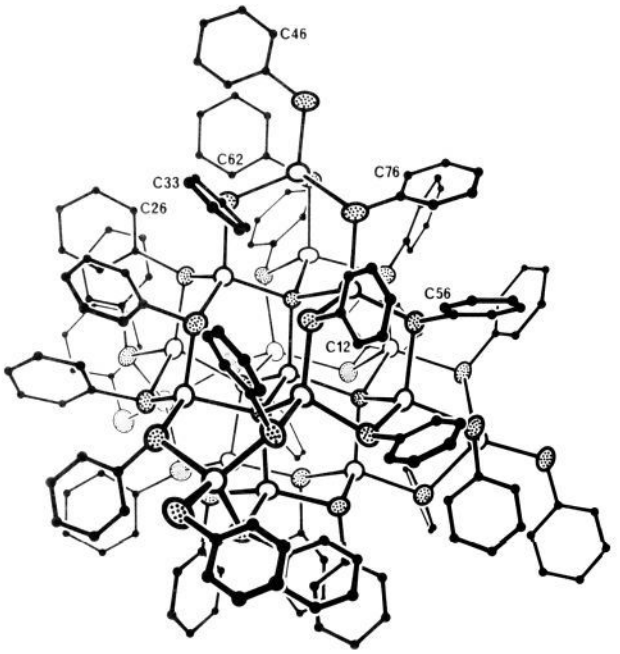

Figure 2. The actual structure of **6**. All S atoms are marked as dotted ellipsoids, all Cd atoms as open ellipsoids, and all phenyl carbon atoms drawn as small circles. Mean values of bond lengths (Å, [sample standard deviations]) are as follows: Cd^{i}–S^{2-}, 2.497; S^{2-}–Cd^{c}, 2.53 [2]; Cd^{c}–S^{c}, 2.52 [4]; Cd^{c}–S^{o}, 2.52 [2]; Cd^{o}–S^{o}, 2.556 [9]; Cd^{o}–S^{t}, 2.482.

$[S_4Cd_{17}(SPh)_{28}]^{2-}$, **6**, as its Me_4N^+ salt which has been characterized crystallographically.[9] Figure 1 is an idealized structural diagram of **6**, defining atom types: the actual molecular structure of **6**, with exact symmetry D_2, is shown in Figure 2. A central cadmium atom, Cd^{i}, is connected to four quadruply bridging S^{2-} ions, each of which is connected to three cadmium atoms, Cd^{c}, which are part of a cuboctahedron, $(Cd^{c})_{12}$. Four of the eight faces of the $(Cd^{c})_{12}$ cuboctahedron, and 12 of its 24 edges, are internally spanned by μ_4-S^{2-} ligands. The 12 edges which are not so spanned are doubly bridged by thiolate ligands SPh^{c}, and these 12 μ-SPh^{c} ligands constitute a tetratruncated tetrahedron. The four triangular faces of the Cd_{12} cuboctahedron which are internally bridged by the μ_4-S^{2-} ligands are also linked to external cadmium atoms Cd^{o} by tripodal $(\mu\text{-}SPh^{o})_3Cd^{o}(SPh^{t})$ caps. The 17 cadmium atoms occur as three types: one Cd^{i} with tetrahedral $(\mu_4\text{-}S)_4$ coordination; 12 Cd^{c}, each with tetrahedral $(\mu_4\text{-}S)(\mu\text{-}SPh^{c})_2(\mu\text{-}SPh^{o})$ coordination; and four Cd^{o} each with tetrahedral $(\mu\text{-}SPh^{o})_3(SPh^{t})$ coordination. With Cd–Cd distances ranging from 4.07 to 4.20 Å, **6** is the largest metal chalcogenide molecular aggregate not dependent on the substantial M–M bonding which occurs in $[Se_{22}Ni_{34}(PPh_3)_{10}]$[10] and congeners.[10,11]

