as the key process to form the enediyne moiety within these ring systems.

Scheme IV outlines the sequence by which this parent series of monocyclic conjugated enediynes were constructed. Thus, the alkyl dibromides **9a–h** were reacted with excess of the anion derived from tetrahydro-2-(2-propynyloxy)-2*H*-pyran and *n*-BuLi to afford the bis(acetylenic) compounds **10a–h** which were deprotected under methanolic acid conditions leading to diols **11a–h** in 59–92% overall yields. The dibromides **12a–h** were prepared by the action of tri-*n*-butylphosphine and carbon tetrabromide in good to excellent yields. These substrates were then reacted with sodium sulfite under high dilution conditions to furnish the cyclic sulfides **13a,b** in varying yields (9% for **13a**, to 72% for **13f**). These sulfides were first oxidized to the corresponding sulfoxides **14a–h** with stoichiometric amounts of *m*-chloroperbenzoic acid (50–85% yields) and then monochlorinated using sulfuryl chloride forming **15a–h**. The crude products **15a–h** were oxidized further with excess *m*-chloroperbenzoic acid to afford the chlorosulfones **16a–h** in 37–82% overall yields for the two steps. Finally, treatment of chlorosulfones **16c–h** with potassium *tert*-butoxide gave the desired enediynes **17–22** in 32–52% isolated yields. Treatment of the 10- and 11-membered ring sulfones **16a** and **16b** with potassium *tert*-butoxide led to the formation of a product thought to be an allene with no enediyne being formed. However, upon exposure to methyllithium, **16b** led to the desired 10-membered ring enediyne **27** (12% yield) along with the acyclic enediyne **25b**[19] (12%, Scheme V). Similarly treatment of **16a** with methyllithium led exclusively to the acyclic enediyne **25a** (24%) with no trace of the nine-membered ring enediyne (Scheme V). Products **25a** and **25b** are presumed to arise as speculated in Scheme V. Thus, initial base-induced formation of the episulfones **23a** and **23b** is followed by either cheletropic sulfur dioxide elimination to afford the desired cyclic enediyne (path a), or it may undergo a Cope-type rearrangement (path b) to give the bis(allene) sulfones **24a** and **24b** or their equivalent annulated thiepin sulfone[20] diradicals **24'a** and **24'b**. Spontaneous rearrangement of these highly strained compounds accompanied by loss of sulfur dioxide then leads to the observed products **25a** and **25b**. The different partitioning between paths a and b can be explained by the increased ring strain in **23a** compared with **23b** and the difference in the cd distance within these compounds (Scheme V) as revealed by MM2 calculations. The alternative pathway to **25a** and **25b** involving Bergman cyclization of **26** and **27** to **28a** and **28b**, respectively, followed by reverse Bergman

Scheme IV[a]



[a] Synthesis of enediynes **17–22**. Reagents and conditions: (a) $THPOCH_2C{\equiv}CH$, *n*-BuLi, HMPA, THF, −78 °C; (b) PPTS, MeOH; (c) $(n\text{-}Bu)_3P$, CBr_4, Et_2O, 0 °C; (d) $Na_2S{\cdot}9H_2O$, EtOH–H_2O, high dilution, 25 °C; (e) mCPBA, CH_2Cl_2, −78 °C; (f) SO_2Cl_2, pyr. CH_2Cl_2, −78 °C; (g) mCPBA, CH_2Cl_2, 0 °C; (h) 1.2 equiv of KO-*t*-Bu, THF, −78 °C.

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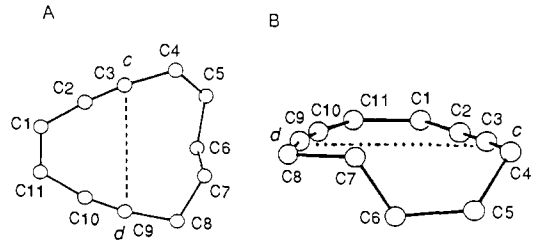
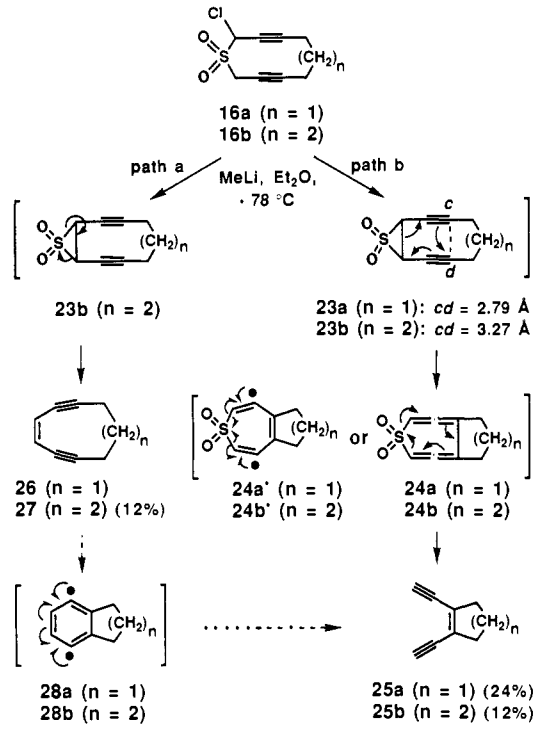


Figure 1. ORTEP drawing of **17** (n = 3): (A) top view and (B) side view. *cd* distance: 3.661 (5) Å.

Scheme V. Mechanistic Pathways Leading to Enediynes **25ab** and **27**



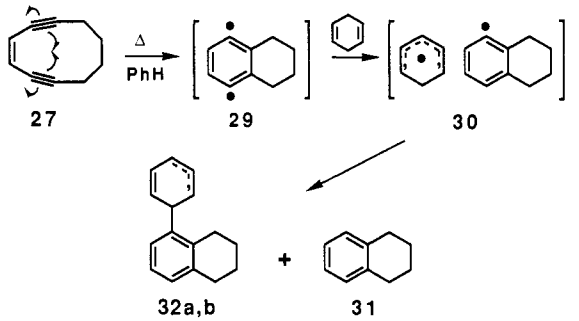
reaction in the other direction (see Scheme V) is not likely, since isolated **27** does not lead to **25b**. Furthermore, in the case of **16a**, no indane was detected in its reaction with methyllithium in ether in the presence or absence of 1,4-cyclohexadiene, pointing against the intermediacy of the benzenoid diradical **28a**.

Properties of Cyclo[*n*]enediynes

While cyclononaenediyne **26** proved elusive and cyclodecaenediyne **27** exhibited ambient temperature reactivity toward Bergman cyclization (vide infra), the higher members (**17–22**) were found to be quite stable. Cycloundecaenediyne **17** crystallized nicely from pentane in large colorless plates, mp 36–36.5 °C. An X-ray crystallographic analysis[21] on **17** was undertaken in order to compare the experimentally derived molecular parameters with the calculated ones. Figure 1 shows two ORTEP drawings of **17**, whereas Table II lists calculated (MM2) and observed values for some selected parameters of this enediyne. The high degree of agreement between the experimental and calculated values enhances our confidence in using the MM2 and related programs for these systems. Quite striking is the planar arrangement of all but two carbons in **17** as illustrated from the side view ORTEP drawing (Figure 1B).

The parent cyclodecaenediyne system **27**, while stable enough at ambient temperatures for purification and characterization purposes, slowly decomposes upon standing in solution or neat. Thus, **27** underwent smooth Bergman cyclization in the presence of excess 1,4-cyclohexadiene in benzene solution on heating to 50 °C, leading to tetralin (**31**, 55%) and a mixture of cross coupling products **32a,b** (Scheme VI). Presumably and according to Bergman,[3] the initially formed benzenoid diradical **29** abstracts

Scheme VI. Bergman Cycloaromatization of Cyclodecenediyne **27**



a hydrogen atom from 1,4-cyclohexadiene to give the solvent caged pair **30**. The benzenoid radical could then abstract a second hydrogen atom to produce tetralin (**31**), or the two radicals could combine to give the two isomeric products **32a,b**. Kinetic studies on the cyclization of **27** (Scheme VI) were carried out in order to determine its rate of cycloaromatization at various temperatures and its activation energy (E_a). Thermolysis of **27** was studied in benzene solution (0.01 M, containing 100 equiv of 1,4-cyclohexadiene) at 37, 50, 60, and 70 °C. Starting material disappearance and product formation were monitored by HPLC. Plots of the natural log of the ratio of the initial concentration to the concentration of **27** at the recorded time versus time at various temperatures are taken. From these plots the rate constants for the reaction were determined (Table III), whereas the Arrhenius plot gave the energy of activation (E_a = 23.82 ± 0.04 kcal/mol). The $\Delta G^{\ddagger}$ for this reaction at 37 °C was calculated to be 24.6 kcal/mol.

The thermal behavior of the 11- and 12-membered ring enediynes was also studied. Although the decomposition of these systems followed rather smooth kinetics at 150–170 °C and 210–230 °C, respectively, a complex mixture of products was formed, and isolation was not pursued. The relatively high temperatures for their reaction was, however, quite striking and is presumably due to the formation of a medium ring during the Bergman reaction.

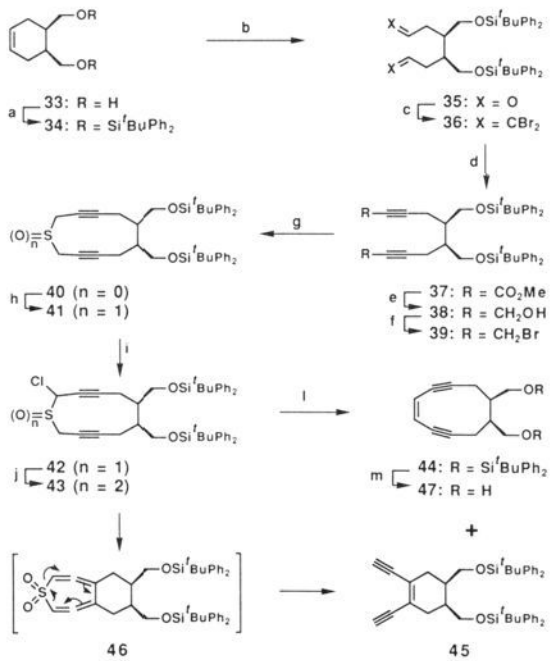
6-Cyclodecene-4,8-diyne-1,2-dimethanol (47). The First Designed, Water-Soluble DNA-Cleaving Enediyne. Synthesis

On the basis of the knowledge that simple 10-membered ring enediynes undergo Bergman cyclization at physiological temperatures, with reasonable rates, we proceeded to attempt mimicking the DNA-cleaving action of the calicheamicins and esperamicins. In order to endow the projected molecule with at least partial water solubility and potential for tethering to delivery systems and other moieties, structure **47** was designed and targeted for synthesis. The crucial expectation was that **47** would be sufficiently stable for isolation and handling at ambient temperatures but that it would undergo Bergman cyclization at physiological temperatures at useful rates to cause DNA cleavage. These expectations were based on a calculated cd distance of 3.20 Å and the experimental data obtained with the parent cyclodecaenediyne **27**.

Starting with the readily available diol **33**[22] and following the general strategy based on the Ramberg–Bäcklund reaction[18] used for the synthesis of the parent enediynes, the sequence shown in Scheme VII was devised and executed. Thus, diol **33** was converted to its bis(silyl) ether **34** under standard conditions (86%). Ozonolysis of **34** followed by reductive workup and condensation with Ph_3P–CBr_4 led to tetrabromide **36** via dialdehyde **35** (76% overall yield). Exposure of **36** to *n*-BuLi followed by quenching with methyl chloroformate gave the diester **37** (82%) which was reduced with excess DIBAL to diol **38**.

