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Synthesis and Investigations of Enetetraynes

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Abstract: Several enetetrayne containing compounds have been synthesized and their chemistry explored vis-a-vis the Bergman cycloaromatization. With one exception the compounds were unreactive along this pathway. AM1 calculations were performed in order to gain further insights into these reactions. The results indicate that the strain of constraining the resulting benzodiyne in a small ring raises the energy of the transition state of the initial Bergman reaction.

Introduction In recent years much attention has been focused on the enediyne antibiotics. This class of compounds includes the calicheamicins,[1] esperamicins,[2] neocarzinostatin chromophore,[3] kedarcidin,[4] C-1027 chromophore,[5] and dynemicin A[6] (Figure 1). It is postulated that after suitable activation steps these toxins undergo a Bergman rearrangement to yield an aromatic 1,4 diradical,[7] which is capable of generating oxidative lesions on DNA leading ultimately to strand scission and cell death.[8]

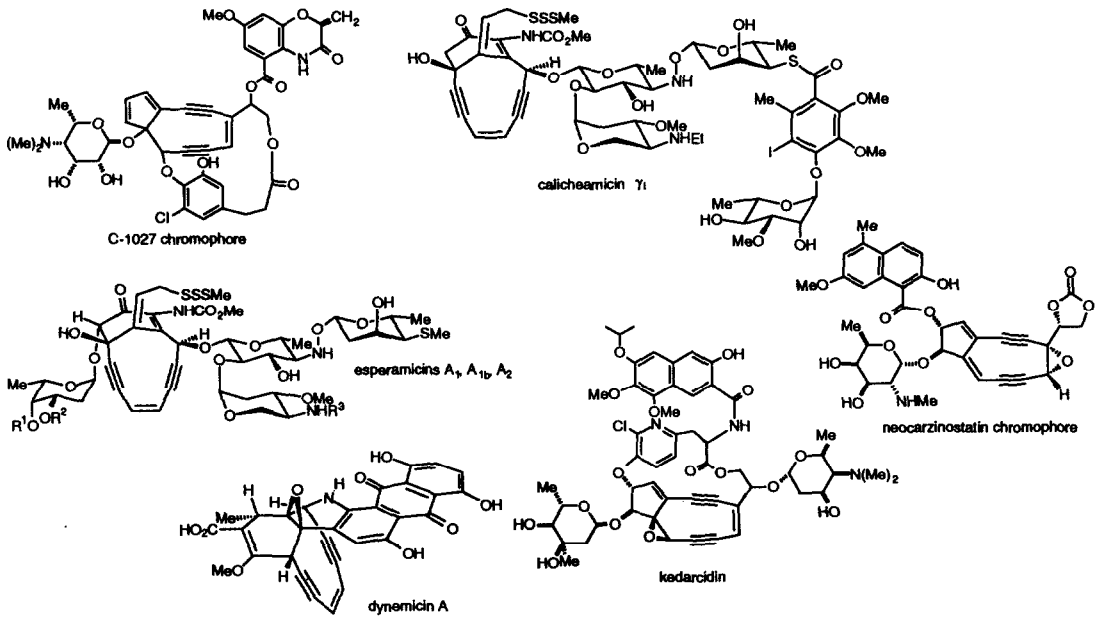
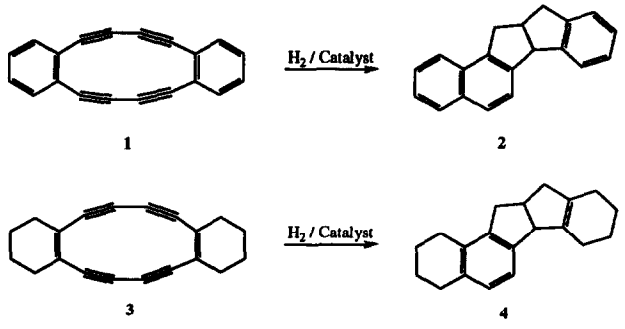


Figure 1 Structures of Members of the Enediyne Class of Antibiotics.

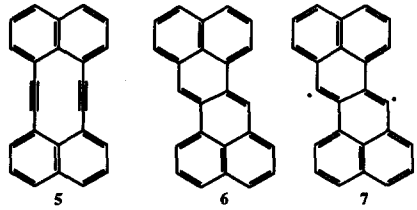
During the course of our synthetic studies on dynemicin A we became intrigued by several reports in the literature of diynes and tetraynes. Some of these structures were shown to undergo transannular bond formation, presumably via radical intermediates. In particular, Behr *et al.*[9] reported the construction of compound **1** (Scheme I). Although this material does not undergo a Bergman cyclization, presumably due to the strain that would develop in the transition state, an attempt to hydrogenate the four acetylenes gave the expected bis-butane product in only 50% yield. An additional 40% of the starting material was converted into compound **2**, the product of transannular bond formation. In addition, Pilling and Sondheimer[10] found similar results in their attempt to hydrogenate **3**, giving in this case compound **4**.

Scheme I



1 2 3 4

Moreover, both Sondheimer[11] and Staab[12] attempted to construct compound **5** (Figure 2). However, they were able to obtain only compound **6**, which they pointed out could arise from diradical **7**. They were unable to provide any direct evidence for this diradical.



5 6 7

Figure 2 Transannular chemistry of rigid acetylenes.

Two interesting X-ray structures of enetetraynes have been reported. In 1959, Grant and Speakman[13] published an X-ray derived electron density map of compound **1**. Despite the fact that no model was constructed, it is apparent that the acetylenes are fairly close together. Recently, Diederich and co-workers[14] reported an X-ray structure of compound **8** (Figure 3), which has the same cyclic core structure seen in compound **1**.

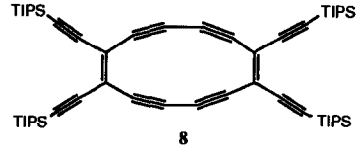


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Figure 3 Newest cyclodienetetrayne.

In light of the fascinating chemistry of acetylenes in close proximity, we set out to investigate the effect of introducing additional acetylenes onto an enediyne. Originally our studies focused on enetetraynes **9** and **10** (Figure 4). Our studies further expanded to encompass compounds **11** and **12.** As a number of highly unsaturated natural products, including polyacetylenes,[15] are known, it is not beyond the realm of possibility that similar structures may be found in nature.

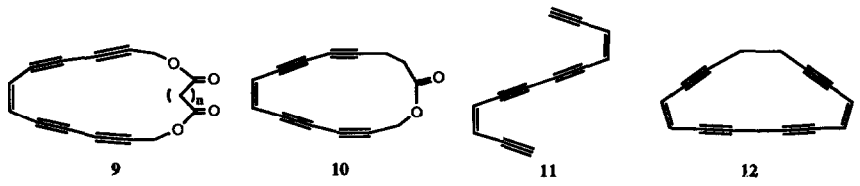
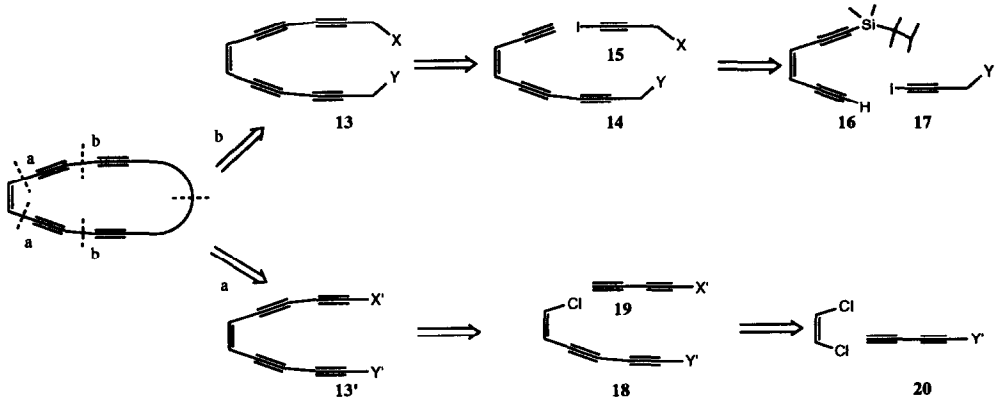


Figure 4 Target Structures

Results and Discussion

Synthesis We envisioned two possible routes to the basic enetetrayne framework (Scheme II). The diynes could be introduced as a single unit (path a) or by construction onto an already existing enediyne (path b). Path a was favored initially, however, studies using the known monotrimethylsilyl 1,4-butadiyne, **19**[16] (X'=TMS) proved fruitless. Recourse was then sought in path b.

Scheme II



The optimisation studies of the coupling reaction described in eq 1 are outlined in Table I. Initially conditions originally developed by Cadiot and Chodkeiwcz for the production of unsymmetrical diynes were tested.[17, 18] These proved to be somewhat disappointing. Recourse was then sought in a palladium and copper catalyzed process that has recently been used for acetylene couplings.[19, 20] Variation of the palladium catalyst led to the use of bis-benzylideneacetone palladium and tri(2-furyl)phosphine.[21] The optimal solvent was determined to be benzene.