Although the structure of **6** is unique, its central $Cd^{i}(\mu_4\text{-}S)_4(Cd^{c})_{12}$ core reciprocates (by Cd/S interchange) the core of **4**. Four adamantanoid cages occur in both **1** and **6**, sharing edges and one vertex in **6** but fused in **1**. The capping cages $\{S(Cd^{c})_3(\mu\text{-}SPh^{o})_3Cd^{o}\}$ of **6** are barrelanoid rather than adamantanoid and thus are similar to the hexagonal (wurtzite) lattice of metal chalcogenides. Two new structural features in **6** are (a) the open cleft which occurs along each of the edges of the approximately tetrahedral molecule, with the cyclic atom sequence $\overline{Cd^{o}SR^{o}Cd^{c}SR^{c}Cd^{c}SR^{o}Cd^{o}SR^{o}Cd^{c}SR^{c}Cd^{c}SR^{o}}$, and arising as a consequence of the microhexagonal topology of the cap and (b) facial $\overline{Cd^{c}SR^{c}Cd^{c}SR^{c}Cd^{c}SR^{c}}$ triangles in chair conformation with $(axial)_3$ substituent configuration.

The molecule **6** is the prototype of another infinite series of molecular aggregates, $\mathbf{7}^{[n]}$.[12] The next two members are $[S_{14}M_{32}(SR)_{40}]^{4-}$ ($\mathbf{7}^{[4]}$) and $[S_{32}M_{54}(SR)_{52}]^{8-}$ ($\mathbf{7}^{[5]}$). The structural principles which generate and differentiate the series $\mathbf{2}^{[n]}$, $\mathbf{5}^{[n]}$, and $\mathbf{7}^{[n]}$ will be elaborated[13] in the context of the questions of (i) possible additional structural types for molecular aggregates and (ii) the structures of colloids and of fragments of nonmolecular metal chalcogenides.

The ^{113}Cd NMR spectrum of **6** redissolved in DMF is temperature and time dependent and indicates the presence of both fast and slow rearrangement processes. Laser desorption FT-ICR mass spectra of **6** contain negative and positive ions of m/z ca. 4900.[14]

Acknowledgment. The support of this research by the Australian Research Grants Scheme is gratefully acknowledged. Dr A. D. Rae assisted with the program RAELS, and Dr. G. D. Willett obtained the FT-ICR spectra.

Supplementary Material Available: Atomic positional and thermal parameters, bond lengths, bond angles, and the polycrystalline diffraction pattern (i.e., d-spacings (Å) and relative intensities) for **6** (6 pages). Ordering information is given on any current masthead page.

(9) Crystallography: $Cd_{17}S_{32}N_2C_{176}H_{164}$, M = 5244.0, orthorhombic space group $Ccca$, a = 30.930 (5) Å, b = 32.772 (5) Å, c = 19.997 (2) Å, V = 20270 (5) Å^3, Z = 4, d_{obsd} = 1.76 (2), d_{calcd} = 1.73 g cm^{-3}; 4712 unique reflections (using two crystals, to compenstate for radiation damage), Mo Kα radiation, to θ = 20°; solution by direct methods, least-squares refinement with Cd and S anisotropic, the Ph substituents as constrained planar groups, and spherically disordered Me_4N groups; R = 0.059, R_w = 0.079 for 2187 observed reflections. Full details of this structure will be published separately.

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(11) (a) Cecconi, F.; Ghilardi, C. A.; Midollini, S. *Inorg. Chem.* **1983**, *22*, 3802. (b) Agresti, A.; Bacci, M.; Cecconi, F.; Ghilardi, C. A.; Midollini, S. *Inorg. Chem.* **1985**, *24*, 689. (c) Fenske, D.; Hachgenei, J.; Ohmer, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 706. (d) Cecconi, F.; Ghilardi, C. A.; Midollini, S.; Orlandini, A.; Zanello, P. *Polyhedron* **1986**, *5*, 2021. (e) Chevrel, R.; Hirrien, M.; Sergent, M. *Polyhedron* **1986**, *5*, 87. (f) Fenske, D.; Ohmer, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 148.

(12) n is the number of layers of M atoms in the core, and thus **6** is $\mathbf{7}^{[3]}$. Structural isomerism can arise in larger members of the series by alternative core truncations and alternative cap rotations.

(13) Dance, I. G., in preparation.

(14) NMR and mass spectroscopic data for **6** will be reported separately.