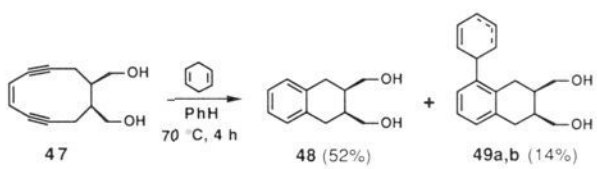
(19) Pilling, G. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1968**, *90*, 5610. Pilling, G. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1971**, *93*, 1970.
(20) William, L. M. *J. Am. Chem. Soc.* **1967**, *89*, 1281.
(21) This X-ray crystallographic analysis was carried out by Dr. Patrick Carrol.
(22) Mundy, B. P.; Theodore, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 2005.

Scheme VII[a]



[a] Synthesis of designed enediyne **47**. Reagents and conditions: (a) t-BuPh$_2$SiCl, imidazole, DMF, 71%; (b) O_3; $(MeO)_3P$, CH_2Cl_2, MeOH; (c) CBr_4, Ph_3P, CH_2Cl_2, 25 °C, 75% from **34**; (d) n-BuLi, THF, −78 °C, then $MeCO_2Cl$, 82%; (e) DIBAL, CH_2Cl_2, −78 °C → 0 °C, 99%; (f) CBr_4, $(n\text{-Bu})_3P$, Et_2O, 0 °C, 74%; (g) $Na_2S{\cdot}Al_2O_3$, CH_2Cl_2, EtOH; (h) mCPBA, Et_2O, −30 °C, 79% from **39**; (i) SO_2Cl_2, pyr, CH_2Cl_2, −78 °C, 76%; (j) mCPBA, Et_2O, 25 °C; 99%; (l) MeLi, THF, −78 °C, **44**, 15% plus **45**, 23%; (m) $(n\text{-Bu})_4NF$, THF, 0 °C, 79%.

Scheme VIII. Bergman Cycloaromatization of **47**



The dibromide **39** was then produced from **38** under standard conditions and was treated with $Na_2S{\cdot}9H_2O$ impregnated in basic alumina in EtOH–CH_2Cl_2 solution. This improved sulfide displacement procedure led to a rapid and reproducible reaction, forming the cyclic sulfide **40** in high yield, which was then oxidized in situ with stoichiometric amounts of mCPBA to afford sulfoxide **41** in 79% overall yield. Sulfoxide **41** was converted to the α-chlorosulfoxide **42** with sulfuryl chloride and then to the corresponding α-chlorosulfone **43** upon exposure to mCPBA (99% yield).

Treatment of **43** with methyllithium in THF at −78 °C produced the expected enediyne **44** (12% yield) together with the opened enediyne **45** (15%), the latter presumably been formed via the intermediacy of bisallene **46** (Scheme VII). Compound **44** was then desilylated under standard conditions to afford the targeted enediyne diol **47** (79% yield).

Kinetic Studies with Enediyne 47

The thermal behavior of **47** was next studied in the presence of hydrogen atom donors in order to determine its half-life. Heating **47** in benzene solution containing excess 1,4-cyclohexadiene at 70 °C produced cleanly products **48** and **49a,b** (Scheme VIII). Kinetic studies at 37, 45, 50 and 60 °C in THF-d_8 (followed by ^{1}H NMR spectroscopy) led to the rate constants (Table IV) and an Arrhenius plot from which an energy of activation of 31.5 kcal/mol was derived. The $\Delta G^{\ddagger}$ for this Bergman cyclization reaction at 37 °C for enediyne **47** was calculated to be 24.8 kcal/mol.

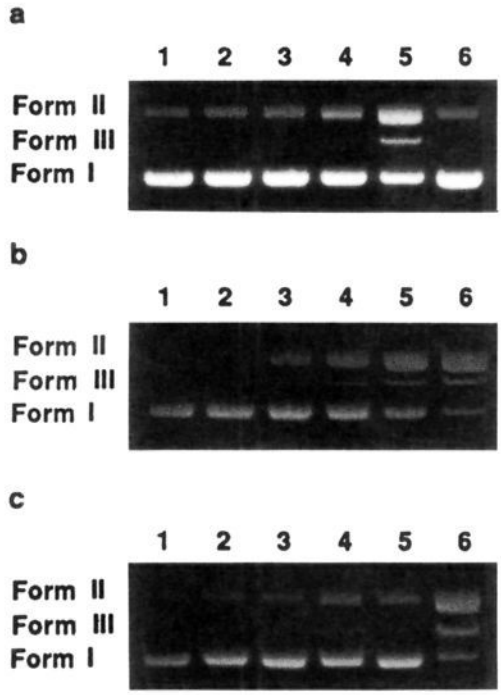
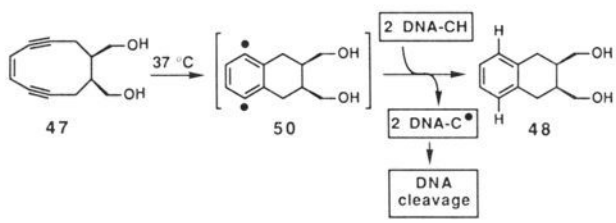


Figure 2. Supercoiled DNA interaction with compound **47**. (a) ΦX174 DNA (50 μM/base pair) was incubated with **47** in Tris-acetate buffer (pH 8.5, 50 mM) for 12 h at 37 °C and analyzed by agarose gel electrophoresis (ethidium bromide). Lane 1, DNA alone; lanes 2–5, DNA + **47** at 1.0, 10, 100, and 500 μM, respectively; lane 6, DNA + **48** at 2 mM. (b) ΦX174 DNA (50 μM/base pair) was incubated with compound **47** for various times at 37 °C in Tris-acetate buffer (pH 8.5, 50 mM) and analyzed as described under Figure 2a. Lane 1, DNA alone; lanes 2–6, DNA + **47** (500 μM) for 0, 6, 12, 24, and 48 h, respectively. (c) ΦX174 DNA (50 μM/base pair) was incubated with compound **47** for various temperatures and analyzed as described under Figure 2a. Lane 1, DNA alone, 22 °C, 24 h; lane 2, DNA + **47** (100 μM), 22 °C, 24 h; lane 3, DNA alone, 37 °C, 24 h; lane 4, DNA + **47** (100 μM), 37 °C, 24 h; lane 5, DNA alone, 50 °C, 24 h; lane 6, DNA + **47** (100 μM), 50 °C, 24 h. Key: Form I, supercoiled DNA; Form II, nicked DNA; Form III, linear DNA.

Scheme IX. Presumed Mechanism of DNA-Cleaving Action of Designed Enediyne **47**

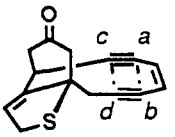
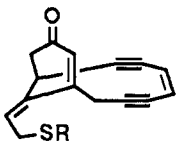
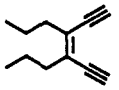


DNA Cleavage with Enediyne 47

The DNA cleaving properties of compound **47** were explored using ΦX174 double-stranded supercoiled DNA. As expected, this enediyne caused cleavage of double-stranded DNA in the absence of any additives. Thus, incubation of **47** with ΦX174 form I DNA aerobically at 37 °C produced form II and form III DNA as shown by gel electrophoresis analysis. The extent of DNA cleavage was shown to be dependent on (a) the concentration of **47** (Figure 2a), (b) the incubation time (Figure 2b), and (c) the temperature (Figure 2c). As expected, incubation of **48** with DNA did not cause any cleavage (Figure 2a).

It is interesting to note that addition of catalase or superoxide dismutase did not alter the DNA cleaving profile of **47** nor did the addition of EDTA. These results exclude the intermediacy of hydrogen peroxide, superoxide radicals, or metals in the mode of action of this compound. The cleavage data are consistent with a Bergman cyclization of **47** leading to diradical species **50** (Scheme IX) which proceeds to abstract hydrogen atoms from

Table I. Calculated[a] Strain Energies and Distances between Acetylenic Carbons in Cyclic Conjugated Enediynes

Entry	Compound	Ring size	Strain Energy (kcal/mole)	*ab* (Å)	*cd* (Å)	Stability	Ref.
1	**4a**	10	21.2	2.51	2.99	cyclized <25 °C	7
2	**4b**	10	19.71	2.54	3.01	cyclized <25 °C	7
3	**5**	10	16.50	2.58	3.03	cyclized at 25 °C	8
4		10	15.52	2.56	3.17	should cyclize at 25 °C	unknown
5		10	16.42	2.65	3.36	should be stable at 25 °C	unknown
6	**6**	10	22.67	2.55	3.16	cyclized at 25 °C	1
7	**1**	10	23.25	2.65	3.35	stable at 25 °C	1
8		—	0.43	2.86	4.12	stable at 25 °C	3a
9		—	5.38	2.76	3.94	stable at 25 °C	3c
10		12	2.79	2.74	3.77	stable at 25 °C	16
11	**26**	9	14.80	2.51	2.84	should cyclize at 25 °C	unkonwn
12	**27**	10	11.40	2.60	3.25	cyclized at 25 °C	this work
13	**17 (n = 3)**	11	8.96	2.72	3.61	stable at 25 °C	this work
14	**18 (n = 4)**	12	7.60	2.80	3.90	stable at 25 °C	this work
15	**19 (n = 5)**	13	7.37	2.87	4.14	stable at 25 °C	this work
16	**20 (n = 6)**	14	8.21	2.87	4.15	stable at 25 °C	this work
17	**21 (n = 7)**	15	8.39	2.93	4.33	stable at 25 °C	this work
18	**22 (n = 8)**	16	11.35[b]	2.88[b]	4.20[b]	stable at 25 °C	this work

[a] MM2 calculations were performed using MacroModel. [b] The origin of this seemingly anomalous result is unknown at present.

the backbone of DNA and cause rupture in a mechanistic mode similar to the one proposed for the calicheamicins and esperamicins.

As anticipated, compound **47** exhibited in vitro cytotoxic activity [e.g., Molt-4 T cell leukemia, IC_{50} 10^{-6} M]. Although the biochemical and biological profiles of **47** suggest its potential in

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(25) Mueller, P.; Rey, M. *Helv. Chim. Acta.* **1982**, *65*, 1157. Peters, H. M.; Archer, R. A.; Mosher, H. S. *J. Org. Chem.* **1967**, *33*, 1382.

Table II. Calculated and Experimental Parameters of Enediyne 17 (n = 3)

method	C1–C11 (Å)	C2–C10 (Å) (ab value)	C3–C9 (Å) (cd value)	C1–C2 (Å)	C4–C8 (Å)	C4–C3–C2 (deg)
MM2	1.34	2.72	3.61	1.43	4.41	175.3
X-ray	1.327 (5)	2.778 (5)	3.661 (5)	1.410 (5)	4.357 (6)	173.2 (4)

method	C3–C2–C1 (deg)	C2–C1–C11 (deg)	C1–C11–C10 (deg)	C11–C10–C9 (deg)	C10–C9–C8 (deg)
MM2	174.6	119.1	119.2	172.1	171.9
X-ray	172.6 (4)	121.1 (3)	120.3 (3)	169.4 (4)	170.5 (4)

Table III. Rate Constants for the Decomposition of Enediyne 27 at Different Temperatures

temp (°C)	rate constant (k, s^{-1})
37	1.07×10^{-5}
50	5.11×10^{-5}
60	1.63×10^{-4}
70	4.35×10^{-4}

Table IV. Rate Constants for the Decomposition of Enediyne 47 at Different Temperatures

temp (°C)	rate constant (k, s^{-1})
37	2.02×10^{-5}
45	1.12×10^{-4}
50	1.79×10^{-4}
60	7.50×10^{-4}

chemotherapy and biotechnology (as a footprinting agent for example), its relative chemical instability make it unlikely that it would become a useful agent itself. The principles, however, that it demonstrates may prove more far reaching.