As compounds of the general form of **9** seemed to provide us with the greatest flexibility with regard to ring size, we elected to attempt their construction first. The synthesis (Scheme III) began with the coupling of the known monosilyl enediyne[22] with the known iodoacetylene derived from tetrahydropyranyl propargyl alcohol[23] under the conditions described above.

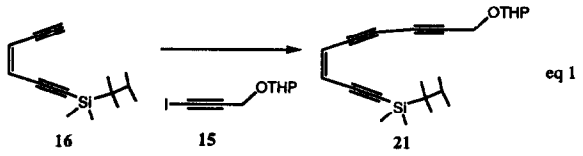
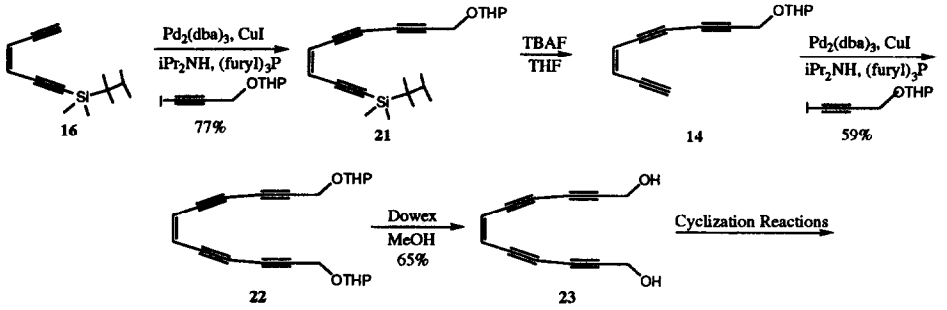


Table I

Catalyst	Additives	Solvent	Yield (%)	Ref.
CuCl	NH_2OH-HCl, $BuNH_2$	EtOH	15	18
$(Ph_3P)_4Pd$, CuCl	NH_2OH-HCl, $BuNH_2$	EtOH	0	this work
$(Ph_3P)_2PdCl_2$, CuI	iPr_2NH	THF	12	19
$(CH_3CN)_2PdCl_2$, CuI	iPr_2NH	Benzene	52	20
$Pd_2(dba)_3$, CuI	iPr_2NH, $(furyl)_3P$	Benzene	77	this work

Deprotection of the silyl acetylene **21** using tetrabutylammonium fluoride (TBAF) provided the enetriyne **14** in 85-90% yield.[24] With the terminal acetylene in hand we again applied the palladium and copper catalyzed coupling procedure, which provided the desired enetetrayne.

Scheme III



Our first attempts at removing the tetrahydropyranyl (THP) groups using trifluoroacetic acid in chloroform-water led to rapid decomposition of the enetetrayne. However, Dowex resin (50W x 8; HCl form) accomplished the desired transformation in 65% yield. With the desired diol enetetrayne **23** in hand, our efforts focused on the requisite macrocyclization reaction. These reactions are summarized in Table II.

It was believed that the length of the bridging group could be adjusted from 5-7 atoms by the construction of the carbonate, oxalate, or malonate respectively. Just and Singh[25] demonstrated that the corresponding enediyne systems can be constructed. Attempts to produce the carbonate or oxalate proved unrewarding. Only starting material and a baseline spot by TLC, believed to be due to the diester, were observed. Despite these negative results we were nevertheless encouraged, as they indicated that the diyne was somewhat rigid. This, in turn, would lead to structures, which when cyclized, would have their diyne moieties in close proximity. Treatment of the diol with malonyl dichloride in methylene chloride using pyridine as base gave the desired cyclic

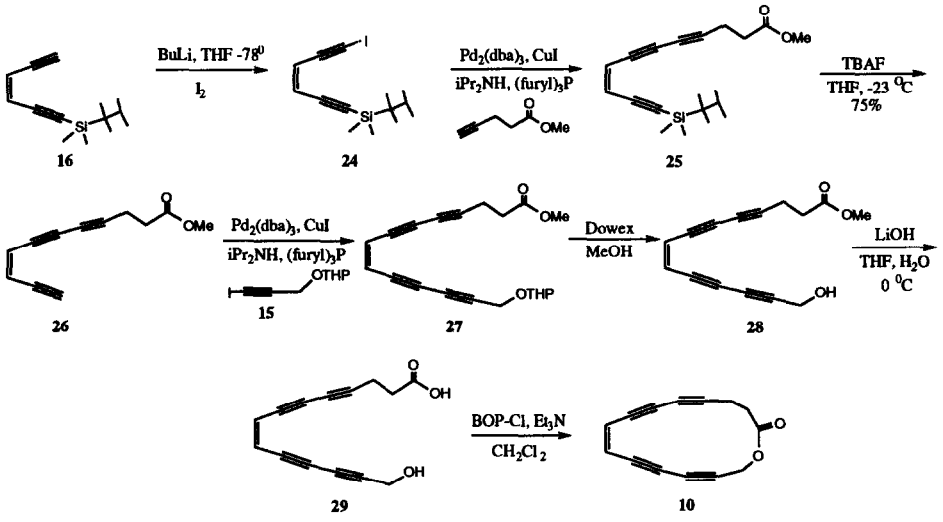
enetetrayne **9** (n=1) with varying amounts of starting material recovered. The yield of product did not exceed 25%, however, the total mass balance was on the order of 90%.

TABLE II

Coupling Agent	Base	Yield(%)
1,1'-Carbonyl Diimidazole	Pyridine	0
Oxalyl chloride	Pyridine	0
Malonic Dichloride	Pyridine	25

In order to overcome the difficulty in producing the enetetrayne with a five atom spacer we elected to change the ring closure reaction. We envisioned that a lactonization, in which the activating agent could be used in excess, would serve the purpose. We thus set out to construct compound **10**. Again we chose to introduce additional acetylenes onto a preexisting enediyne. However, the iodoacetylene from methyl-4-pentynoate was difficult to produce due to the acidity of the protons α to the carbonyl. It thus became apparent that one of the couplings would have to involve an iodoacetylene either on the enediyne or enetriyne as one of the components. Accordingly, we first investigated the iodination of **14** (the chemistry to which had already been developed, see Scheme III). Ultimately, this proved to be quite difficult. Our troubles were attributed to the acidity of the propargylic hydrogens. This route was abandoned in favor of the route described in Scheme IV.

Scheme IV



In the event, iodoenediyne **24** was produced in 93% yield from 1-thexyldimethylsilyl-3-ene-1,5-hexadiyne by treatment of the latter with butyl lithium and iodine in THF at -78 °C. Coupling to methyl-4-pentynoate using the previously described palladium(0) and copper(I) catalyzed conditions produced enetriyne **25** in 69% . Removal of the silyl group proved to be troublesome. Under the usual conditions (TBAF, THF, 0 °C) the reaction gave not the desired product but instead a compound whose ^{1}H NMR spectrum is consistent with **30**

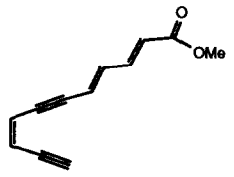


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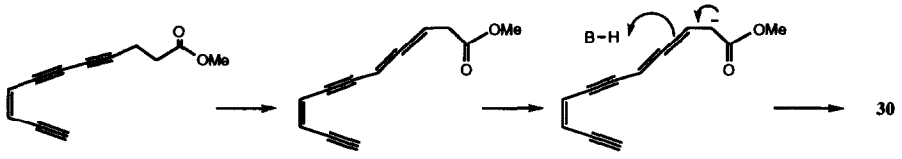
Figure 5 Fluorescent side product from deprotection reaction.

(Figure 5). This compound presumably arose by the mechanism described in Scheme V. Rearrangement to the allene followed by deprotonation of the methylene α to the ester and reprotonation to give the most extended π system would yield the product shown.

Scheme V



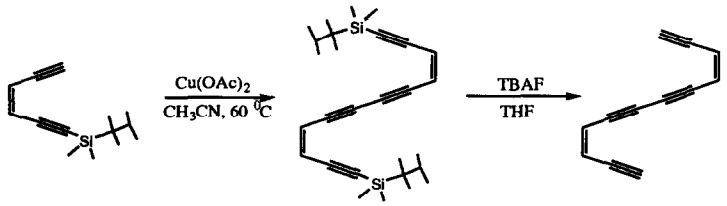
Examination of the literature provided other examples of rearrangments of diynes to dieneynes under basic conditions.[26] This unwanted side reaction could be suppressed, often completely, by running the reaction at -23 °C instead of 0 °C. Most important was the use of a fresh source of TBAF, which reduces the amount of hydroxide to which the compound is exposed.