A Novel Mechanism of Glycoside Anomerization

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Mechanisms of acid-catalyzed glycoside anomerization are reasonably well understood,[1] but base-catalyzed anomerizations are not.[2] We have investigated the carbonate-catalyzed anomerization of protected 2,4-dinitrophenyl β-D-glucopyranosides[3] by using a variety of techniques and have shown the reaction to proceed via a novel mechanism involving nucleophilic aromatic substitution (Scheme I). A similar mechanism probably obtains for the previously reported[4] base-catalyzed anomerization of penta-*O*-acetyl-β-D-glucopyranose.

Treatment of 2,4-dinitrophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**1**) (β-2,4-DNPG) with K_2CO_3 or dimethylsulfinyl anion in DMSO affords an equilibrium mixture of the α and β anomers (80:20, respectively).[5] We have considered four possible mechanisms for this transformation. These involve (i) base-catalyzed proton abstraction at C(1) forming a carbanion intermediate; (ii) phenolate departure forming an oxocarbonium ion intermediate, with possible participation of the C(2)-acetoxy

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(5) 2,4-Dinitrophenyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside also undergoes anomerization but more slowly.

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Scheme I

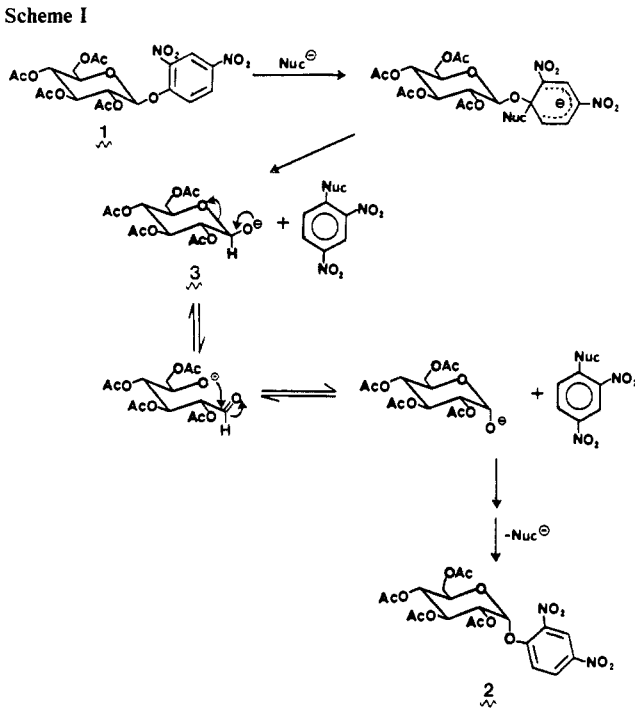


Table I. Substituent Effects on Anomerization Rate[7]

β-2,4-DNPG substrate	[DNPG] (mM)	$[(Me_4N)_2CO_3]$ (mM)	rel rate (disapprnce of β-anomer)
β-2,4-DNPG (**1**)	0.0138	0.0167	1.00
2,3,4-tri-*O*-acetyl-6-deoxy	0.0150	0.0167	1.05
2,3,6-tri-*O*-acetyl-4-deoxy	0.0153	0.0167	0.13
2,3,6-tri-*O*-acetyl-4-deoxy-4-fluoro	0.0136	0,0167	0.40
β-2,4-DNPG (**1**)	0.0121	0.0182	1.00
3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro	0.0134	0.0182	0.90

group; (iii) proton abstraction at C(2) forming a glucal intermediate with expulsion of phenolate; and (iv) nucleophilic aromatic substitution at C(1) of the aromatic ring by dimethylsulfinyl anion[6] displacing a glycosyl oxyanion intermediate **3**, which anomerizes under the basic conditions and recombines with the reactive aromatic species.

A deuterium kinetic isotope effect of 1.09 ± 0.06[7] was measured for the anomerization of [1-^{2}H]-β-2,4-DNPG.[8] This is clearly not a primary isotope effect and therefore is incompatible with mechanism (i) but is still consistent with the secondary isotope effect possible for any of the other mechanisms.