Conclusion

The proposition of the 10-membered ring moiety of the naturally occurring enediyne anticancer antibiotics acting as the chemical warhead responsible for the DNA cleaving action of these compounds has been tested and confirmed by the design, synthesis, and study of simple enediynes. These investigations began with theoretical considerations of the homologous series of monocyclic enediynes. These calculations indicated that constraining the enediyne grouping within a small enough ring should lead to shortening of the cd distance between the acetylenic carbons that form a bond during the Bergman cyclization reaction. This recognition, in turn led to the prediction that this reaction should proceed spontaneously at ambient temperatures. The development of a general sequence for the synthesis of these compounds based on the Ramberg–Bäcklund reaction allowed their preparation. The above hypothesis was confirmed when the cyclodecaenediynes **27** and **47** were found to cyclize spontaneously at physiological temperatures and by the ability of compound **47** to cleave double-stranded DNA at 37 °C.

The described chemistry provided the foundation onto which the molecular design of simple structures of the enediyne type could be based. The incorporation of these rather simple enediyne warheads into more sophisticated molecular assemblies equipped with locking, triggering, tethering, detection devices, and delivery systems became the next phase of this program.

Experimental Section

General Techniques. NMR spectra were recorded on a Bruker WM-250. ^{1}H NMR multiplicities were reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrometer. UV spectra were recorded on a Perkin-Elmer Model 553 UV–vis spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions. Melting points were obtained with a Thomas-Hoover Unimelt apparatus.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) by using UV light and either 7% ethanolic phosphomolybdic acid-heat or 5% anisaldehyde and 5% sulfuric acid in ethanol-heat as a developing reagent. Preparative thin-layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Gradient elutions were carried out by using equal volumes of solvent in 10% increments for the 10 → 100% region and 2.5% increments for the 0 → 10% region.

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

Molecular Mechanics Calculations. All molecular mechanics calculations were performed using the program MacroModel[15] on a Digital Equipment VAX 11/750 computer. The force field used was MM2 with either the BDNR or FMNR minimization schemes. The structures were minimized to a derivative RMS of <0.01 kJ/Å. The global minimum structure was obtained by an iterative process either manually or using the multiconformer subroutine.

Nona-2,7-diyne-1,9-diol (11a). Representative Procedure (A). To a cooled (−78 °C) solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (15.5 mL. 15.5 g. 110 mmol. 2.24 equiv) in THF (100 mL) was added *n*-butyllithium (1.6 M in hexanes. 70 mL, 112 mmol, 2.3 equiv). This was followed after 10 min by HMPA (30 mL) and 1,3-dibromopropane (**9a**, 5.0 mL. 9.9 g. 49 mmol.). The reaction was then allowed to warm to room temperature over 2 h and stirred for 16 h. It was then added to saturated aqueous NH_4Cl (150 mL) and ethyl ether (50 mL). The organic phase was then washed with 1 N HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and saturated brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue (crude product **10a**) was then dissolved in methanol (150 mL), and pyridinium *p*-toluenesulfonate (2.71 g, 10.8 mmol, 0.22 equiv) was added. After 18 h, the solution was concentrated in vacuo and dissolved in ethyl acetate (200 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (75 mL) and saturated brine (75 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (80–100% ethyl ether in petroleum ether) to give the product **11a**[23] (4.419 g. 59% yield).

Deca-2,8-diyne-1,10-diol (11b) was prepared in 74% yield as above (procedure A). **11b**: white solid: mp 50–51 °C (from ethyl ether/petroleum ether): R_f 0.19 (silica. 2% methanol in methylene chloride); IR (neat) ν_{max} 3190, 2960. 2870. 2230. 1470. 1240. 1140, 1040, 990. 780 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.25 (m, 4 H, O–CH_2), 2.41 (m, 2 H, O*H*), 2.26 (t, J = 2.2 Hz, 4 H, C≡CCH_2). 1.62 (qn, J = 3.2 Hz, 4 H, CH_2): HRMS for $C_{10}H_{18}NO_2$ (M + NH_4). calcd 184.1337. found 184.1341.

Undeca-2,9-diyne-1,11-diol (11c) was prepared in 80% yield as above (procedure A). **11c**: white solid: mp 40–41 °C (from ethyl ether/hexane); R_f 0.35 (silica. 70% ethyl ether in petroleum ether); IR (neat) ν_{max} 3340, 2940, 2860, 2290. 2230, 1435, 1225, 1135, 1015, 720 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.23 (t, J = 2.2 Hz, 4 H. O-CH_2), 2.21 (t, J = 2.0 Hz, 4 H, C≡CCH_2), 1.73 (s, 4 H, O*H*). 1.62 (s, 6 H, CH_2); HRMS for $C_{11}H_{20}NO_2$ (M + NH_4), calcd 198.1493, found 198.1488.

Dodeca-2,10-diyne-1,12-diol (11d)[24] was prepared in 92% yield as above (procedure A).

Trideca-2,11-diyne-1,13-diol (11e) was prepared in 79% yield as above (procedure A). **11e**: white solid: mp 57–58 °C (from ethyl acetate/hexane): R_f 0.28 (silica, 70% ethyl ether in petroleum ether); IR (film) ν_{max} 3210. 2940. 2860. 2220. 1470, 1370, 1140. 1030, 1015. 720 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.23 (t. J = 2.1 Hz, 4 H, O-CH_2), 2.21 (m, 4 H. C≡CCH_2). 1.56–1.32 (m, 12 H, O*H* and CH_2); HRMS for $C_{13}H_{24}NO_2$ (M + NH_4). calcd 226.1806, found 226.1821.

Tetradeca-2,12-diyne-1,14-diol (11f)[24] was prepared in 74% yield as above (procedure A).

Pentadeca-2,13-diyne-1,15-diol (11g) was prepared in 72% yield as above (procedure A). **11g**: white solid: mp 72–73 °C (from ethyl acetate/hexane); R_f 0.36 (silica. 70% ethyl ether in petroleum ether): IR (film) ν_{max} 3180, 2940, 2850. 1470. 1370, 1230, 1140, 1020. 970. 785, 720 cm^{-1}; ^{1}H NMR (250 MHz. $CDCl_3$) δ 4.25 (dt, J = 5.9, 2.1 Hz, 4 H. O-CH_2). 2.19 (m. 4 H. C≡CCH_2). 1.58 (t. J = 5.9 Hz. 2 H. O*H*),

1.51–1.26 (m. 14 H, CH_2); HRMS for $C_{15}H_{28}NO_2$ (M + NH_4). calcd 254.2120, found 254.2082.

Hexadeca-2,14-diyne-1,16-diol (11h)[23] was prepared in 78% yield as above (procedure A).

1,10-Dibromodeca-2,8-diyne (12b). Representative Procedure (B). To a cooled (0 °C) solution of compound **11b** (3.5 g, 21 mmol) and carbon tetrabromide (27.9 g, 84.1 mmol, 4.0 equiv) in ethyl ether (70 mL) was added slowly tri-*n*-butylphosphine (21 mL. 17 g, 84 mmol, 4.0 equiv) in ethyl ether (20 mL). After 15 min. the reaction was diluted with methylene chloride (90 mL) and filtered through a plug of silica (50% ethyl ether in methylene chloride). The residue was purified by flash column chromatography (0 → 4% ethyl ether in petroleum ether) to give the product (3.05 g, 50% yield). **12b**: pale yellow oil; R_f 0.31 (silica, 25% methylene chloride in petroleum ether); IR (neat) ν_{max} 3010, 2960, 2880, 2240. 1430, 1330, 1210, 1145, 910, 690 cm^{-1}; ^1H NMR (250 MHz. $CDCl_3$) δ 3.92 (t, J = 2.4 Hz, 4 H, Br-CH_2). 2.26 (m, 4 H, C≡CCH_2). 1.59 (qn. J = 3.8 Hz, 4 H, CH_2); HRMS for $C_{10}H_{11}Br_2$ (M − H), calcd 288.9228. found 288.9243.

1,9-Dibromonona-2,7-diyne (12a)[23] was prepared in 75% yield as above (procedure B).

1,11-Dibromomoundeca-2,9-diyne (12c) was prepared in 92% yield as above (procedure B). **12c**: colorless oil; R_f 0.38 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 3000, 2950, 2860, 2310. 2240. 1470, 1430. 1350. 1330, 1215, 1170. 870, 710, 670, 610 cm^{-1}; ^1H NMR (250 MHz. $CDCl_3$) δ 3.90 (t, J = 2.4 Hz, 4 H, Br-CH_2), 2.22 (m. 4 H, C≡CCH_2). 1.50 (m. 6 H, CH_2): HRMS for $C_{11}H_{13}Br_2$ (M − H). calcd 302.9384. found 302.9398.

1,12-Dibromododeca-2,10-diyne (12d) was prepared in 89% yield as above (procedure B). **12d**: clear oil; R_f 0.47 (silica, 25% methylene chloride in petroleum ether): IR (neat) ν_{max} 3010, 2950. 2870, 2240, 1460. 1430, 1330. 1220. 1150, 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.93 (t, J = 2.4 Hz. 4 H, Br-CH_2), 2.25 (tt, J = 2.4, 6.9 Hz, 4 H. C≡CCH_2), 1.55–1.37 (m, 8 H, CH_2); HRMS for $C_{12}H_{15}Br_2$ (M − H). calcd 316.9541. found 316.9520.

1,13-Dibromotrideca-2,11-diyne (12e) was prepared in 64% yield as above (procedure B). **12e**: colorless oil; R_f 0.43 (silica, 20% methylene chloride in petroleum ether): IR (neat) ν_{max} 3010, 2960, 2860, 2240, 1470. 1430, 1330, 1210. 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.90 (t. J = 4.7 Hz, 4 H, Br-CH_2), 2.22 (m, 4 H, C≡CCH_2), 1.55–1.27 (m, 10 H, CH_2); HRMS for $C_{13}H_{22}Br_2N$ (M + NH_4). calcd 350.0118, found 350.0162.

1,14-Dibromotetradeca-2,12-diyne (12f) was prepared in 62% yield as above (procedure B). **12f**: colorless oil; R_f 0.52 (silica. 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 3010. 2960, 2860, 2310, 2240, 1470, 1430. 1330. 1220, 1170, 620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.91 (t, J = 2.4 Hz, 4 H, Br-CH_2), 2.21 (m. 4 H, C≡CCH_2), 1.54–1.28 (m, 12 H. CH_2): HRMS for $C_{14}H_{24}Br_2N$ (M + NH_4), calcd 364.0275, found 364.0261.