Elaboration of the enetriyne **26** was now effected by its coupling to the iodoacetylene **15**. Deprotection of both the hydroxyl and carboxylate under standard conditions then provided the seco acid **29**. Lactonization using N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic (BOP) chloride and triethylamine in methylene chloride[27] gave the desired cyclic enetetrayne **10** in good yield.

Given the observed inability of the compounds thus far examined to undergo a Bergman cyclization (see below) we began to investigate whether there was some property of the diyne moiety that might prevent this rearrangement. In order to test this hypothesis we sought to construct compound **11**. Although this structure has been previously described,[28] its thermal reactivity has not been investigated.

The synthetic strategy was straightforward. Our approach began with enediyne **16**, which was dimerized readily to **31** via treatment with cupric acetate.[26, 29] Deprotection with TBAF followed by rapid work-up yielded the unstable compound **11** as an oil (Scheme VI). Within several hours a black precipitate, presumably a polymerization product, formed.

Scheme VI

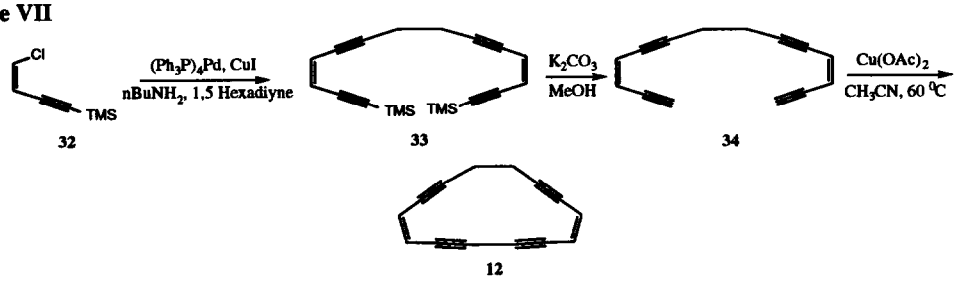


16 31 11

We envisioned the possiblity that one additional molecule might possess the properties we sought: compound **12**. Once again the synthesis was straightforward (Scheme VII). The known

trimethylsilylchloroeneyne **32**[30] could be coupled to 1,5-hexadiyne under standard palladium(0) and copper(I) catalysis.[31] The resulting bis-enediyne was deprotected with potassium carbonate in methanol to yield the acyclic material **34**, which was immediately subjected to cupric acetate, acetylene-coupling conditions[26, 29] to affect a cyclization. The desired compound was isolated as a dark solid, which proved to be shock sensitive. Scraping with metal or glass utensils invariably led to an explosive decomposition.

Scheme VII

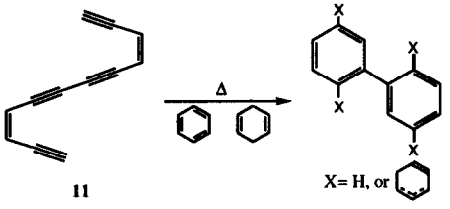


Thermolysis Studies In an attempt to induce the synthetic enetetraynes to undergo a Bergman cycloaromatization, they were individually heated in benzene in the presence of 1,4-cyclohexadiene. Compounds **9** and **10** both proved to be disappointing. In both cases, only starting material and an insoluble solid could be recovered from the reaction mixture. NMR analysis revealed the absence of aromatic signals. In addition, mass spectral analysis of the crude material showed no ions with the mass of the aromatized product. When compound **12** was subjected to these conditions, despite its shock sensitivity, only insoluble decomposition products were produced (without explosion).

In order to try to enhance the reactivity of compound **10** we attempted to introduce unsaturation α to the carbonyl. Darby *et al.* previously reported[32] a compound in which the introduction of a double bond in the starting material facilitates the Bergman cyclization, presumably by increasing the strain of the ground state relative to the transition state. Unfortunately, attempts to introduce unsaturation using either selenation-oxidation,[33] or Saegusa conditions[34] were unsuccessful.

Compound **11** proved to be the most interesting one. When heated in refluxing benzene the majority of the starting material was consumed. The NMR of the reaction mixture showed numerous aromatic peaks. In order to further analyze this mixture, the crude material was subjected to GC/MS. The results showed that biphenyl, the product of two Bergman reactions was present, albeit in low yield. Numerous other products showed parent ions that indicate the incorporation of one or more cyclohexadienes onto the biphenyl nucleus. (See Scheme VIII)

Scheme VIII



Calculations Our search for an explanation for the lack of reactivity along the Bergman pathway focused on the strain introduced into the diyne portion of the compounds by virtue of their ring constraints. Previous studies by Snyder,[35] and Magnus and co-workers[36] have suggested that the propensity for an enediyne to undergo a Bergman reaction is dependent upon the difference in strain between the ground state and the transition state. In general, the more strain present in the ground state the faster the cycloaromatization is expected to be. For

example, as the ring size of simple cyclic enediynes decreases, and therefore the strain of the ground state increases, the rate of cyclization increases.[37] However, in bicyclic model and natural systems the strain that would be introduced in the transition state leading to the aromatic nucleus is sufficient to prevent the Bergman reaction. An example is the enone of calicheamicin. The presence of the olefin inhibits the Bergman cyclization because it would occupy a bridgehead position in the product, a position known to be unfavorable for double bonds.

It has also been established that sp hybridized carbons tend to have fairly low bending force constants.[38] The bond angles of these carbons can be deformed readily to as far as 165°. The best examples that demonstrate the ease of deformation are the crystal structures of compounds **1**, **3**, and **8**. Moreover, each of these compounds was constructed accidentally during attempts to produce the trimers of the diynes from which they are derived. Despite the fact that the trimers are predicted to have bond angles at the sp carbons of 180°, the dimers with bent acetylenes are the major products.[9, 10, 14] Futhermore, the enediyne antibiotics, which possess ten membered cyclic enediynes (calicheamicin, esperamicin, and dynemicin A), have sp bond angles on the order of 170°. Given the above information we believed that it would be possible for the enetetraynes to undergo at least one Bergman cycloaromatization. We envisioned that the low energy vibrational modes of the acetylenes would provide access to varied conformations at minimal energetic expense.

In order to investigate this further, calculations using the AM1 protocol with 3X3 configuration interaction were performed.[39, 40] Specifically, compounds **10** and **11** were modeled. The calculations were performed starting from the appropriate singlet radical and then lengthening the bond formed in the Bergman reaction. This allows determination of the free energy of formation for the various radical species, the transition states, and the starting materials. The results are summarized in Figures 6 and 7.

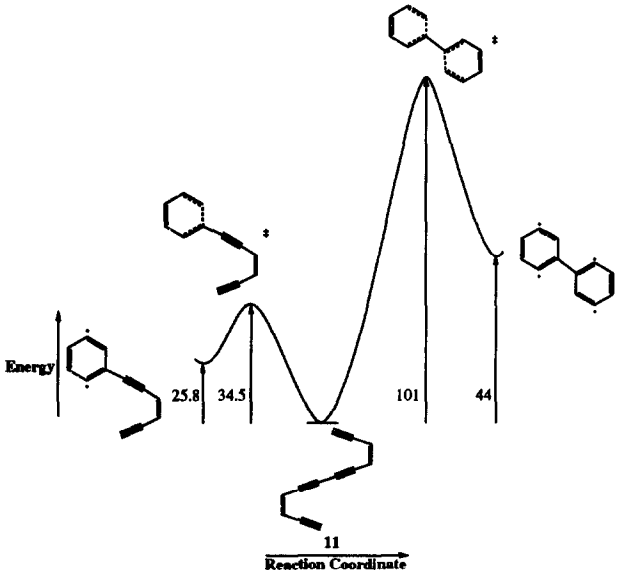


Figure 6 Calculated energy profile for compound **11** (Energy in kcal/mole).

Of the two compounds examined, only the acyclic species **11** is predicted to cyclize. The activation energy for a single cycloaromatization in this system is 34.5 kcal/mole. This is in close agreement with the experimental activation energy for the cyclization of 3-hexen-1,5-diyne, which is 32 kcal/mole.[7b] Interestingly,

although the observed product could have been produced by either simultaneous or sequential single cycloaromatization events, the calculations indicate that the activation energy for the simultaneous cyclization is 101 kcal/mole. We therefore believe that the biphenyl produced in this reaction arose from 2 individual cyclizations.