Rates of anomerization were measured for several deoxy and deoxyfluoro derivatives of the parent sugar to probe the involvement of cationic or anionic intermediates (Table I).[9] Since the deoxyfluoro DNPG substrates react at approximately the same rate as the parent sugar, whereas both deoxy DNPG substrates react significantly more slowly, this suggests a mechanism involving an anionic intermediate and is therefore inconsistent with mechanism (ii).

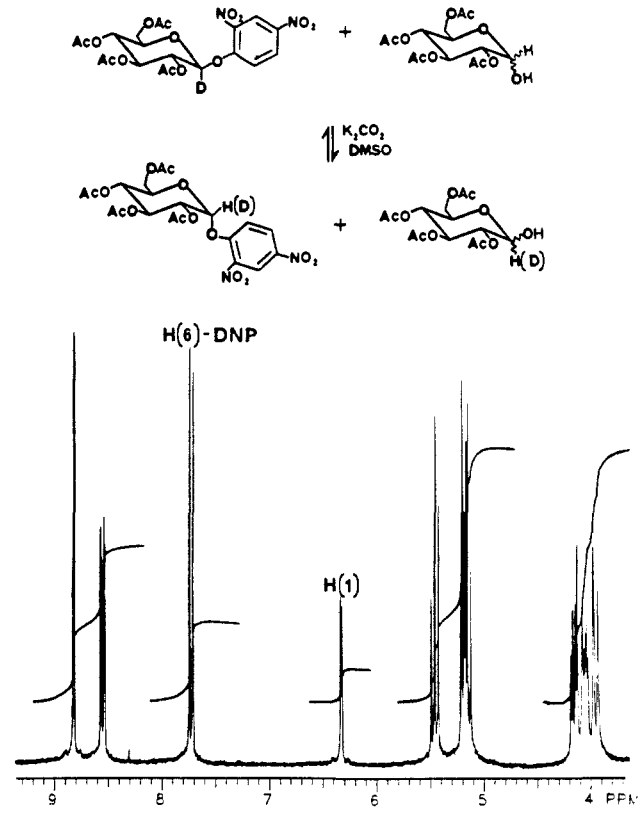


Figure 1. ^{1}H NMR spectrum (300 MHz; DMSO-d_6) of α-2,4-DNPG isolated from exchange experiment shown.

Attempts were made to demonstrate the intermediacy of a dinitrophenolate anion by looking for the exchange of added dinitrophenolate anion with that which might be generated during reaction. Two reactions were performed in which, in one case, β-2,6-DNPG[10] was anomerized in the presence of added potassium 2,4-dinitrophenolate, and, in the other, β-2,4-DNPG was anomerized in the presence of added potassium 2,6-dinitrophenolate. In both cases, ^{1}H NMR spectra of the isolated product mixture indicated that no exchange of the phenolate groups had occurred. Possible proton abstraction (mechanisms (i) or (iii)) was also investigated by means of exchange experiments in which β-2,4-DNPG was anomerized in the presence of a deuteron source (*t*-BuOD) or [1-^{2}H]-β-2,4-DNPG was anomerized in the presence of a proton source (*t*-BuOH). ^{1}H NMR analysis of isolated product mixtures indicated *no* exchange of the proton (deuteron) at C(1) or C(2). A third exchange experiment was performed (Figure 1) to test for the intermediacy of a protected glucosyl oxyanion **3** (mechanism (iv)) in which 1 equiv of [1-^{2}H]-β-2,4-DNPG was anomerized in the presence of 1 equiv of added 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (non-deuteriated). ^{1}H NMR analysis of the isolated α-2,4-DNPG **2** showed it to possess only 50% of its deuterium label at C(1). The glucosyl oxyanion **3** (mechanism (iv)) must therefore be an intermediate in the reaction mechanism, and this strongly supports mechanism (iv). Further, when the anomerizations were performed under scrupulously anhydrous conditions, a deep purple coloration (λ_{max} = 574 nm) appeared initially in the reaction mixtures. Such purple colorations have been observed previously in nucleophilic aromatic substitution reactions and attributed to Meisenheimer complexes.[11]

Possible candidates for the aryldimethylsulfinyl intermediates are **4** or **5**. We have eliminated **4** as a candidate by synthesizing