1,15-Dibromopentadeca-2,13-diyne (12g) was prepared in 73% yield as above (procedure B). **12g**: colorless oil; R_f 0.49 (silica, 20% methylene chloride in petroleum ether): IR (neat) ν_{max} 3000, 2940, 2860. 2230. 1465, 1430, 1330. 1210. 1160, 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.91 (t. J = 2.3 Hz. 4 H, Br-CH_2) 2.22 (tt, J = 7.0, 2.4 Hz, 4 H, C≡CCH_2). 1.54–1.28 (m, 14 H. CH_2): HRMS for $C_{15}H_{26}Br_2N$ (M + NH_4). calcd 378.0432, found 378.0405.

1,16-Dibromohexadeca-2,14-diyne (12h) was prepared in 100% yield as above (procedure B). **12h**: colorless oil; R_f 0.51 (silica, 20% methylene chloride in petroleum ether): IR (neat) ν_{max} 3000, 2930, 2850. 2230, 1465. 1440, 1340, 1220. 1160. 720. 610 cm^{-1}; ^1H NMR (250 MHz. $CDCl_3$) δ 3.91 (t. J = 2.3 Hz. 4 H, Br-CH_2), 2.21 (tt, J = 7.0. 2.4 Hz, 4 H, C≡CCH_2). 1.53–1.25 (m, 16 H, CH_2): HRMS for $C_{16}H_{28}Br_2N$ (M + NH_4). calcd 392.0589, found 392.0579.

3,4,8,9-Tetradehydro-5,6,7,10-tetrahydro-2*H*-thiecin (13a). Representative Procedure (C). To a solution of compound **12a** (8.07 g. 29 mmol) in ethanol (200 mL) was added sodium sulfide on alumina (23.112 g. 0.8 g/mmol) in ethanol (175 mL) and methylene chloride (440 mL). After 18 h, the reaction mixture was filtered and concentrated in vacuo. The residue was then dissolved in ethyl ether (200 mL), washed with 5% aqueous K_2CO_3 (100 mL) and saturated brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (5 → 10% ethyl ether in petroleum ether) to give the product **13a** (0.398 g. 9% yield). **13a**: colorless oil; R_f 0.31 (silica, petroleum ether): IR (neat) ν_{max} 2940. 2910. 2850, 2230, 1435. 1410. 1330, 1250, 1230. 1200, 1140, 850, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.34 (m. 4 H. SCH_2). 2.58 (t. J = 7.6 Hz, 4 H, C≡CCH_2). 1.95 (qn, J = 7.6 Hz, 2 H, CH_2): HRMS for C_9H_8 (M − SH_2), calcd 116.0626, found 116.0634.

Thiaundeca-3,9-diyne (13b). Representative Procedure (D). Solutions of compound **12b** (3.0 g, 10 mmol) in ethanol (50 mL) and sodium sulfide nonahydrate (3.0 g, 12.5 mmol, 1.2 equiv) in ethanol (15 mL) and water (35 mL) were added separately and simultaneously via syringe pump over 4 h, to ethanol (100 mL). The reaction mixture was concentrated in vacuo and then added to saturated aqueous NH_4Cl (50 mL) and ethyl ether (50 mL). The organic layer was washed with $NaHCO_3$ (20 mL). water (20 mL), and saturated brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (50% methylene chloride in petroleum ether) to give the product **13b** (0.70 g, 41% yield). **13b**: colorless oil; R_f 0.20 (silica, 25% methylene chloride in petroleum ether); IR (neat) ν_{max} 3190, 2960, 2870, 2230, 1470. 1240, 1040, 1140, 990, 780 cm^{-1}; ^1H NMR (250 MHz. $CDCl_3$) δ 3.41 (m, 4 H, S-CH_2), 2.30 (m, 4 H, C≡CCH_2), 1.72 (m, 4 H, CH_2); HRMS for $C_{10}H_{12}S$ (M^+), calcd 164.0660, found 164.0650.

Thiadodeca-3,10-diyne (13c) was prepared in 31% yield by procedure D. **13c**: colorless oil; R_f 0.33 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 2960, 2860, 2220, 1450, 1435, 1410, 1400, 1330, 1250, 1230. 1140, 900, 740, 705, 670 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.13 (m, 4 H. S-CH_2), 2.37–2.21 (m, 4 H, C≡CCH_2), 1.53–1.23 (m. 6 H, CH_2); HRMS for $C_{11}H_{18}NS$ (M + NH_4), calcd 196.1160, found 196.1144.

Thiatrideca-3,11-diyne (13d) was prepared in 57% yield by using sodium sulfide nonahydrate (procedure D) or in 91% yield by using sodium sulfide on alumina (procedure C). **13d**: colorless oil; R_f 0.27 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 2940, 2860, 1440, 1430, 1230 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.13 (m, 4 H, S-CH_2), 2.37–2.21 (m, 4 H, C≡CCH_2), 1.53–1.23 (m, 6 H, CH_2); HRMS for $C_{12}H_{20}NS$ (M + NH_4), calcd 210.1316, found 210.1320.

Thiatetradeca-3,12-diyne (13e) was prepared in 62% yield by procedure D. **13e**: colorless oil; R_f 0.25 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 2960, 2860, 1460, 1250. 1230 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.44 (t, J = 4.1 Hz, 4 H, S-CH_2), 2.22 (m, 4 H. C≡CCH_2). 1.53–1.45 (m, 10 H, CH_2); HRMS for $C_{13}H_{22}NS$ (M + NH_4). calcd 224.1473. found 224.1462.

Thiapentadeca-3,13-diyne (13f) was prepared in 72% yield by procedure D. **13f**: colorless oil; R_f 0.24 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 2960. 2860, 1460. 1435, 1415, 1330, 1250. 1230 cm^{-1}; ^1H NMR (250 MHz. $CDCl_3$) δ 3.48 (t, J = 2.1 Hz. 4 H, S-CH_2), 2.23 (tt, J = 6.8, 2.1 Hz, 4 H, C≡CCH_2), 1.58–1.39 (m. 12 H, CH_2): HRMS for $C_{14}H_{24}NS$ (M + NH_4), calcd 238.1629, found 238.1653.

Thiahexadeca-3,14-diyne (13g) was prepared in 53% yield by procedure D. **13g**: colorless oil; R_f 0.33 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 2940, 2920, 2870, 2240, 1470, 1450, 1440, 1350, 1330, 1250, 1230, 1190, 900, 830, 715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.13 (t, J = 2.2 Hz, 4 H, S-CH_2), 2.51 (s, 4 H, C≡CCH_2), 1.57–1.39 (m, 14 H, CH_2); HRMS for $C_{15}H_{26}NS$ (M + NH_4), calcd 252.1785, found 252.1827.

Thiaheptadeca-3,15-diyne (13h) was prepared in 60% yield by procedure D. **13h**: colorless oil: R_f 0.34 (silica, 20% methylene chloride in petroleum ether); IR (neat) ν_{max} 2940, 2860, 2230, 1465. 1435, 1415, 1330. 1230, 900, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.42 (t. J = 2.3 Hz, 4 H, S-CH_2), 2.22 (m, 4 H, C≡CCH_2), 1.53–1.30 (m, 16 H. CH_2); HRMS for $C_{16}H_{28}NS$ (M + NH_4), calcd 266.1942, found 266.1942.

3,4,8,9-Tetradehydro-5,6,7,10-tetrahydro-2*H*-thiecin-1-oxide (14a). Representative Procedure (Procedure E). To a cooled (−30 °C) solution of compound **13a** (0.398 g, 2.65 mmol) in methylene chloride (40 mL) was added *m*-chloroperbenzoic acid (0.465 g, 2.70 mmol, 1.02 equiv). After 30 min, methyl sulfide (2 mL) was added, and, after a further 10 min, the reaction mixture was concentrated in vacuo. The residue was then dissolved in ethyl ether (50 mL), washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and saturated brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (2% methanol in methylene chloride) to give the product **14a** (0.221 g, 50% yield). **14a**: white solid; mp 155–156 °C (from ethyl acetate/hexane); R_f 0.19 (silica, 2% methanol in methylene chloride); IR (neat) ν_{max} 2940, 2900, 1460, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.75 (m. 4 H S-CH_2), 2.35 (m, 4 H, C≡CCH_2), 1.71 (m, 2 H. CH_2); HRMS for $C_9H_{11}OS$ (M + H), calcd 167.0531, found 167.0537.

Thiaundeca-3,9-diyne-1-oxide (14b) was prepared in 85% yield as above (procedure E). **14b**: colorless oil: R_f 0.33 (silica. ethyl ether): IR (neat) ν_{max} 3190. 2960. 2870, 2230. 1470, 1240. 1140, 1040, 990, 780 cm^{-1}; ^1H NMR (250 MHz. $CDCl_3$) δ 3.74 (m, 4 H, S-CH_2), 2.15 (s, 4 H, C≡CCH_2), 1.66 (m, 4 H, CH_2); HRMS for $C_{10}H_{13}OS$ (M + H), calcd 181.0687, found 181.0709.

Thiadodeca-3,10-diyne-1-oxide (14c) was prepared in 68% yield by procedure E. **14c**: white solid; mp 111–112 °C (from ethyl ether/ethyl acetate); R_f 0.34 (silica, ethyl ether): IR (neat) ν_{max} 2940. 2860, 1450, 1410. 1045 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (dt, J = 16.3, 2.4 Hz, 2 H, S-CH_aH_b), 3.72 (dt, J = 15.7, 2.6 Hz, 2 H, S-CH_aH_b) 2.24 (m, 4 H, C≡CCH_2). 1.72 (qn. J = 7.2 Hz, 2 H, CH_2), 1.42 (qn, J = 6.6 Hz,

4 H. C≡CCH$_2$CH$_2$): HRMS for $C_{11}H_{15}OS$ (M + H), calcd 195.0843, found 195.0816.

Thiatrideca-3,11-diyne-1-oxide (14d) was prepared in 92% yield (procedure E). **14d**: colorless oil; R_f 0.29 (silica. ethyl ether); IR (neat) ν_{max} 3190, 2960. 2870. 2230, 1470, 1240, 1140. 1040, 990, 780 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.80 (dt, J = 16.3, 2.4 Hz, 2 H. S-CH$_a$H$_b$), 3.72 (dt. J = 15.7, 2.6 Hz, 2 H. S-CH$_a$H$_b$) 2.24 (m, 4 H. C≡CCH$_2$), 1.72 (qn. J = 7.2 Hz. 4 H. CH$_2$), 1.42 (qn. J = 6.6 Hz, 4 H, C≡CCH$_2$CH$_2$): HRMS for $C_{12}H_{20}NOS$ (M + NH$_4$), calcd 226.1265, found 226.1284.

Thiatetradeca-3,12-diyne-1-oxide (14e) was prepared in 75% yield by procedure E. **14e**: colorless oil; R_f 0.42 (silica. ethyl ether); IR (neat) ν_{max} 2950, 2910, 2870. 2240. 2110, 1470, 1450. 1415, 1325, 1225, 1180. 1065, 900, 840, 730 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.77 (t, 4 H. S-CH$_2$) 2.24 (m. 4 H, C≡CCH$_2$), 1.51 (m. 10 H, CH$_2$): HRMS for $C_{13}H_{19}OS$ (M + H), calcd 223.1156. found 223.1188.

Thiapentadeca-3,13-diyne-1-oxide (14f) was prepared in 65% yield by procedure E. **14f**: white solid; mp 108–109 °C (from ethyl acetate/hexane): R_f 0.19 (silica, 2% methanol in methylene chloride); IR (neat) ν_{max} 3000. 2960, 2860, 2230, 1460. 1430, 1400, 1390, 1330. 1240, 1170, 1120. 1050, 870, 830 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.46 (t, J = 2.1 Hz. 4 H, S-CH$_2$), 2.23 (m. 4 H, C≡CCH$_2$), 1.56–1.35 (m, 12 H, CH$_2$): HRMS for $C_{14}H_{21}OS$ (M + H), calcd 237.1313, found 237.1297.