As the activation energy for the simultaneous process is much higher than anticipated it is worthy of comment. Although the calculation may have over estimated the magnitude of this energy, we believe that it is significantly higher than that of the single process. One possible explanation focuses on the direction of deformation of the diyne. In the previous systems which contain deformed diynes (compounds **1**, **3**, and **8**) the deformation was such that the diyne begins to resemble a *Z, Z* diene. In compound **11** the deformation leads ultimately to an *E, E* diene-like structure. Despite the low bending force constant for an individual sp carbon, deformations resulting in *E, E*-like dienes may be energetically more costly. This can be seen to a small extent in the bending modes of acetylene. Infrared and Raman spectroscopy reveals that the bend toward a *Z* olefin is active at a longer wavelength than the one leading to an *E* olefin.[38]

For compound **10** the situation is more complex. Again the calculated energy required for double cycloaromatization is well above that for the first single cyclization (97.3 and 43.3 kcal/mole respectively). The question arises as to what may be the origin of the additional 11.3 kcal/mole for the first cyclization. In previous studies of enediynes the relative energies of the transition states have been rationalized based on the differential strain between the ground state and the transition state.[35, 36] In those cases there were usually large energetic penalties (eclipsed ethane like, or syn-pentane like) that were apparent. In our system, there is no such obvious interaction (Figure 8); thus, the increased ring strain owing to the placement of the benzodiyne in an eleven-membered ring appears to be the retarding factor. This is revealed by a deformation of the ester in the transition state lactone. In the ground state the dihedral angle at the ester (C2-C1-O15-C14) is calculated to be 166°. In the transition state, the angle is calculated to be -149°. The additional 17 degrees of deformation may account for some of the energy, but it should be well short of the total. (A crude estimate of the energy contribution can be made by solving the equation E ≅ [cos(17)]10 kcal/mole, where 10 kcal/mole is taken to be the barrier to rotation of an ester.)

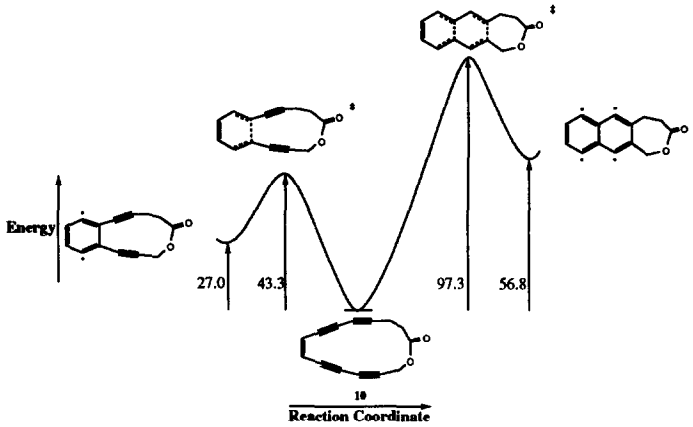


Figure 7 Calculated energy profile for compound **10** (Energy in kcal/mole)

The increased strain is also apparent in the developing aromatic ring. In the prototypical Bergman cyclization of 3-hexene-1,5-diyne, the transition state is reached when C1 and C6 are 1.902 Å apart.[41] In the case of compound **10**, however, the transition state is not reached until the bonding carbons are 1.796 Å from one another. Thus, we conclude that the tether forces the bonding carbons apart. In order to pass over the energy

barrier the developing bond must be more completely formed than in the simpler system. The shortening of the bond length also translates into deviations in the bond angles at C6 and C7 as compared to the corresponding carbons in the prototypical reaction. All of these effects conspire to raise the energy of the transition state to a point where other pathways (decomposition) become more favorable.[42]

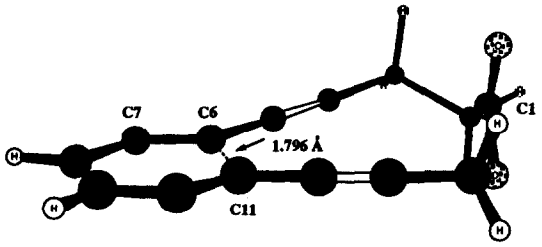


Figure 8 Chem 3D representation of calculated transition state for the first Bergman cyclization of compound **10**

Conclusions Several novel enetetraynes and related analogs have been synthesized and investigated. Although one compound was found to be explosive, the anticipated Bergman chemistry was not evident in these systems. Enhanced strain in the transition state is apparent in the AM1 calculations, and this strain is suggested to be responsible for the unexpected lack of reactivity in the compounds reported in this study.

Experimental Section

General Experimental Methods

Procedures All reactions were performed in flame or oven-dried glassware under a positive pressure of nitrogen or argon. Air and moisture sensitive compounds were introduced via syringe or cannula through a rubber septum. Cooling was performed using the following baths: Ice-water (0 °C), dry ice-carbon tetrachloride (-23 °C), dry ice-acetone (-78 °C).

Physical Data Melting points were measured with a Mel-Temp apparatus and are uncorrected. Infrared spectra (IR) were recorded using a Nicolet 5PC FT-IR spectrometer (υ max. in cm^{-1}). Bands are characterized as strong(s), medium(m), and weak(w). Samples were prepared as thin films by evaporation onto a salt plate (NaCl), or as solutions in noted solvents using a NaCl solution cell. ^1H NMR spectra were recorded on either a Bruker AM-500 (500 MHz) or AM-400 (400 MHz) spectrometer as noted at ambient temperature. Data are reported as follows: chemical shift in ppm using residual protio solvent as internal standard (7.24 for $CDCl_3$ and 3.30 for CD_2HOD) on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant(s) in Hz, and integration. ^{13}C NMR spectra were recorded on a Bruker AM-500 (125 MHz) or AM-400 (100 MHz) spectrometer and are reported in ppm using solvent resonance as internal standard (77.0 for $CDCl_3$, and 47.0 for CD_3OD). All ^{13}C spectra were determined with complete proton decoupling. Mass spectra were obtained using either a JEOL AX-505 or SX-102 instrument in the Harvard University Mass Spectrometry Laboratory by Dr. Andrew N. Tyler and Ms. Laura Romo. UV-Vis spectra were obtained using an HP8452A UV-Vis spectrophotometer.

Chromatography Analytical thin layer chromatography (TLC) was performed using EM reagent 0.25mm silica gel 60-F plates. Components were visualized by illumination with ultraviolet light (254nm) and by staining with one of the following reagents: p-anisaldehyde in ethanol-sulfuric acid; 7% phosphomolybdic acid in ethanol; ceric ammonium molybdate in 10% sulfuric acid; or potassium permanganate in water. Preparative TLC was performed using EM 0.5 mm silica gel 60-F plates which were preeluted with the indicated solvent. Flash column chromatography was performed as previously described.[43] High performance liquid chromatography (HPLC) was performed using a Waters 510 liquid chromatograph equipped with a μ porasil column (1 x 25 cm).

Solvents and Reagents Solvents were distilled and/or stored over 4 Å molecular sieves prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium metal/benzophenone ketyl. Acetonitrile, triethylamine, diisopropylamine, and benzene were distilled from calcium hydride. Methanol was distilled from $Mg(OMe)_2$. Methylene chloride was distilled from phosphorous pentoxide. Organolithium

reagents were titrated against 2,6-di-*tert*-butyl-4-methylphenol in ether at 0 °C using 1,10 phenanthroline as indicator. Bis-acetonitrile palladium (II) chloride was prepared by refluxing palladium (II) chloride in acetonitrile.[44] Tetrakistriphenylphosphine palladium (0) was prepared according to the *Inorganic Synthesis* procedure.[45] Bisdibenzylideneacetone palladium (0) was obtained from the Lancaster company and used without further purification. Deuterochloroform was stored over granular anhydrous potassium carbonate. All other reagents were used as obtained from commercial sources or purified according to standard procedures.[46]

Computational methods Semiempirical quantum mechanics (AM1) calculations with configuration interaction (CI) were performed for compounds **10** and **11**. The geometries of the molecules and their radicals were optimized. Transition structures were calculated by lengthening the appropriate internuclear distances of the singlet radicals as the reaction coordinate. These transitions structures were then optimised by freezing the appropriate distances while the remainder of the molecule was relaxed.

1-Thexyldimethylsilyl-hex-1, 5-diyne-3-ene (16) 6.8 mL of the supernatant from a 5% potassium carbonate in methanol suspension was added to a solution of 1-Trimethylsilyl-6-thexyldimethylsilyl enediyne (2 g, 6.9 mmols, 1 equiv) in 10 mL of methanol. The reaction was stirred at rt for 20-30 min. The reaction was diluted with hexane and water, and the aqueous layer was washed 3 times with hexane, and the combined organic layers were dried with magnesium sulfate filtered and concentrated *in vacuo*. Spectral data match those obtained from other preparative methods. The crude material was used directly.