(6) (a) The pK_a of carbonate in DMSO is unknown but may (being a dianion) be sufficiently high in this solvent to deprotonate DMSO (pK_a = 35) to a small extent, see: Brauman, J. I.; Bryson, J. A.; Kahl, D. G.; Nelson, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 6679. (b) Mechanisms of base-catalyzed glycoside hydrolysis invovling nucleophilic aromatic substitution have been proposed previously for nitrophenyl glycosides: Horton, D.; Leutzow, A. E. *J. Chem. Soc., Chem. Commun.* **1971**, 79. Rosenberg, S.; Kirsch, J. F. *Biochemistry* **1981**, *20*, 3196.

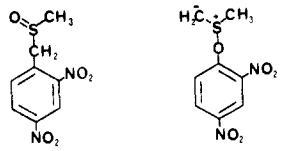
(7) All kinetic studies were performed by use of ^{1}H NMR to measure reaction progress in homogeneous solution [$(Me_4N^+)_2CO_3^{2-}$ in DMSO] in sealed NMR tubes. Reaction was followed by integration of the aromatic resonances associated with each anomer and standardized, as necessary, against the acetate resonance integral.

(8) Berven, L.; Withers, S. G. *Carbohydr. Res.* **1986**, *156*, 282.

(9) Rates of glycoside hydrolyses proceeding via oxocarbonium ions are severely influenced by deoxygenation or fluorination in the sugar ring; see, for example: Withers, S. G.; MacLennan, D. J.; Street, I. P. *Carbohydr. Res.* **1986**, *154*, 127. (b) Buncel, E.; Bradley, P. R. *Can. J. Chem.* **1967**, *45*, 515.

(10) Protected glycosides of other phenols of pK_a less than 4.0 (2,6-dinitrophenol and 2,6-dichloro-4-nitrophenol) were also found to anomerize at comparable rates.

(11) Bowden, K.; Nadvi, N. S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 189.



4 5

it by an independent route[12] and demonstrating it to be unreactive under the reaction conditions employed, thus we suggest the intermediate is **5**. Unfortunately, all of our attempts to synthesize **5** have failed, as indeed did the attempts of others[15-17] in trying to prepare this and similar intermediates. However its accepted[15-17] chemistry is consistent with that required by this mechanism.

Acknowledgment. We thank Dr. Gary Gray for helpful discussions. We also thank the Natural Sciences and Engineering Research Council of Canada for support of this work.

(12) Nitration (HNO_3/H_2SO_4) of *p*-nitrobenzyl chloride gave 2,4-dinitrobenzyl chloride that was converted into 2,4-dinitrobenzyl methyl sulfide by treatment with methyl mercaptan essentially according to ref 13. Oxidation of this product to 2,4-dinitrobenzyl methyl sulfoxide was achieved with *m*-chloroperbenzoic acid essentially according to ref 14. Satisfactory spectral and analytical data were obtained for all compounds.

(13) Russell, G. A.; Pecoraro, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 3331.
(14) Plieninger, L. A. *Chem. Ber.* **1950**, *83*, 264.
(15) Burdon, M. G.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 5855.
(16) Marino, J. P.; Pfitzner, K. E.; Olofson, R. A. *Tetrahedron* **1971**, *27*, 4181.
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Cyclic Conjugated Enediynes Related to Calicheamicins and Esperamicins: Calculations, Synthesis, and Properties