Thiahexadeca-3,14-diyne-1-oxide (14g) was prepared in 79% yield by procedure E. **14g**: white solid; mp 96–97 °C (from ethyl acetate/hexane); R_f 0.40 (silica, ethyl ether): IR (neat) ν_{max} 3000, 2930. 2860, 2230, 1460, 1430. 1410, 1360, 1330. 1240. 1170, 1050, 890 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.83 (dt, J = 15.6, 2.3 Hz, 2 H. S-CH$_a$H$_b$), 3.70 (dt, J = 15.7. 2.3 Hz, 2 H, S-CH$_a$H$_b$), 2.29 (s, 4 H, C≡CCH$_2$), 1.56–1.40 (m, 14 H, CH$_2$): HRMS for $C_{15}H_{26}NOS$ (M + NH$_4$), calcd 268.1735, found 268.1739.

Thiaheptadeca-3,15-diyne-1-oxide (14h) was prepared in 76% yield by procedure E. **14h**: white solid; mp 119–120 °C (from ethyl ether/ethyl acetate); R_f 0.41 (silica, ethyl ether): IR (neat) ν_{max} 2940, 2860, 1460, 1330, 1180. 1050 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.83 (dt, J = 15.6, 2.3 Hz. 2 H, S-CH$_a$H$_b$), 3.63 (dt, J = 15.6, 2.3 Hz, 2 H, S-CH$_a$H$_b$), 2.27 (m. 4 H. C≡CCH$_2$), 1.57–1.33 (m, 14 H, CH$_2$); HRMS for $C_{16}H_{28}NOS$ (M + NH$_4$), calcd 282.1891, found 282.1880.

2-Chloro-3,4,8,9-tetradehydro-5,6,7,10-tetrahydro-2*H*-thiecin-1,1-dioxide (16a). Representative Procedure (Procedure F). To a cooled (−78 °C) solution of compound **14a** (241.2 mg, 1.23 mmol) and pyridine (0.36 mL, 350 mg, 4.45 mmol. 3.5 equiv) in methylene chloride (10 mL) was added sulfuryl chloride (0.22 mL, 370 mg. 2.7 mmol, 2.1 equiv). After 40 min, water (4 mL) was added. and the cooling bath was removed. Upon warming to room temperature, the organic layer was washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), saturated aqueous $CuSO_4$ (2 × 5 mL). and saturated brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue (crude **15a**) was dissolved in methylene chloride (15 mL) and cooled (0 °C). *m*-Chloroperbenzoic acid (699.9 mg. 4.06 mmol, 3.1 equiv) was then added. the cooling bath was removed, and the reaction mixture was stirred for 16 h at ambient temperature. Methyl sulfide (1 drop) was then added, and the reaction mixture was washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by recrystallization (ethyl ether/ethyl acetate) to give the product **16a** (226.8 mg, 81% yield). **16a**: solid; mp 128–129 °C; R_f 0.33 (silica, methylene chloride): IR (neat) ν_{max} 2920. 2220, 1400, 1335, 1270, 1190, 1155. 1125, 880, 850. 790, 760, 730 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.15 (dd, J = 4.3, 2.1 Hz, 1 H. Cl-CH), 4.61 (dt, J = 18.0, 2.7 Hz, 1 H, S-CH$_a$H$_b$), 3.70 (ddd, J = 17.6, 4.4, 2.3 Hz, 1 H. S-CH$_a$H$_b$), 2.64–2.19 (m, 4 H. C≡CCH$_2$), 1.77 (qn, J = 5.9 Hz. 2 H. CH$_2$): HRMS for $C_9H_{13}ClNO_2S$ (M + NH$_4$), calcd 234.0356, found 234.0379.

2-Chlorothiaundeca-3,9-diyne-1,1-dioxide (16b) was prepared in 59% yield as above by procedure F. **16b**: white solid: mp 135–136 °C (from ethanol); R_f 0.19 (silica, 2% methanol in methylene chloride); IR (neat) ν_{max} 3030. 2940, 2860, 2235. 1340, 1190. 1120, 870 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.53 (dd, J = 4.1. 2.1 Hz, 1 H. Cl-CH). 4.21 (dt, J = 17.8, 3.2 Hz. 1 H. S-CH$_a$H$_b$), 3.48 (dt, J = 17.6, 2.1 Hz, 1 H, S-CH$_a$H$_b$), 2.37–2.14 (m. 4 H. C≡CCH$_2$), 1.75–1.58 (m, 4 H, CH$_2$); HRMS for $C_{10}H_{15}ClNO_2S$ (M + NH$_4$). calcd 248.051, found 248.049.

2-Chlorothiadodeca-3,10-diyne-1,1-dioxide (16c) was prepared in 76% yield as above by procedure F. **16c**: colorless oil: R_f 0.38 (silica, 30% ethyl ether in petroleum ether): IR (neat) ν_{max} 3030, 2940, 2860. 2240, 1460, 1430. 1400, 1340, 1250. 1170. 1130, 910, 850. 740 cm^{-1}; ^{1}H NMR (250 MHz. $CDCl_3$) δ 5.29 (dd, J = 3.9. 2.1 Hz, 1 H, Cl-CH), 4.61 (dt, J = 17.9. 2.6 Hz, 1 H. S-H$_a$H$_b$), 3.77 (ddd, J = 17.9, 4.1. 2.3 Hz, 1 H, S-CH$_a$H$_b$), 2.41–2.26 (m. 4 H. C≡CCH$_2$), 1.82–1.43 (m, 6 H. CH$_2$); HRMS for $C_{11}H_{17}ClNO_2S$ (M + NH$_4$), calcd 262.0668, found 262.0636.

2-Chlorothiatrideca-3,11-diyne-1,1-dioxide (16d) was prepared in 56% yield by procedure F. **16d**: colorless oil; R_f 0.24 (silica, 50% methylene chloride in petroleum ether): IR (neat) ν_{max} 2940, 2860, 2240, 1450, 1435, 1410, 1330. 1185, 1040, 910, 730, 710 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.29 (dd, J = 3.9, 2.1 Hz, 1 H, Cl-CH), 4.61 (dt, J = 17.9, 2.6 Hz, 1 H, S-H$_a$H$_b$), 3.77 (ddd, J = 17.9, 4.1, 2.3 Hz, 1 H, S-CH$_a$H$_b$), 2.41–2.26 (m, 4 H, C≡CCH$_2$), 1.83–1.43 (m, 6 H, CH$_2$): HRMS for $C_{12}H_{19}ClNO_2S$ (M + NH$_4$), calcd 276.0824, found 276.0797.

2-Chlorothiatetradeca-3,12-diyne-1,1-dioxide (16e) was prepared in 42% yield by procedure F. **16e**: colorless oil; R_f 0.40 (silica, 30% ethyl ether in petroleum ether); IR (neat) ν_{max} 3020, 2930, 2860, 2230, 1460, 1340. 1170, 1150, 1130 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.29 (dd, J = 3.9, 2.1 Hz, 1 H. Cl-CH). 4.61 (dt. J = 16.9, 2.1 Hz, 1 H, S-H$_a$H$_b$), 3.77 (ddd, J = 16.9, 2.7. 1.8 Hz, 1 H, S-CH$_a$H$_b$), 2.42–2.17 (m, 4 H. C≡CCH$_2$), 1.64–1.25 (m, 10 H, CH$_2$); HRMS for $C_{13}H_{21}ClNO_2S$ (M + NH$_4$), calcd 290.0981, found 290.0990.

2-Chlorothiapentadeca-3,13-diyne-1,1-dioxide (16f) was prepared in 37% yield by procedure F. **16f**: colorless oil; R_f 0.19 (silica, 2% methanol in methylene chloride); IR (neat) ν_{max} 3030, 2940, 2860, 2240, 1460, 1350, 1170, 1130, 880 cm^{-1}: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.80 (t, J = 1.9 Hz, 1 H, Cl-CH), 4.39 (dt. J = 16.8, 2.0 Hz, 1 H, S-H$_a$H$_b$), 4.01 (dt, J = 16.8, 2.4 Hz, 1 H, S-CH$_a$H$_b$), 2.40–2.22 (m, 4 H, C≡CCH$_2$), 1.54–1.27 (m. 12 H. CH$_2$): HRMS for $C_{14}H_{23}ClNO_2S$ (M + NH$_4$). calcd 304.1137, found 304.1165.

2-Chlorothiahexadeca-3,14-diyne-1,1-dioxide (16g) was prepared in 59% yield by procedure F. **16g**: colorless oil; R_f 0.49 (silica, 30% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3020, 2940, 2860, 2240, 1460, 1350, 1240, 1170, 1130, 870 cm^{-1}; ^{1}H NMR (250 MHz. $CDCl_3$) δ 5.82 (t, J = 2.3 Hz, 1 H, Cl-CH). 4.30 (dt, J = 16.8. 2.4 Hz. 1 H, S-H$_a$H$_b$), 4.03 (dt, J = 16.8, 2.4 Hz, 1 H, S-CH$_a$H$_b$), 2.40–2.27 (m, 4 H, C≡CCH$_2$). 1.52–1.38 (m. 14 H, CH$_2$); HRMS for $C_{15}H_{25}ClNO_2S$ (M + NH$_4$), calcd 318.1294, found 318.1277.

2-Chlorothiaheptadeca-3,15-diyne-1,1-dioxide (16h) was prepared in 54% yield by procedure F. **16h**: colorless oil; R_f 0.51 (silica, 30% ethyl ether in petroleum ether): IR ($CHCl_3$) ν_{max} 3020, 2930. 2860, 2240, 1460, 1430, 1350, 1240, 1170, 1130, 880 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.81 (t, J = 2.2 Hz, 1 H, Cl-CH), 4.14 (m, 2 H, S-CH$_2$), 2.40–2.26 (m, 4 H, C≡CCH$_2$), 1.55–1.23 (m, 16 H, CH$_2$); HRMS for $C_{16}H_{27}ClNO_2S$ (M + NH$_4$), calcd 332.1451, found 332.1480.

Cycloundeca-1,5-diyn-3-ene (17). Representative Procedure (Procedure G). To a cooled (−78 °C) solution of compound **16c** (1.205 g, 4.91 mmol) in THF (30 mL) was added potassium *tert*-butoxide (1.414 g, 10.1 mmol, 2.0 equiv). After 3 h, the reaction mixture was added to saturated aqueous NH_4Cl (30 mL) and ethyl ether (50 mL). The organic layer was washed with water (30 mL) and saturated brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (2.5 → 5% ethyl ether in petroleum ether) to give the product **17** (0.228 g, 32% yield). **17**: while solid; mp 35–36 °C: R_f 0.22 (silica, petroleum ether); IR ($CHCl_3$) ν_{max} 2940, 2860, 2840, 2210. 2190. 1460, 1430, 1350, 1320 cm^{-1}; UV λ_{max} 262 (sh), 269, 274 (sh), 285 nm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.78 (s, 2 H. C=CH), 2.45 (t, J = 3.1 Hz, 4 H, C≡CCH$_2$), 2.01 (qn. J = 3.5 Hz, 2 H, CH$_2$), 1.59 (qn, J = 3.3 Hz, 4 H, C≡CCH$_2$CH$_2$); HRMS for $C_{11}H_{12}$ (M$^+$), calcd 144.0939, found 144.0934.