9-Thexyldimethylsilyl-non-2, 4, 8-triyne-6-ene-1-tetrahydropyranyl ether (21) Thexyldimethylsilyl enediyne **16** (6.9 mmol, 1 equiv used directly from the deprotection) was dissolved in 60 mL of benzene. Diisopropyl amine (1.7 mL, 12.4 mmol, 1.8 equiv) and copper iodide (26.6 mg, 0.14 mmol, 0.02 equiv) were added. The solution was degassed with argon in the dark for 20 min. In a separate flask the iodoacetylene (1.8g, 6.9 mmols, 1 equiv) was degassed similarly in 10 mL of benzene with a small volume (<0.1 mL) of diisopropyl amine. Trifuryl phosphine (138.7 mg, 0.6 mmol, 0.08 equiv) and bisdibenzylidenacetone palladium (64 mg, 0.07 mmol, 0.02 equiv in palladium) were added to the enediyne solution. The iodoacetylene solution was then added via syringe pump over 2 h, and stirring was continued for an additional 10 h. The dark suspension was diluted with hexane and stirred for 30 min. The suspension was filtered through a pad of celite, and the collected filtrate was washed with saturated ammonium chloride until the aqueous layer was no longer blue (at least 3 times) and once with brine. The resulting yellow organic phase was dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude dark oil was purified by chromatography (SiO_2, 1% ethyl acetate/hexane) to yield 1.97 g (80%) of the product as a dark yellow oil.: R_F 0.34 (10% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (d, J=11 Hz, 1H), 5.81 (d, J=11 Hz, 1H), 4.80 (t, J=3 Hz, 1H), 4.38 (s, 2H), 3.81 (tdd, J=3, 2, 9 Hz, 1H), 3.52 (m, 1H), 1.79 (m, 1H), 1.70 (m, 2H), 1.59 (m, 2H), 1.51 (m, 2H), 0.92 (s, 6H), 0.90 (d, J=6 Hz, 6H), 0.18 (s, 6H,); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123, 119, 105, 103, 97, 81, 80, 75, 70, 62, 55, 35, 30, 25, 23, 20, 19, 18; IR (neat) 2957, 2869, 1466, 1358, 1345, 1252, 1202, 1121, 1080, 1057, 1040, 1026, 943, 903, 872, 839, 818, 777, 745, 675 cm^{-1}; UV-Vis (c=1.1exp-6, $CHCl_3$) λ_{max} 240 (110000), 278 (158000) nm; MS (CI) *m/e* calc'd for $C_{22}H_{36}NO_2Si$: 374.2516, found 374.2537; 374 ($[M+NH_4]^+$).

Nona-2, 4, 8-triyne-6-ene-1-tetrahydropyranyl ether.(14) Thexyldimethylsilyl enetriyne **22** (1.97 g, 5.5 mmol, 1 equiv) was dissolved in 30 mL THF, and cooled to 0 °C. 6.5 mL of a 1 M solution of tetrabutylammonium fluoride (6.5 mmol, 1.2 equiv) was added slowly. The reaction turns black. After stirring for 20 min at 0 °C the reaction was quenched with saturated ammonium chloride and diluted with ether. After being warmed to rt the ethereal layer was washed twice with water and once with brine. The combined aqueous layers were washed once with ether. The combined ether was dried with magnesium sulfate, filtered, and the solvent removed *in vacuo*. Purified by chromatography (SiO_2, 5% ethyl acetate./hexane) to yield 863 mg (4.02 mmol, 73%) of the product as a yellow oil which darkens quickly.: R_F 0.24 (10% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.9 (d, J=2 Hz, 2H), 4.8 (t, J=3 Hz, 1H), 4.3 (d, J=2 Hz, 2H), 3.8 (m, 1H), 3.5 (m, 1H), 3.4 (d, J=2 Hz, 1H), 1.8 (m, 2H), 1.6 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 122, 120, 97, 86, 82, 81, 80, 75, 70, 62, 55, 30, 25, 19; IR (neat) 3293, 2946, 2872, 2853, 2225, 2137, 2093, 1441, 1345, 1264, 1202, 1183, 1121, 1078, 1057, 1024, 966, 943, 901, 870, 816, 748, 639 cm^{-1}; UV-Vis (c=2.33exp-5, $CHCl_3$) λ_{max} 258 (3800), 272 (6900), 288 (12000), 306 (12000) nm; MS (CI) *m/e* calc'd for $C_{14}H_{18}NO_2$: 232.1338, found 232.1334; 232 ($[M+NH_4]^+$).

Dodeca-2, 4, 8,10-tetrayne-6-ene-1,12-bis-tetrahydropyranyl ether (22) Enetriyne **14** (863 mg, 4.02 mmol, 1 equiv), diisopropyl amine (1.0 mL, 7.4 mmol, 1.8 equiv), and copper iodide (15.6 mg, 0.082 mmol, 0.02 equiv)

were dissolved in 40 mL of benzene, and degassed with argon in the dark for 20 min. In a separate flask the iodoacetylene **16** (1.09 g, 4.02 mmol, 1 equiv) was dissolved in 7.5 mL of benzene with a small volume (<0.1 mL) of diisopropyl amine, and similarly degassed. After degassing, trifuryl phosphine (76.6 mg, 0.33 mmol, 0.08 equiv) and bisdibenzylydeneacetone palladium (37.5 mg, 0.041 mmol, 0.02 equiv in palladium) were added to the acetylene solution. The iodoacetylene solution was added via syringe pump over 3 h. and the reaction was stirred in the dark for an addtional 5 h. The dark suspension was diluted with chloroform and washed three times with saturated ammonium chloride. The combined aqueous layers were back extracted once with chloroform. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude dark oil was purified by chromatography (SiO_2, 10% ethyl acetate/hexnae) to yield 845 mg (2.4 mmol, 59%) of the product as an orange brown oil.: R_F 0.47 (30% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.9 (s, 2H), 4.8 (t, J=4 Hz, 2H), 4.4 (s, 4H), 3.8 (m, 2H), 3.5 (m, 2H), 1.8 (m, 4H), 1.6 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121, 97, 83, 82, 75, 70, 62, 55, 30, 25, 19; IR (neat) 2944, 2870, 2851, 2226, 2133, 1455, 1441, 1387, 1343, 1264, 1202, 1183, 1121, 1078, 1057, 1026, 966, 941, 901, 870, 816, 743 cm^{-1}; UV-Vis (c=8.5exp-6, $CHCl_3$) λ_{max} 244 (4500), 314 (16000), 334 (18000) nm; MS (CI, NH_3) *m/e* calc'd for $C_{22}H_{28}NO_4$: 370.2018, found 370.2007; 370 ([M+NH_4]$^+$), 286 ([M-THP+NH_4]$^+$), 202 ([M-2THP+NH_4]$^+$).

1,12-Dihydroxy-dodeca-2, 4, 8,10-tetrayne-6-ene (23) The bistetrahydropyranyl enetetrayne **22** (845 mg, 2.4 mmol, 1 equiv) was dissolved in 24 mL of methanol, and Dowex resin (50w X 8 HCl form, 1.2 g, 1.5 wt. equiv) was added. The suspension was stirred vigorously for 4 h at rt. Filtration to remove the resin, and removal of solvent at reduced pressure provided the crude product. Purification by chromatography (SiO_2, 40% ethyl acetate/hexane) yielded 266 mg (1.4 mmol, 58%) of the product as a white solid.: m.p. 90° (dec.); R_F 0.1 (30% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, CD_3OD) δ 6.0 (s, 2H), 4.2 (s, 4H), 4.1 (s, 1H, OH); ^{13}C NMR (125 MHz, CD_3OD) δ 123, 86, 82, 76, 69, 51; IR (Nujol) 3195, 2726, 2675, 1460, 1377, 1350, 1262, 1248, 1219, 1181, 1026, 970, 901, 739, 723, 666 cm^{-1}; UV-Vis (c=1exp-6, $CHCl_3$) λ_{max} 234 (42000), 312 (105000), 334 (120000) nm; MS (CI, NH_3) *m/e* calc'd for $C_{12}H_{12}NO_2$: 202.0868, found 202.0885; 202 ([M+NH_4]$^+$).

Malonyl Enetetrayne (9, n=1) The diol **23** (24.7 mg, 0.13 mmol, 1 equiv) was azeotroped with xylenes and then dissolved in 13 mL of methylene chloride. Pyridine (0.21 mL, 2.6 mmol, 20 equiv) was added and the solution was cooled to 0 °C. Freshly distilled malonyl dichloride (0.125 mL, 1.3 mmol, 10 equiv) was added dropwise. The reaction was stirred at 0 °C until TLC showed no starting material (approximately 1 h) and then 15 min at rt. The reaction was quenched with saturated ammonium chloride, and diluted with ether. The ethereal solution was washed with saturated ammonium chloride, and the combined aqueous layers were washed twice with ether. The resulting ethereal solution was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude material was purified by preparative thin layer chromatography (SiO_2, 50% ethyl acetate/hexane) to yield 7.2 mg (0.03 mmol, 23%) of the product as an off white solid.: R_F 0.64 (50% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 6.0 (s, 2H), 4.8 (s, 4H), 3.4 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165, 124, 83, 80, 78, 72, 54, 41; IR (neat) 3056, 2946, 2134, 1740, 1426, 1362, 1273, 1256, 1183, 1146, 995, 976, 735 cm^{-1}; UV-Vis (c=6.55exp-5, $CHCl_3$) λ_{max} 246 (5500), 318 (14000), 340 (15000) nm; MS (EI) *m/e* calc'd for $C_{15}H_8O_4$: 252.0423, found 252.0428; 252 ([M]$^+$).