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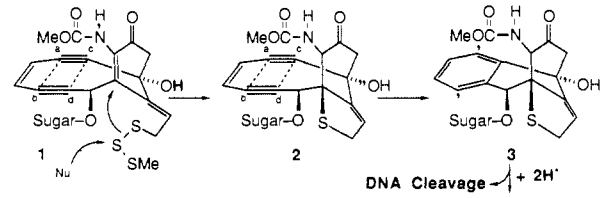
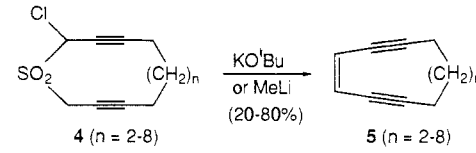
A series of novel naturally occurring compounds with powerful biological properties, the calichemicins, were recently isolated by Lederle scientists.[1] This new class of compounds isolated from *Micromonospora echinospora ssp. calichencsis*, includes calicheamicin $\gamma^{I}_{1\alpha}$ (**1**), whose structure was determined on the basis of chemical and spectroscopic data and an X-ray crystallographic analysis on a partial structure. A similar group of natural products, the esperamicins, was simultaneously reported by a Bristol-Myers group.[2] The phenomenal biological profile of the calicheamicins and esperamicins includes the following: (a) subpicogram potency against Gram positive bacteria, (b) activity in the biochemical induction assay at very low concentrations, (c) high potency against a number of animal tumor models, and (d) induction of double-stranded DNA cleavage with minimal concurrent single-stranded breakage. A fascinating hypothesis regarding the mode of action of these compounds has been advanced.[1,2] According to this mechanism (Scheme I), after recognition and appropriate interaction with DNA, the aglycon framework of the molecule **1** undergoes an intramolecular conjugate addition to tricycle **2** followed by a Bergman cyclization[3] leading to a highly reactive benzenoid diradical **3** which damages DNA. Intrigued by the novel architecture and mode of action of these potent biomolecules, we initiated a program directed toward the understanding of their chemistry and the investigation of strategies for their total synthesis. In this communication, we report (a) calculations on structural parameters of cyclic conjugated enediynes relating to calicheamicins and esperamicins, (b) methodology for the construction of these systems, (c) the application of this strategy to the first synthesis of cyclodecenediyne **5** (n = 2), the parent molecule of the active skeleton of these natural products, and (d) the properties of **5** (n = 2), including its thermal cyclization to a benzenoid diradical analogous to the species postulated in the biological mode of action of these compounds.[4]

Scheme I[a]



[a] Presumed DNA-cleaving mechanism of calicheamicin $\gamma_{1\alpha}$ (**1**).

Scheme II[a]



[a] Synthesis of enediynes **5** (n = 2-8).

Crucial for the cascade of Scheme I is the geometrical change in going from structure **1** to **2**. Specifically, it was hypothesized that saturation of the double bond in **1** after the conjugate addition (**1** → **2**) must result in shortening of the distance between the acetylenic groups (Scheme I, distances ab and cd).[5] Indeed, molecular mechanics calculations (MacroModel, MM2)[6] on the aglycons of **1** and its cyclic product (entries 6 and 7, Table I) revealed that the distances ab and cd shortened in going from structures of type 1 to structures of type 2. In particular, cd goes from 3.35 to 3.16 Å, which apparently is close enough for spontaneous cyclization to take place (Scheme I, **2** → **3**). Table I also includes a number of other, known model systems and their calculated ab and cd distances. Inspection of these values leads to the conclusion that the crucial turning point from stability to spontaneous cyclization must be in the cd range of 3.31-3.20 Å. Examples of compounds with lower than 3.20 Å cd values have been claimed as transient intermediates, suffering spontaneous cyclization to benzenoid systems (Table I, entries 1-3).[7,8] On

† Dean's Graduate Fellow, University of Pennsylvania, 1988.
‡ Merck Sharp and Dohme Postdoctoral Fellow, 1988.
§ Visiting scientist from Kyowa Hakko Kogyo, Japan, 1987-1988.

(1) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

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

(4) For some other elegant studies in this area, see synthetic: (a) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631. (b) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 0000. Theoretical: Houk, K. N. *J. Am. Chem. Soc.*, submitted for publication. We thank these authors for sharing their results with us prior to publication.

(5) This is a simplifying assumption, since obviously other considerations such as strain energies of substrates, transition states, and products may play a role in complex systems. The distances between the acetylenic groups, however, seems to correlate well with the rates of cyclization of all enediynes mentioned in this work.

(6) We thank Professor W. C. Still, Columbia University, for supplying this program to us. The values in Table I were obtained by using standard MM2 force field parameters. Using the altered sp bending constants (Allinger, N. L.; Pathiaseril, A. *J. Comput. Chem.* **1987**, *8*, 1225) resulted in only small changes in the cd distance and a comparable fit to the X-ray derived parameters for **5** (n = 3).

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