Cyclododeca-1,5-diyn-3-ene (18). Prepared in 33% yield by using potassium *tert*-butoxide as described above (procedure G) or in 62% yield by using potassium hydroxide. **18**: colorless oil: R_f 0.22 (silica, petroleum ether); IR ($CHCl_3$) ν_{max} 3030, 2930, 2860, 2200, 1560, 1455, 1430 cm^{-1}; UV λ_{max} 260 (sh), 267, 273 (sh). 282 nm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.73 (s, 2 H. C=CH). 2.43 (t, J = 6.0 Hz, 4 H, C≡CCH$_2$), 1.76–1.60 (m, 6 H, CH$_2$); HRMS for $C_{12}H_{14}$ (M$^+$). calcd 158.1095, found 158.1115.

Cyclotrideca-1,5-diyn-3-ene (19) was prepared in 24% yield by procedure G. **19**: colorless oil; R_f 0.24 (silica, petroleum ether): IR ($CHCl_3$) ν_{max} 3020. 2920. 2850, 2220. 2200, 1670, 1570, 1460. 1430. 1395. 1350. 1320. 1160. 740 cm^{-1}; UV λ_{max} 256 (sh), 265, 269 (sh), 280 nm; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.71 (s. 2 H, C=CH), 2.41 (t, J = 5.3, 4 H. C≡CCH$_2$), 1.58 (m, 10 H, CH$_2$): HRMS for $C_{13}H_{16}$ (M$^+$), calcd 172.1252, found 172.1246.

Cyclotetradeca-1,5-diyn-3-ene (20) was prepared in 49% yield by procedure G. **20**: colorless oil; R_f 0.28 (silica, petroleum ether); IR ($CHCl_3$) ν_{max} 3010, 2940, 2870, 2220, 1465. 1435, 1330 cm^{-1}; UV λ_{max} 254 (sh), 263, 268 (sh), 277 nm: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.71 (s. 2 H, C=CH). 2.42 (t, J = 5.8 Hz, 4 H, C≡CCH$_2$), 1.65–1.39 (m, 12 H, CH$_2$); HRMS for $C_{14}H_{18}$ (M$^+$), calcd 186.1405. found 186.1422.

Cyclopentadeca-1,5-diyn-3-ene (21) was prepared in 32% yield by procedure G. **21**: colorless oil: R_f 0.26 (silica. petroleum ether); IR (neat) ν_{max} 2930, 2860. 2230, 1450. 1400, 1320, 750 cm^{-1}; UV λ_{max} 255 (sh), 264, 270 (sh), 279.5 nm: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.71 (s 2 H. C=CH). 2.44 (t. J = 5.0 Hz. 4 H, C≡CCH$_2$), 1.54–1.41 (m, 14

H, CH_2): HRMS for $C_{15}H_{24}N$ (M + NH_4), calcd 218.1909, found 218.1906.

Cyclohexadeca-1,5-diyn-3-ene (22) was prepared in 44% yield by procedure G. **22**: colorless oil; R_f = 0.30 (silica, petroleum ether); IR ($CHCl_3$) ν_{max} 3020, 2940, 2860, 2210, 1470, 1200, 910 cm^{-1}; UV λ_{max} 256 (sh), 264. 270 (sh), 278 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 5.70 (s, 2 H. C=C*H*). 2.44 (t. J = 5.8 Hz, 4 H. C≡CCH_2), 1.57–1.23 (m, 16 H, CH_2): HRMS for $C_{16}H_{26}N$ (M + NH_4), calcd 232.2065, found 232.2062.

1,2-Diethynylcyclopentene (25a). To a cooled (−78 °C) solution of MeLi (1.29 M in ethyl ether, 50 μL, 64 μmol, 1.3 equiv) in THF (1 mL) was added compound **16a** (11 mg, 50 μmol) in THF (2 mL). After 10 min. saturated aqueous NH_4Cl (5 mL) and pentane (10 mL) were added. After warming to room temperature, the organic layer was filtered and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (petroleum ether) to give the product **25a** (1.4 mg. 24% yield). **25a**: colorless oil; R_f 0.31 (silica, petroleum ether); IR (neat) ν_{max} 3290, 2940, 2860. 2840, 2100. 1450, 1440 cm^{-1}; UV λ_{max} 250 (sh). 259. 263 (sh). 272 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 3.34 (s, 2 H. C≡C*H*), 2.58 (t. J = 7.6 Hz, 4 H. C≡C-CH_2), 1.95 (qn, J = 7.6 Hz. 2 H, CH_2); ^{13}C NMR (62.5 MHz. $CDCl_3$) δ 130.8, 84.1, 79.8, 36.9, 22.8.

Cyclodeca-1,5-diyn-3-ene (27) and 1,2-Diethynylcyclohexene (25b).[19] To a cooled (−78 °C) solution of MeLi (1.6 M in ethyl ether. 0.75 mL, 1.2 mmol, 1.2 equiv) in ethyl ether (10 mL) was added compound **16b** (230 mg. 1.0 mmol) in ethyl ether (20 mL). Immediately after the addition was complete, saturated aqueous NH_4Cl (5 mL) was added. The organic layer was diluted with pentane (10 mL) and washed with water (10 mL). The organic layer was then filtered through Celite, dried (Na_2SO_4). and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (petroleum ether) to give products **27** (15 mg. 12% yield) and **25b**[19] (15 mg, 12% yield). **27**: colorless oil: R_f 0.31 (silica, petroleum ether); IR ($CHCl_3$) ν_{max} 3000, 2970, 2930, 2860. 1445, 1380, 1110 cm^{-1}: UV λ_{max} 259. 263 (sh), 282 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 5.80 (s, 2 H, C=C*H*). 2.38 (m, 4 H, C≡CCH_2). 1.91 (m, 4 H. CH_2): ^{13}C (62.5 MHz. $CDCl_3$) δ 123.6, 104.7. 82.6. 29.4, 21.9.

Thermolysis of Cyclodeca-1,5-diyn-3-ene (27). Compounds 32a,b. Sealed tubes containing 50 μL of a solution of **27** (0.01 M). 1.4-cyclohexadiene (1 M), and phenyl ether (0.004 M) in degassed benzene were prepared. They were placed into an oven at the desired temperature (±0.01 °C) and incubated. The products were analyzed on a Varian Model 5000 HPLC using a Partisil 10 column and hexane as eluent with UV detection (274 nm). Digital integration of the peaks was performed, and the ratios relative to phenyl ether were determined. The different absorbances of tetralin and the internal standard were taken into account by calibration with authentic samples. The products formed were determined by NMR spectral data and comparison to an authentic sample of tetralin. The rate constants for the decomposition of **27** at 37, 50. 60 and 70 °C are given in Table III. **32a,b**: retention times: 5.99 and 6.29 min; ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–6.91 (m, 3 H, Ar-*H*), 6.09–5.63 (m, 4 H, C=C*H*). 3.84 (m, 1 H, C*H*), 2.84–2.65 (m. 6 H, C=CCH_2). 1.88–1.67 (m. 4 H. CH_2); HRMS for $C_{16}H_{18}$ (M^+), calcd 210.1409, found 210.1428.

(*R*,S)-1,2-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-4-cyclohexene (34).** To a solution of 1,2,3,6-tetrahydrophthalyl alcohol[21] (**33**, 89.33 g, 628 mmol) and *tert*-butylchlorodiphenylsilane (343 g, 1.25 mol, 2.0 equiv) in DMF (750 mL) was added imidazole (107.6 g, 1.58 mol, 2.5 equiv). After stirring for 16 h, the reaction mixture was poured into water (1000 mL) and petroleum ether (1000 mL). The organic phase was then washed with water (1000 mL) and saturated brine (1000 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (0→10% ethyl ether in petroleum ether) to give the product **34** (333.77 g, 86% yield). **34**: white solid; mp 63 °C: R_f 0.44 (silica. 2.5% ethyl ether in petroleum ether); IR (film) ν_{max} 3060. 2950. 2850, 1590, 1470. 1425. 1390, 1210, 1110, 1000, 820. 750. 735, 700, 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.21 (m. 20 H. Ar-*H*), 5.57 (s, 2 H. C=C*H*), 3.57 (m, 4 H, O-CH_2). 2.13–1.92 (m, 6 H, C*H* and CH_2). 1.00 (s, 18 H, CH_3); HRMS for $C_{40}H_{50}O_2Si_2$ (M + H), calcd 619.3427, found 619.3471.

(*R*,S)4,5-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-1,1,8,8-tetrabromo-1,7-octadiene (36).** To a cooled (−78 °C) solution of **34** (50.399 g. 81.4 mmol) in methylene chloride (200 mL) and methanol (30 mL) was bubbled ozone. After 1 h, trimethylphosphite (20 mL, 21 g, 170 mmol, 2.0 equiv) was added, and the reaction mixture was allowed to warm to room temperature over 1.5 h. It was then added to saturated aqueous $NaHCO_3$ solution (150 mL). The organic phase was washed with 1 N NaOH (100 mL) and saturated brine (100 mL). dried ($MgSO_4$), and concentrated in vacuo. The residue (crude **35**) was azeotroped with benzene (30 mL) and dissolved in methylene chloride (50 mL). This solution was added via cannula to a cooled (0 °C) solution of carbon tetrabromide (67.448 g, 203 mmol, 2.5 equiv) and triphenylphosphine (107.288 g, 4.08 mmol, 5.0 equiv). After 30 min, the cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 16 h. The solution was concentrated in vacuo, and the residue was washed with 50% ethyl ether in petroleum ether (5 × 500 mL). The combined washings were then concentrated in vacuo. The residue was purified by flash column chromatography (25% methylene chloride in petroleum ether) to give the product **36** (59.66 g, 75% yield). **36**: white solid; mp 81–82 °C: R_f 0.50 (silica, 25% methylene chloride in petroleum ether): IR ($CHCl_3$) ν_{max} 3080, 2940, 2860, 1590, 1480, 1430. 1400, 1120, 1000, 830, 710, 620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.71–7.60 (m, 8 H, Ar-*H*), 7.47–7.33 (m, 12 H. Ar-*H*), 6.19 (t, J = 7.0 Hz, 2 H, C=C*H*). 3.59 (dd, J = 10.7. 5.5 Hz, 2 H, O-CH_aH_b), 3.54 (dd, J = 10.6, 5.1 Hz, 2 H, O-CH_aH_b). 2.12 (t, J = 6.7 Hz, 4 H, C=CCH_2), 1.85 (m, 2 H, C*H*), 1.04 (s, 18 H, CH_3); HRMS for $C_{42}H_{51}Br_4O_2Si_2$ (M + H), calcd 959.0162, found 959.0077.