6-Iodo-1-thexyldimethylsilyl-hexa-1, 5-diyne-3-ene. (24) Butyl lithium (7.6 mL of a 2.5 M solution in hexane, 18.9 mmols, 1.1 equiv) was added dropwise to a solution of thexyldimethylsilyl enediyne **16** (17.2 mmols, 1 equiv) in 86 mL of THF at -78 °C. The dark solution was stirred at -78 °C for 45 min. A solution of iodine (4.8 g, 18.9 mmols, 1.1 equiv) in a minimum volume of THF was added via canulla, and stirring was continued for an additional 45 min at -78 °C. The reaction was quenched with saturated ammonium chloride and warmed to rt. Ether was added, and the dark solution was extracted twice with saturated sodium thiosulfate, once with sodium bicarbonate, and once with brine. The organic layer was dried with magnesium sulfate, filtered and the solvent was removed *in vacuo*. The resulting oil (93% yield) was used without further purification.

11-Thexyldimethylsilyl methyl undeca-4, 6, 10-triyne-8-enoate (25) To a solution of methyl-4-pentynoate (773.5mg 6.9 mmols, 1 equiv) in 61 mL of benzene was added diisopropyl amine (1.7 mL 12.4 mmols 1.8 equiv) and copper iodide (399 mg 2.1 mmols 0.3 equiv). The solution was degassed with argon for 20 min. A solution of iodoenediyne (**24**) (6.9mmols) in 10 mL benzene, with a small volume (<0.1 mL) of diisopropyl amine, was simultaneously degassed with argon. Bisdibenzylideneacetone palladium (64 mg 0.7 mmols 0.2 equiv in palladium)and trifuryl phoshine (139.2 mg 0.6 mmols 0.8 equiv) were added to the acetylene solution in the dark.

The iodoendiyne solution was added via syringe pump over 2.5 h in the dark, and stirring was continued for 1 h. The brown solution was diluted with hexane and stirred for 20-30 min. A precipitate was apparrent. The suspension was filtered through celite, and the filtrate was extracted with saturated ammonium chloride until the aqueous layer no longer appeared blue (at least three times). The combined aqueous extracts were washed with hexane, and the resulting organic solution was subsequently washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed at reduced pressure to yield a brown oil. Purification by chromatography over silica gel eluting with a gradient of 4-6% ethyl acetate/hexane gave a brown oil in 69% yield.: R_F 0.27 (10% Ethyl Acetate/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (d, J=10 Hz, 1H), 5.78 (d, J=10 Hz, 1H), 3.69 (s, 1H), 2.66 (t, J=7 Hz, 2H), 2.56 (t, J=7 Hz, 2H), 1.7 (m, 1H), 0.90 (s, 6H), 0.88 (d, J=5 Hz, 6H), 0.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172, 123, 119, 104, 103, 85, 82, 73, 66, 52, 35, 33, 23, 21, 19, 16; IR (neat) 3025, 2959, 2869, 2334, 2141, 1744, 1464, 1437, 1420, 1393, 1377, 1364, 1333, 1296, 1252, 1200, 1169, 1130, 1090, 1038, 976, 941, 876, 839, 820, 777, 747, 693, 675, 608 cm^{-1}; UV-Vis (c=1.8exp-5, $CHCl_3$) λ_{max} 240 (7900), 280 (12000), 298 (24000), 316 (26000) nm; MS (CI NH_3) *m/e* calc'd for $C_{20}H_{32}NO_2Si$: 346.2202, found 346.2187; 346 (100).

Methyl undeca-4, 6, 10-triyne-8-enoate (26) The enetriyne **25** (1.56g, 4.76 mmols, 1 equiv) was dissolved in 23 mL THF, and then cooled to -23 °C. Tetrabutyl ammonium fluoride (4.76 mL of a 1M solution in THF, 1 equiv) was added dropwise. The solution turned black before addition was complete. After being stirred at -23 °C for 20 min the reaction was quenched with saturated ammonium chloride, and warmed to rt. It was diluted with ether and the organic layer was washed with saturated ammonium chloride, water, and brine. The organic solution was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The crude oil was purified by chromatography over silica gel eluting with 8% ethyl acetate/hexane to give a dark yellow oil 63% yield. : R_F 0.21 (10% Ethyl Acetate/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (s, 2H), 3.69 (s, 3H), 3.40 (s, 1H), 2.66 (t, J=8 Hz, 2H), 2.56 (t, J=8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172, 121, 120, 86, 85, 82, 80, 72, 66, 52, 33, 16; IR (neat) 3455, 3291, 3048, 3002, 2953, 2847, 2233, 2093, 1734, 1568, 1437, 1420, 1393, 1366, 1296, 1252, 1204, 1171, 1035, 1003, 988, 939, 922, 882, 833, 777, 748, 644 cm^{-1}; UV-Vis (c=4exp-5, $CHCl_3$) λ_{max} 272 (8000), 288 (15000), 306 (15000) nm; MS (EI) *m/e* calc'd for $C_{12}H_{10}O_2$: 186.0681, found 186.0683; 186 (100), 155 (25), 126 (35), 115 (50).

Methyl tetradeca-4, 6, 10, 12-tetrayne-8-enoate-14-tetrahydropyranyl ether (27) A solution of enetriyne **26** (564.5 mg, 3 mmols, 1 equiv), diisopropyl amine (0.75 mL, 5.4 mmols, 1.8 equiv), and copper iodide (11.4 mg, 0.06 mmols, 0.2 equiv) in 26 mL benzene was degassed for 20 min with argon. Simultaneuosly a solution of iodoacetylene **15** (798.6 mg, 3 mmols, 1 equiv) in 5 mL benzene was similarly degassed. Bisbenzylideneacetone palladium (27.5 mg, 0.03 mmols, 0.2 equiv in palladium) and trifuryl phosphine (55.7 mg, 0.24 mmols, 0.8 equiv) were added to the enetriyne solution in the dark. The iodoacetylene was added via syringe pump over 2.5 h in the dark, and stirring was continued for 1 h after completion of the addition. The brown solution was diluted with hexane and stirred for 20-30 min. A precipitate formed. The suspension was filtered through a pad of celite, and the filtrate was extracted with saturated ammonium chloride until the aqueous layer no longer appeared blue (at least three times if no blue color was apparrent). The combined aqueous extracts were washed with hexane, and the combined organic layers were subsequently washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed at reduced pressure to yield a brown oil. The crude material was purified by chromatography over silica gel eluting with 15% ethyl acetate/hexane. The pure oil was isolated in 43% yield.: R_F 0.18 (20% Ethyl Acetate/Hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 2H), 4.80 (s, 1H), 4.40 (s, 2H), 3.80 (m, 1H), 3.69 (s, 3H), 3.50 (m, 1H), 2.68 (t, J=7 Hz, 2H), 2.58 (t, J=7 Hz, 2H), 1.75 (m, 2H), 1.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172, 122, 121, 97, 86, 83, 82, 81, 75, 72, 70, 66, 62, 55, 52, 33, 30, 25, 19, 16; IR (neat) 2950, 2872, 2851, 2234, 2140, 1740, 1455, 1437, 1389, 1364, 1345, 1323, 1298, 1285, 1262, 1248, 1202, 1173, 1121, 1078, 1057, 1028, 1003, 941, 903, 872, 745 cm^{-1}; UV-Vis (c=1.5exp-5, $CHCl_3$) λ_{max} 244 (4200), 295 (10000, sh), 314 (22000), 336 (25000) nm; MS (EI) *m/e* calc'd for $C_{20}H_{20}O_4$: 324.1361, found 324.1376; 324 (70), 240 (50), 223 (60), 181 (100), 152 (90).

14-Hydroxy-methyl-tetradeca-4, 6, 10, 12-tetrayne-8-enoate (28) The enetetrayne **27** (427 mg, 1.3 mmol, 1 equiv) was dissolved in 20 mL methanol. 640 mg (1.5 wt. equiv) of Dowex 50W x 8 resin (HCl form) were added. The reaction was stirred vigorously at rt for 3 h. The reaction was filtered and the solvent removed *in vacuo*. The crude material was purified by chromatography on silica gel (30% ethyl acetate:hexane), and the product (yellow solid) was isolated in 92% yield.: R_F 0.1 (50% Ethyl Acetate:Hexane); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 5.93 (s, 1H), 5.92 (s, 1H), 4.40 (d, J=6 Hz, 2H), 3.70 (s, 3H), 2.68 (t, J=8 Hz, 2H), 2.55 (t, J=8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172, 122, 121, 86, 84, 83, 81, 76, 72, 70, 66, 51.9, 51.7, 33, 16; IR (neat) 3214, 2232, 1736, 1671, 1572, 1435, 1375, 1304, 1281, 1248, 1219, 1204, 1181, 1167, 1028, 988, 978, 968, 920, 884, 776, 739, 712, 667 cm^{-1}; MS (EI) *m/e* calc'd for $C_{15}H_{12}O_3$: 240.0796, found 240.0790; 240 ($[M]^+$).

14-Hydroxy-tetradeca-4, 6, 10, 12-tetrayne-8-enoic acid (29) Lithium hydroxide (144 mg, 6 mmols, 5 equiv) was added to a solution of hydroxyester **28** (293.5 mg, 1.2 mmols 1 equiv) in 12 ml of 3:1 methanol:water. The solution was stirred in a 4 °C cold room overnight. The reaction was warmed to rt, and diluted with 1.2 M hydrochloric acid. The aqueous layer was washed three times with ether, and the ethereal extracts were washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed at reduced pressure. The crude solid was purified by chromatography over silica gel eluting with 60% ethyl acetate/hexane. A pure white solid, which goes dark on prolonged exposure to light was obtained in 77% yield.: m.p. 120° (dec.); R_F 0.1 (50% Ethyl Acetate/Hexane); ^1H NMR (500 MHz, CD3OD) δ 5.95 (s, 1H), 4.23 (s, 2H), 2.57 (t, J=7 Hz, 2H), 2.47 (t, J=7 Hz, 2H); ^{13}C NMR (125 MHz, CD3OD) δ 175, 123, 122, 88, 86, 83, 82, 76, 73, 70, 66, 51, 34, 16; IR ($CHCl_3$) 3034, 2928, 2674, 2234, 1727, 1383, 1231, 1204, 1134, 1051, 1017, 895, 798 cm^{-1}; UV-Vis (c=7.96exp-6, MeOH) λ_{max} 210 (79000), 222 (82000), 294 (26000, sh), 310 (42000), 332 (46000) nm; MS (EI) *m/e* calc'd for $C_{14}H_{10}O_3$: 226.0630, found 226.0619; 226 (100, $[M]^+$), 208 (65, $[M-H_2O]^+$), 163 (65), 152 (75).

Lactone (10) The seco acid **29** (57.5 mg, 0.25 mmol, 1 equiv) was dissolved in a small volume of ethyl acetate. The solution was diluted with 250 mL of dichloromethane. Triethylamine (0.24 mL, 1.75 mmol, 7 equiv.) was added followed by BOP-Cl (190.9 mg, 0.75 mmol, 3 equiv). The reaction was stirred overnight. The solvent was removed under reduced pressure. Purification by chromatography over silica gel (20% ethyl acetate:hexane) gave a white solid in 24% yield.: m.p. 115° (dec.); R_F 0.8 (50% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (d, J=9 Hz, 1H), 5.91 (d, J=9 Hz, 1H), 4.8 (s, 2H), 2.7 (bs, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170, 122 (121), 86, 83, 81, 79, 76, 72, 71, 66, 53, 32, 15; IR ($CHCl_3$) 2930, 2857, 1746, 1381, 1352, 1292, 1248, 1159, 1049, 909 cm^{-1}; UV-Vis (c=3.6exp-5, $CHCl_3$) λ_{max} 232 (2700), 244 (2900), 295 (5000, sh), 314 (8200), 334 (7800) nm; MS (EI) *m/e* calc'd for $C_{14}H_8O_2$: 208.0524, found 208.0498; 208 ($[M]^+$).

1, 12-Bisthexyldimethylsilyl-dodeca-1, 5, 7, 11-tetrayne-3, 9-diene (31) Cupric acetate (2.974 g, 14.9 mmol, 9 equiv) was dissolved in 16 mL acetonitrile. The blue solution was heated to 60 °C. Thexyldimethylsilylenediyne **16** (361.7 mg, 1.66 mmols, 1 equiv) was added in a small volume of acetonitrile, and the reaction was stirred at 60 °C for 2 h. The reaction was cooled and the brownish solution was diluted with water and hexane. The aqueous layer was washed 3 times with hexane. The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. After the solvent was removed *in vacuo*, the crude brown oil was purified by chromatography over silica gel (2% ethyl acetate:hexane) to give a yellow oil (245.7 mg, 0.57 mmol, 67% yield).: R_F 0.56 (5% Ethyl Acetate:Hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 5.94 (d, J=10 Hz, 2H), 5.89 (d, J=10 Hz, 2H), 1.69 (m, 2H), 0.92 (s, 12H), 0.91 (d, J=8 Hz, 12H), 0.19 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123, 119, 105, 81.5, 81.2, 35, 24, 21, 19, -3; IR (neat) 2959, 2867, 2149, 1671, 1464, 1408, 1379, 1250, 1198, 1130, 1078, 1053, 1015, 930, 874, 837, 818, 775, 743, 675 cm^{-1}; MS (EI) *m/e* calc'd for $C_{28}H_{42}Si_2$: 434.2825, found 434.2819; 434 ($[M]^+$).

Dodeca-1, 5, 7, 11-tetrayne-3, 9-diene (11) The bissilyl dienetetrayne **31** (247.5 mg, 0.57 mmol, 1 equiv) was dissolved in 6 mL of THF, and cooled to 0 °C. Tetrabutylammonium fluoride (1.2 mL, 1.0 M in THF, 2.1 equiv) was added, and the reaction stirred for 20 min. Saturated ammonium chloride was added, and the cold solution was immediately extracted 2 times with pentane. The combined organic layers were dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure without heating. The crude material was purified by chromatography over silica gel (pentane with less than 1% ether). The resulting dark oil must be used immediately. Storage in solution in the dark for more than several hours was impossible.: R_F 0.56 (5% Ethyl Acetate:Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.99 (d, J=11 Hz, 2H), 5.94 (dd, J=2, 11 Hz, 2H), 3.45 (d, J=2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122, 120, 87, 81, 80.9, 80.4; IR (neat) 3300, 2200, 2100, 750, 620 cm^{-1}; MS (EI) *m/e* calc'd for $C_{12}H_6$: 150.0469, found 150.0474; 150 ($[M]^+$).

1, 14-Bisthexyldimethylsilyl-tetradeca-1, 5, 9, 13-tetrayne-3, 11-diene (33) Tetrakistriphenyphosphine palladium (490.5 mg, 0.43 mmol, 0.02 equiv), and butylamine (1.7 mL, 17 mmol, 2 equiv) were added to a solution of the known chloroeneyne (1.348 g, 8.5 mmol, 2 equiv) in 32 mL benzene. The solution was degassed

with argon in the dark for 20 min. Copper iodide (323 mg, 1.7 mmol, 0.2 equiv) and 1,5-hexadiyne (0.5 mL of a 50% v/v solution in hexane, 4.25 mmol, 1 equiv) were added. The reaction was stirred in the dark for 7 h. The dark brown solution was diluted with hexane and stirred for 20 min; after which it was filtered through a pad of celite. The filtrate was washed with saturated ammonium chloride until the aqueous layer no longer appeared blue (at least 3 times) then with brine. The organic layer was dried with magnesium sulfate, filtered, and the solvent removed *in vacuo*. The crude dark oil was purified by chromatography over silica gel (pentane to 1% ether: pentane gradient) to give a yellowish white solid in 33% yield.: m.p. 32-34°; R_F 0.4 (5% Ethyl Acetate:Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (d, J=11 Hz, 2H), 5.76 (d, J=11 Hz, 2H), 2.68 (s, 4H), 0.2 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121, 119, 102.3, 102, 97, 79, 20, -0.1; IR (neat) 3044, 3029, 2959, 2899, 2216, 2141, 1682, 1570, 1426, 1408, 1393, 1337, 1250, 1140, 1020, 953, 841, 760, 700, 633 cm^{-1}; MS (EI) *m/e* calc'd for $C_{20}H_{26}Si_2$: 322.1573, found 322.1566; 322 ([M]$^+$), 307 ([M-CH3]$^+$), 249 ([M-TMS]$^+$).

Cyclotetradeca-1, 5, 7, 11-tetrayne-3, 9-diene (12) Bistrimethylsilyldienetetrayne **33** (503.6 mg, 1.6 mmol, 1 equiv) was dissolved in 4.6 mL methanol; 3.2 mL of the supernatant from a 5% suspension of potassium carbonate in methanol (1 mL per mmol) was added. The reaction was stirred at rt for 1 h. The solution was diluted with water and pentane. The aqueous layer was washed 2 times with pentane. The combined organic layers were dried with magnesium sulfate, filtered, and the solvent removed under reduced pressure without heating. The resulting bis terminal diyne was immediately added to a solution of cupric acetate (2.875 g, 14.4 mmol, 9 equiv) in 140 mL acetonitrile at 60 °C. The reaction was stirred at 60 °C for 2 h, then cooled to rt, and diluted with 500 mL of water. The aqueous solution was extracted 2 times with pentane. The pentane was dried over magnesium sulfate, fitered and the solvent removed as above. The crude oil was purified by chromatography over silica gel (1% ether:pentane). The yellow-white solid product was isolated in 47% yield. **Caution: physical agitation (scraping) of the product results in explosive decomposition.**: R_F 0.38 (10% Ethyl Acetate:Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.0 (d, J=10 Hz, 2H), 5.6 (d, J=10 Hz, 2H), 2.7 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127, 119, 99, 87, 83, 79, 19; IR ($CDCl_3$) 3054, 2913, 2253, 2205, 2186, 2130, 1711, 1667, 1543, 1427, 1339, 1321, 1196, 1124 cm^{-1}; MS (EI) *m/e* calc'd for $C_{14}H_8$: 176.0626, found 176.0611; 176 ([M]$^+$).