(*R*,S)-5,6-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-2,8-decadiynedioic Acid Dimethyl Ester (37).** To a cooled solution of **36** (59.66 g, 62.0 mmol) in THF (300 mL) was added *n*-butyllithium (1.6 M in hexane, 185 mL, 296 mmol, 4.8 equiv). After stirring for 30 min, the mixture was added to a cooled (0 °C) solution of methyl chloroformate (50 mL, 61.1 g, 647 mmol, 10.4 equiv) in THF (250 mL) and stirred for 1 h at that temperature. The reaction mixture was then added to saturated aqueous NH_4Cl (150 mL). The organic phase was washed with saturated brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by recrystallization (ethyl acetate/hexane) to give the product **37** (38.651 g, 82% yield). **37**: white solid; mp 142–143 °C; R_f 0.30 (silica, 20% ethyl ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3080, 2960, 2940, 2860. 2240. 1725, 1590, 1470, 1430, 1270, 1120, 1000, 830. 710, 620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.61 (m, 8 H, Ar-*H*), 7.46–7.33 (m, 12 H, Ar-*H*), 3.81 (dd, J = 10.6, 3.4 Hz, 2 H, O-CH_aH_b), 3.74 (s, 6 H, CH_3), 3.65 (dd, J = 10.5, 4.9 Hz, 2 H, O-CH_aH_b). 2.55 (dd, J = 17.3, 4.4 Hz, 2 H, C≡CCH_aH_b), 2.43 (dd, J = 17.4, 6.7 Hz. 2 H. C≡CCH_aH_b), 1.99 (m, 2 H, C*H*), 1.04 (s, 18 H. CH_3): HRMS for $C_{42}H_{45}O_6Si_2$ (M − C_4H_9), calcd 701.2755, found 701.2798.

(*R*,S)-5,6-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-2,8-decadiyne-1,10-diol (38).** To a cooled (−78 °C) solution of **37** (25.002 g, 32.9 mmol) in methylene chloride (400 mL) was added diisobutylaluminum hydride (1.0 M in hexane, 150 mL, 150 mmol, 4.6 equiv). The reaction mixture was allowed to warm to 0 °C over 2.5 h. Methanol (2 mL) was then added followed by saturated aqueous sodium potassium tartrate (150 mL). The cooling bath was removed, and the mixture was stirred for 10 min at ambient temperature. The aqueous phase was then extracted with ethyl acetate (50 mL), and the combined organic phases were washed with saturated brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo to give the product **38** (22.87 g, 99% yield). **38**: white solid; mp 102–103 °C; R_f 0.42 (silica, 70% ethyl ether in petroleum ether); IR (film) ν_{max} 3480, 3080, 2940, 2860, 2230, 1590, 1475, 1430, 1120, 1010, 830, 740, 710, 620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.64 (m, 8 H, Ar-*H*), 7.46–7.33 (m, 12 H, Ar-*H*), 4.10 (s, 4 H, HOCH_2), 3.80 (dd, J = 10.3. 4.0 Hz. 2 H. O-CH_aH_b). 3.69 (dd. J = 10.2. 5.4 Hz. 2 H, O-CH_aH_b). 2.43–2.31 (m, 4 H. C≡CCH_2). 1.98 (m. 2 H, C*H*), 1.04 (s. 18 H, CH_3); HRMS for $C_{40}H_{45}O_4Si_2$ (M − C_4H_9). calcd 645.2856. found 645.2808.

(*R*,S)-1,10-Dibromo-5,6-Bis[[[(1,1-dimethylethyl)diphenylsilyl]-oxy]methyl]-2,8-decadiyne (39).** To a cooled (0 °C) solution of **38** (22.57 g, 32.1 mmol) and carbon tetrabromide (23.341 g, 70.4 mmol, 2.2 equiv) in THF (400 mL) was added tri-*n*-butylphosphine (20 mL, 16.2 g, 80.3 mmol, 2.5 equiv). The cooling bath was then removed, and the reaction mixture was stirred at room temperature for 16 h. after which time further tri-*n*-butylphosphine (20 mL, 16.2 g, 80.3 mmol, 2.5 equiv) was added. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography (20% methylene chloride in petroleum ether) to give the product **39** (26.61 g. 100% yield). **39**: white solid; mp 114–115 °C; R_f 0.34 (silica, 20% methylene chloride in petroleum ether); IR (film) ν_{max} 3080, 2960, 2940. 2860. 2240, 1590, 1475, 1430, 1210, 1120, 1000, 830, 750, 710, 620 cm^{-1}: ^1H NMR (250 MHz, $CDCl_3$) δ 7.67–7.61 (m, 8 H, Ar-*H*), 7.46–7.33 (m, 12 H. Ar-*H*). 3.79–3.77 (m. 6 H. BrCH_2 and O-CH_aH_b), 3.66 (dd, J = 10.2, 5.4 Hz, 2 H, O-CH_aH_b), 2.51–2.34 (m, 4 H, C≡CCH_2), 1.95 (m, 2 H, C*H*). 1.04 (s. 18 H. CH_3): HRMS for $C_{44}H_{54}Br_2O_4Si_2Na$ (M + Na), calcd 851.1750, found 851.1750.

(*R*,S)-6,7-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]thiacycloundeca-3,9-diyne (40).** A solution of **39** (8.10 g. 9.77 mmol) in methylene chloride (5 mL) was added to absolute ethanol (450 mL). To the resultant suspension was added a solution of sodium sulfide nonahydrate (16.297 g. 68 mmol, 6.9 equiv) in water (90 mL). The reaction mixture was rapidly heated and refluxed for 30 min. The heating bath was then removed. and the reaction mixture was stirred for an additional

30 min. It was then concentrated in vacuo to a volume of 50 mL and added to saturated aqueous NH_4Cl (150 mL) and ethyl ether (250 mL). The organic phase was washed with saturated brine (50 mL), and the combined aqueous phases were extracted with ethyl ether (100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (20 → 30% methylene chloride in petroleum ether) to give the product **40** (2.98 g, 44% yield) as well as starting material **39** (1.46 g). **40**: pale yellow oil; R_f 0.25 (silica, 25% methylene chloride in petroleum ether); IR (film) ν_{max} 3080. 2940, 2860, 2240, 1590, 1480, 1430, 1120, 910, 830, 740, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.67–7.63 (m, 8 H, Ar-*H*), 7.46–7.31 (m, 12 H, Ar-*H*), 3.73–3.65 (m, 4 H, O-CH_2), 3.32 (m, 4 H, S-CH_2). 2.44–2.26 (m, 4 H, C≡CCH_2), 2.00 (m, 2 H. C*H*), 1.02 (s, 18 H, CH_3); HRMS for $C_{44}H_{53}O_2SSi_2$ (M + H). calcd 701.3305, found 701.3327.

Sodium Sulfide on Alumina. To a solution of sodium sulfide nonahydrate (49.78 g. 207 mmol) in water (250 mL) was added basic alumina (Grade I. 50.063 g). The suspension was then concentrated in vacuo to give a free flowing grey-pink powder (92.22 g. 17.5% Na_2S by weight, 2.24 mmol/g).

(6*R,7*S**)-6,7-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]thiacycloundeca-3,9-diyne-1-oxide (41). Method A.** To a cooled (−30 °C) solution of compound **40** (8.92 g, 12.7 mmol) in methylene chloride (500 mL) was added *m*-chloroperbenzoic acid (2.606 g. 12.8 mmol, 1.01 equiv). After 40 min, methyl sulfide (2 mL) was added. and the reaction mixture was warmed to ambient temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (150 mL) and saturated brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (80 → 100% ethyl ether in petroleum ether) to give the product **41** as a mixture of diastereomers (8.23 g, 90% yield).

Method B. To a degassed solution of **39** (26.04 g, 31.4 mmol) in ethanol (175 mL) and methylene chloride (440 mL) was added sodium sulfide on alumina (5.428 g. 0.91 g/mmol). After stirring for 16 h, the reaction was concentrated in vacuo to a volume of 150 mL, washed with 5% aqueous K_2CO_3 (100 mL) and saturated brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in methylene chloride (500 mL) and cooled to −30 °C. To the resultant solution was added *m*-chloroperbenzoic acid (5.428 g. 31.4 mmol, 1.0 equiv). After 45 min. methyl sulfide (2 mL) was added. the cooling bath was removed, and the reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl acetate (300 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL) and saturated brine (100 mL), dried ($MgSO_4$). and concentrated in vacuo. The residue was purified by flash column chromatography (80→100% ethyl ether in petroleum ether) to give the product **41** as a mixture of diastereomers (17.99 g, 80% yield). **41**: white solid; mp 54–55 °C: R_f 0.28 (silica. 80% ethyl ether in petroleum ether); IR (film) ν_{max} 3080, 2940. 2860. 2240, 1590, 1480, 1430, 1120, 1065. 910, 830, 740, 700, 620 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.66–7.61 (m. 8 H, Ar-*H*), 7.46–7.34 (m. 12 H. Ar-*H*), 3.70–3.51 (m, 8 H, S-CH_2 and O-CH_2), 2.43–2.18 (m, 4 H, C≡CCH_2), 1.91 (m, 2 H, C*H*), 1.03 (s. 18 H. CH_3); HRMS for $C_{44}H_{53}O_3SSi_2$ (M + H), calcd 717.3254. found 717.3202.

(6*R,7*S**)-6,7-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-2-chlorothiacycloundeca-3,9-diyne-1-oxide (42).** To a cooled (−78 °C) solution of **41** (0.756 g. 1.05 mmol) and pyridine (0.30 mL, 290 mg, 3.7 mmol, 3.5 equiv) in methylene chloride (20 mL) was added sulfuryl chloride (0.10 mL, 160 mg. 1.2 mmol, 1.2 equiv). After 30 min. saturated aqueous NH_4Cl (3 mL) was added, and the cooling bath was removed. Upon warming to room temperature, the organic layer was washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (0 → 10% ethyl acetate in methylene chloride) to give the product **42** (601 mg. 76% yield). **42**: yellow oil; R_f 0.21 (silica, methylene chloride): IR (film) ν_{max} 3070. 2940. 2860, 2240, 1590. 1470. 1430. 1120, 1080. 910. 830. 740, 710, 615 cm^{-1}: ^1H NMR (250 MHz, $CDCl_3$) δ 7.64–7.61 (m, 8 H, Ar-*H*). 7.45–7.37 (m, 12 H, Ar-*H*), 5.45 (s, 1 H, Cl-C*H*), 4.12 (t, *J* = 15.4 Hz, 1 H, S-CH_aH_b). 3.73–3.34 (m, 5 H. O-CH_2 and S-CH_aH_b), 2.55–2.16 (m, 4 H. C≡CCH_2), 1.93 (m. 2 H, C*H*), 1.03 (s, 18 H. CH_3): HRMS for $C_{44}H_{51}ClO_3SSi_2Cs$ (M + Cs), calcd 883.1840, found 883.1840.

(6*R,7*S**)-6,7-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-2-chlorothiacycloundeca-3,9-diyne-1,1-dioxide (43).** To a cooled (0 °C) solution of compound **42** (4.33 g, 5.76 mmol) in methylene chloride (250 mL) was added *m*-chloroperbenzoic acid (3.017 g, 17.5 mmol, 1.4 equiv). The cooling bath was removed. and the reaction mixture was stirred for 16 h. Methyl sulfide (5 mL) was then added. and the reaction mixture was concentrated in vacuo. The residue was dissolved in ethyl ether (200 mL), washed with saturated aqueous $NaHCO_3$ (150 mL) and saturated brine (100 mL). dried ($MgSO_4$). and concentrated in vacuo to give the product **43** as a mixture of diastereomers (4.410 g, 99% yield). **43**: yellow solid; R_f 0.37 and 0.27 (silica, 20% ethyl ether in petroleum ether); IR (film) ν_{max} 3070, 2950, 2860, 2240, 1470, 1430, 1360, 1115, 820, 740, 700, 615 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.64–7.62 (m, 8 H, Ar-*H*), 7.45–7.33 (m, 12 H, Ar-*H*), 5.18 (s, 1 H, Cl-C*H*), 4.47 (m, 1 H, S-CH_aH_b). 3.77–3.58 (m, 5 H, S-CH_aH_b and O-CH_2), 2.60–2.19 (m, 4 H, C≡CCH_2), 1.96 (m, 2 H, C*H*), 1.03 (s, 18 H, CH_3); HRMS for $C_{44}H_{51}ClO_4SSi_2Na$ (M + Na). calcd 789.2633, found 789.2641.