Thermolysis Studies The appropriate compounds were dissolved in benzene at 0.01 M. Ten equivalents of 1,4-cyclohexadiene were added. The solution was heated to temperatures ranging from 37 to 200 °C. After 6-24 h the solvent was removed and the residue was examined by NMR and/or mass spectrometry. If no reaction was apparent the sample was directly resubjected to the reaction conditions at a higher temperature.

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References

[1] For a review of the chemistry and biology of the calichemicins see: Lee, M.D.; Ellestad, G.A.; Borders, D.B. *Acc. Chem. Res.* **1991**, *24*, 235

[2] Esperamicins A_1, A_2, A_{1b}: Golik, J.;Dubay, G.; Groenewold, G.; Kawaguchi, H; Konishi, M.;Krishnan, B.; Ohkuma, H.; Doyle, T.W. *J. Am. Chem. Soc.* **1987**, *109*, 3462

[3] Neocarzinostatin (a) Goldgerg, I.H. *Acc. Chem. Res.***1991**, *24*, 191 and references cited therein; (b) Myers, A.G.; Proteau, P.J. *J. Am. Chem. Soc.* **1989**, *111*, 1146.

[4] Kedarcidin: (a) Isolation: Lam, K.S.; Hesler, G.A.; Gustavson, D.R.; Crosswell, A.R.; Veitch, J.M.; Forenza, S.; Tomita, K. *J. Antibiot.* **1991**, *44*, 472. (b) Structure: Leet, J.E.; Schroeder, D.R.; Hofstead, S.J.; Golik, J.; Colson, K.L.; Huang, S.; Klohr, S.E.; Doyle, T.W. *J. Am. Chem. Soc.* **1992**, *114*, 7946

[5] C-1027 chromophore: (a) Isolation: Hu, J.; Xue, Y.-C.; Xie, M.-Y.; Zhang, R.; Otani, T.; Minami, Y.; Yamada, Y.; Marunka, T. *J. Antibiot.* **1988**, *41*, 1575. (b) Structure: Yoshida, K.; Minami, Y.; Azuma, R.; Mayuko, S.; Otani, T. *Tet. Lett.* **1993**, *34*, 2637

[6] Dynemicin A: (a) Isolation: Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G.D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Structure: Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G.D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

[7] Jones, R.R. and Bergman, R.G. *J. Am. Chem. Soc.* **1972**, *94* , 660; Bergman, R.G. *Accts. Chem. Res.* **1973**, *6*, 25 and references cited therein.

[8] For an outstanding review of the chemistry and biology of enediyne antibiotics see: Nicolaou, K.C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.
[9] Behr, O.M.; Eglington, G.; Galbraith, A.R.; Raphael, R.A. *J. Chem. Soc.* **1960**, 3614.
[10] Pilling, G.M.; Sondheimer, F. *J. Am. Chem. Soc.* **1971**, *93*, 1970.
[11] Mitchell, R.H.; Sondheimer, F. *Tetrahedron* **1970**, *26*, 2141.
[12] Staab, H.A.; Nissen, A.; Ipaktschi, J. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 226.
[13] Grant, W.K.; Speakman, J.C. *Proc. Chem. Soc.* **1959**, 231.
[14] Anthony, J.; Knobler, C.B.; Diederich, F. *Angew. chem. Int. Ed. Engl.* **1993**, *32*, 406.
[15] Bohlmann, F. Chapter 14 in *Chemistry of Acetylenes* Viehe, H.G. ed. Marcel Dekker, New York, **1969**.
[16] Holmes, A.B.; Jennings-White, C.L.D.; Schuthess, A.H. *J. Chem. Soc. Chem. Comm.* **1979**, 840.
[17] (a) Chodkiewicz, W.; Alhuwalia, J.S.; Cadiot, P.; Willemart, A. *Compt. Rend.* **1957**, *245*, 322 (b) Cadiot, P.; Chodkiewcz, W. Chapter 9 in *Chemistry of Acetylenes* Viehe, H.G. ed. Marcel Dekker, New York, **1969**.
[18] Carpita, A.; Rossi, R.; Veracini, C.A. *Tetrahedron*, **1985**, *41*, 1919.
[19] Wityak, J.; Chan, J.B. *Syn. Comm.*, **1991**, *21*, 977.
[20] Mhaskar, S.Y.; Lakshminarayana, G. *Tet. Lett.*, **1990**, *31*, 7227.
[21] (a) Farina, V.; Baker, S.R.; Sapino, C. Jr.; *Tet. Lett.* **1988**, *29*, 6043. (b) Farina, V.; Baker, S.R.; Benigni, D.A.; Hauck, S.I.; Sapino, C. Jr. *J. Org. Chem.* **1990**, *55*, 5833.
[22] Porco, J.A. Jr. Ph. D. Thesis, Harvard University, **1992**.
[23] Sundberg, R.J.; Pearce, B.C. *J. Org. Chem*, **1982**, *47*, 725.
[24] The variablity of this reaction has been traced to the age of the bottle of TBAF. This finding suggests that the compound may be base labile, presumably due to a deprotonation at the propargylic postion or allene formation followed by decomposition.
[25] Just, G.; Singh, R. *Tet. Lett.* **1987**, *28*, 5981.
[26] Sondheimer, F.; Wolovsky, R. *J. Am. Chem. Soc.* **1962**, *84*, 260 and references cited therein.
[27] Diago-Msequer, J.; Palomo-Coll, A.L.; Fernandez-Lizarbe, J.R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.
[28] Pilling, G.M.; Sondheimer, F. *J. Am. Chem. Soc.* **1971**, *93*, 1977.
[29] Berscheid, R.; Vogtle, F.; *Synthesis* **1992**, 58
[30] Kende, A.S.; Smith, C.A. *Tetrahedron Lett.*, **1988**, *29*, 4217.
[31] Guillerm, D.; Linstrumelle, G. *Tet. Lett.* **1985**, *26*, 3811.
[32] Darby, N.; Kim, C.U.; Salaun, J.A.; Shelton,K.W.; Takada,S.; Masamune, S. *Chem Comm.* **1971**, 1516
[33] Reich, H.J.; Renga, J.M.; Reich, I.L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
[34] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
[35] (a) Snyder, J.P. *J. Am Chem. Soc.* **1989**, *111*, 7630. (b) Snyder, J.P. *J. Am. Chem. Soc.* **1990**, *112*, 5367
[36] (a) Magnus, P.; Lewis, R.T.; Huffman, J.C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (b) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J.P. *J. Am. Chem. Soc.* **1990**, *112*, 4986.
[37] Nicolaou, K.C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E.J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.
[38] Dale, J. Chapter 1 in *Chemistry of Acetylenes* Viehe, H.G. ed. Marcel Dekker, New York, **1969**. The bending force constant for an sp carbon is given as 0.24×10^{-11} dyne-cm/rad. This corresponds to an energy of 1.8 kcal/mol per radian deformation. The analogous constant for an sp^3 carbon is 0.66×10^{-11} dyne-cm/rad.
[39] (a) Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M.J.S.; Healy, E.F.; Holder, A.J.; Yuan, Y.S. *J. Comput. Chem.* **1990**, *11*, 541. (c) Stewart, J.P.P. *ibid*, **1990**, *11*, 543. (d) Stewart, J.P.P. MOPAC Version 6.0 1989.
[40] For other calculatôns on systems related to enediynes see Koga, N.; Morokuma, K. *J..Am. Chem. Soc.*,**1991**, *113*, 1907.
[41] Nguyen, T.B.; Jorgensen, W.L. unpublished results.
[42] In addition to the strain arguement it may be that, as this system has the possibility for greater electron delocalization than the prototypical enediyne, the ground state is electronically stabalized with respect to the transition state. A similar effect has been observed with benzene and athracene diynes Nicolaou, K.C.; Hong, Y.-P.; Torisawa, S.-C. T.; Dai, W.-M. *J. Am. Chem. Soc.* **1991**, 113, 9878.
[43] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923.
[44] cf. Parker, K.A.; O'Fee, R.P. *J. Org. Chem.* **1983**, *48*, 1547.
[45] Coulson, D.R. *Inorg. Syn.* **1972**, *13*, 121.
[46] Perrin, D.D.; Amarego, W.L. *Purification of Laboratory Chemicals*, 3rd ed. Pergamon: Oxford, England, **1988**.

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