(*R,*S**)1,2-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-cyclodeca-4,8-diyn-6-ene (44) and (*R**,*S**)4,5-Bis[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-1,2-diethynyl-2-cyclohexene (45).** To a cooled (−78 °C) solution of MeLi (1.29 M in ethyl ether, 0.40 mL, 0.52 mmol, 1.6 equiv) in ethyl ether (50 mL) was added compound **43** (250 mg, 0.33 mmol) in ethyl ether (10 mL). After 5 min, saturated aqueous NH_4Cl solution (5 mL) was added, and the cooling bath was removed. The organic layer was washed with saturated brine (10 mL), dried (Na_2SO_4). and concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (5% ethyl ether in petroleum ether) to give products **44** (32 mg, 15% yield) and **45** (49 mg, 23% yield). **44**: colorless oil; R_f 0.36 (silica, 5% ethyl ether in petroleum ether); IR (film) ν_{max} 3070, 2930, 2860, 2190, 1590, 1470, 1430, 1110, 820, 740, 700, 610 cm^{-1}; UV ($CHCl_3$) λ_{max} 261 (sh), 270, 286 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.61 (m. 8 H. Ar-*H*). 7.44–7.31 (m, 12 H, Ar-*H*), 5.79 (s, 2 H, C=C*H*), 3.79 (d, *J* = 6.8 Hz, 4 H, O-CH_2), 2.54 (m, 4 H, C≡CCH_2), 2.20 (m, 2 H, C*H*), 1.02 (s. 18 H, CH_3); HRMS for $C_{44}H_{50}O_2Si_2Cs$ (M + Cs), calcd 799.2404, found 799.2412. **45**: colorless oil: R_f 0.27 (silica, 5% ethyl ether in petroleum ether); IR (film) ν_{max} 3290, 3070, 2930, 2860, 2220, 1470. 1430, 1110, 820, 740, 700, 610 cm^{-1}; UV ($CHCl_3$) λ_{max} 264, 270 (sh), 280 (sh) nm; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.57 (m, 8 H, Ar-*H*), 7.41–7.28 (m, 12 H, Ar-*H*), 3.69–3.46 (m, 4 H, O-CH_2), 3.35 (s, 2 H, C≡C*H*), 2.51–2.03 (m, 6 H, C=CCH_2 and C*H*), 1.04 (s, 9 H, CH_3), 0.99 (s, 9 H, CH_3); HRMS for $C_{44}H_{50}O_2Si_2Cs$ (M + Cs), calcd 799.2404, found 799.2388.

(*R,*S**)6-Cyclodecene-4,8-diyne-1,2-dimethanol (47).** To a cooled (0 °C) solution of compound **44** (94.6 mg, 0.14 mmol) in THF (3 mL) was added tetra-*n*-butylammonium fluoride (1.0 M in THF. 0.44 mL, 0.44 mmol, 3.1 equiv). The reaction mixture was allowed to warm to ambient temperatures over 1 h. After stirring for a further 30 min, the reaction mixture was concentrated in vacuo. The residue was purified by preparative thin-layer chromatography (50% benzene in acetone) to give the product **47** (21.2 mg. 79% yield). **47**: colorless oil; R_f 0.24 (silica, 5% methanol in methylene chloride); IR (film) ν_{max} 3320, 2930, 2190, 1470, 1430, 1200, 1030, 735 cm^{-1}; UV ($CHCl_3$) λ_{max} 262 (sh), 270, 275 (sh), 286 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (s, 2 H, C=C*H*), 3.89 (dd. *J* = 10.3. 6.7 Hz, 2 H, O-CH_aH_b), 3.68 (dd, *J* = 10.3, 4.6 Hz. 2 H, O-CH_aH_b), 2.98 (s, 1 H, O*H*), 2.70 (dd, *J* = 18.2, 7.9 Hz, 2 H, C≡CCH_aH_b), 2.50 (dd, *J* = 18.1. 3.2 Hz, 2 H, C≡CCH_aH_b), 2.25 (m, 2 H, C*H*); HRMS for $C_{12}H_{14}O_2Na$ (M + Na), calcd 213.0892, found 213.0892.

Thermolysis of Cyclodeca-1,5-diyn-3-ene (47). *cis*-2,3-Bis(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (48) and Compounds 49a,b. A solution of **47** (38.0 mg, 0.20 mmol) in 1.4-cyclohexadiene (1.90 mL, 20.0 mmol) and degassed benzene (20 mL) was heated at 70 °C for 4 h. The reaction mixture was concentrated, and the residue was purified by preparative thin-layer chromatography (5% methanol in methylene chloride) to give 20.0 mg (52%) of **48** and 7.0 mg (14%) of **49a,b**. **48**:[24] while solid; mp 95–96 °C: R_f 0.23 (silica, 5% methanol in methylene chloride): ^1H NMR and IR are in accordance with the literature data.[25] HRMS for $C_{12}H_{16}O_2$ (M + H), calcd 193.1229, found 193.1229. **49a,b**: R_f 0.31 (silica, 5% methanol in methylene chloride): IR ($CHCl_3$) λ_{max} 3314 (br), 3015, 2919, 1702, 1583, 1459. 1217, 1040, 757, 665 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.22 (m, 1 H, Ar-*H*), 7.08 (m, 1 H, Ar-*H*), 6.94 (t, *J* = 3.6 Hz, 1 H, Ar-*H*), 6.07–5.62 (m, 4 H, C=C*H*), 4.19 (m, 0.5 H, C*H*). 3.86 (m. 0.5 H, C*H*), 3.84–3.61 (m, 4 H, O-CH_2), 2.97–2.58 (m. 8 H, O*H* and C=CCH_2). 2.29 (m, 2 H. C*H*); HRMS for $C_{18}H_{26}NO_2$ (M + NH_4), 288.1964, found 288.1962.

Kinetic Study of the Thermolysis of 47. Method A. Sealed tubes containing 50 μL of a solution of **47** (0.01 M). 1.4-cyclohexadiene (1 M), and hydrobenzoin (0.0014 M) in degassed benzene were prepared. The tubes were placed into an oven at 37.00 ± 0.01 °C and incubated. The products were analyzed on a Varian Model 5000 HPLC using a Partisil 10 column and 7% isopropyl alcohol in hexane as eluent with UV detection (274 nm). Digital integration of the peaks was performed and the ratios relative to hydrobenzoin were determined. The different absorbances of **48** and the internal standard were taken into account by calibration with authentic samples.

Method B. A freshly prepared sample of **47** (2.0 mg) in THF-d_8 (0.5 mL) was charged in a NMR tube and heated at the indicated temperature. The reaction course was followed by ^1H NMR spectroscopy with use of benzene as the internal standard. The rate constants obtained at

37, 45, 50, and 60 °C for the decomposition of **47** are given in Table IV.

DNA Cleavage. All DNA cleavage experiments were performed with ΦX174 DNA (50 μM/base pair) in a pH 8.5 Tris-acetate buffer (50 mM). The results were analyzed using 1% agarose gel electrophoresis and detection with ethidium bromide fluorescence. Figure 2 shows the pictures of the agarose gel electrophesis results.

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Determination of the Absolute Stereochemistry of Nemadectins α_2 and α

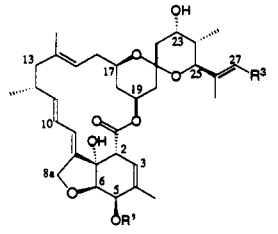
Lee-Chiang Lo,[†] Nikolina Berova,[†] Koji Nakanishi,*[,†] Gerhard Schlingmann,[‡] Guy T. Carter,[‡] and Donald B. Borders*[,‡]

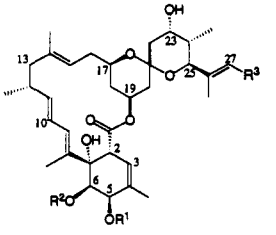
Contribution from the Department of Chemistry, Columbia University, New York, New York 10027, and American Cyanamid Co., Medical Research Division, Pearl River, New York 10965. *Received March 11, 1992*

Abstract: The CD exciton chirality method has been applied to determine the absolute configuration of the nemadectins (formerly LL-F28249 series). The CD spectra of the 5-benzoates **6** and **7** of nemadectins α (**1**) and α_2 (**5**), respectively, show that both have *R* configurations at C-5. Furthermore, what appears to be the short-wavelength wing of a split CD due to an exciton-coupled allylic benzoate system has been observed for the first time at ca. 190 nm. The CD of the 5,6-bis(*p*-methoxycinnamate) 23-acetate (**9**) of nemadectin α_2 also shows that the C-5 and C-6 configurations are both *R*. The consistent results from both approaches establish the absolute configuration of this important group of antiparasitic agents.

Introduction

Nemadectins represent a new family of macrocyclic lactones possessing potent antiparasitic activity against a broad spectrum of endo- and ectoparasites of mammals. Isolation and structures of the four principal nemadectins, α (**1**), β (**2**), λ (**3**), and γ (**4**), were reported previously.[1,2] The nemadectins are distinguished





(1) R^1 = H, R^3 = *i*-Pr (α)
(2) R^1 = H, R^3 = Me (β)
(3) R^1 = Me, R^3 = *i*-Pr (λ)
(4) R^1 = Me, R^3 = Me (γ)
(5) R^1 = H, R^2 = H, R^3 = *i*-Pr (α_2)
(6) R^1 = Bz, R^3 = *i*-Pr
(7) R^1 = Bz, R^2 = H, R^3 = *i*-Pr
(9) R^1 = R^2 = *p*-MeO-Cn, R^3 = *i*-Pr (-OAc instead of -OH at C-23)

from the avermectins[3] and the milbemycins[4] by the presence of unsaturated side chains at C-25 and by the hydroxyl group at C-23. Nemadectin α differs from nemadectin β by having an isopropyl rather than a methyl group at C-27, while nemadectin λ and nemadectin γ are their respective 5-methoxy derivatives. The main congener, nemadectin α, is currently used as starting material for the production of commercial moxidectin (Cydectin) used in veterinary medicine.

Extracts from fermentation broths of *Streptomyces cyaneogriseus* ssp. *noncyanogenus* contain numerous nemadectins, most of which have been isolated and characterized.[5] Of these, we have selected nemadectins α and α_2 (**1** and **5**) for absolute configurational studies by the CD exciton chirality method.[6] The conformation and relative configuration of nemadectin α_2 have also been determined by X-ray crystallography.

Results and Discussion

The structures of nemadectins α and α_2 suggest the possibility of applying two different approaches in the exciton chirality method for elucidation of the absolute stereochemistry, namely, the allylic benzoate method[7] to the allylic alcohol systems composed of the 3-ene/5-hydroxyl in α and α_2 and the biscinnamate method[8] to the 5,6-glycol moiety in nemadectin α_2. In the allylic benzoate method, it has been demonstrated that (i) in both cyclic[7a] and acyclic systems,[7b] the long-axis π-π* electric transition moment

[†] Columbia University.
[‡] American Cyanamid Co.

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