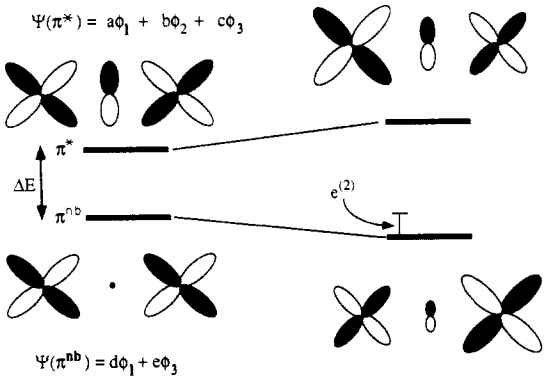


Figure 2. The second-order energy mixing associated with an asymmetric substitution in the M–O–M triatomic system (orbital mixing exaggerated for effect). ϕ_1 and ϕ_3 are the metal d orbitals, and ϕ_2 is the oxygen p orbital. $\Delta E = E_{MOM}(\pi^{nb}) - E_{MOM}(\pi^*)$, $e^{(2)} = (c^\circ e^\circ \delta H_{ii} + c^\circ d^\circ \delta H_{ij})^2/\Delta E$, the second-order energy shift.

with $H_{eh}[Mo_{12-x}W_x]$ being the computed enthalpy of that permutation and

$$H_{ideal}[Mo_{12-x}W_x] = [1 - (x/12)]H_{eh}[Mo_{12}] - (x/12)H_{eh}[W_{12}] \quad (2)$$

where $H_{eh}[Mo_{12}]$ and $H_{eh}[W_{12}]$ are respectively the computed enthalpies of $PMo_{12}O_{40}^{3-}$ and $PW_{12}O_{40}^{3-}$. The weighted excess enthalpy ($wt\Delta H_{excess}$) can be calculated by using the number and frequency of the permutations found for each stoichiometry.

Generally, most isostructural binary solid solutions exhibited positive excess enthalpies of mixing,[9a-e] with the exception of the (Ni,Mg)O system,[9f] for which it is negative, indicating that the formation of a solid solution is thermodynamically favorable. The $wt\Delta H_{excess}$ curve of the $[Mo_{12-x}W_x]$ solution before reduction is found to be close to 0 (Figure 1b). As electrons enter the Keggin $[Mo_{12-x}W_x]$ solution cluster, the $wt\Delta H_{excess}$ curves become increasingly negative (Figure 1c–f), indicating differential cluster stability. Although we should be careful in making such a comparison, this increase in stability is consistent with earlier findings[1,2,4,11] that the multielectron reduction of 12-HPA is a favorable process. However, the most striking feature of our calculations is the positive correlation between the variation in computed redox potential mimicked by $wt\Delta H_{excess}$ with x and the increased yield of products found experimentally.

How does this cooperative behavior originate in electronic terms? A simple orbital argument based on second-order perturbation theory[13] may be extracted from the calculations. The orbital effect which controls the observed behavior is accessible by a study of an isolated M–O–M unit. Upon asymmetric substitution, to Mo–O–W from either W–O–W or Mo–O–Mo, the energy of the $\pi^{nonbonding}$ level of the triatomic system is lowered by a second energy term $\epsilon^{(2)}$ (Figure 2) via mixing with the $\pi^{antibonding}$ orbital which lies slightly higher in energy. δH_{ii} is related to the electronegativity difference between Mo and W, and δH_{ij} is the change in the metal–oxygen p interaction integral on going from Mo to W. Such mixing does not happen when the local oxygen environment is symmetrical and thus does not contribute to the computed values $H_{eh}[Mo_{12}]$ and $H_{eh}[W_{12}]$. These nonbonding levels, which are initially filled during reduction, and their energies are the factors that control the form of the computed curves of Figure 1. Such an explanation of this type of experimental behavior, we believe, is applicable to a wide variety of systems. Elsewhere[9g] we discuss a more general application of these ideas to solid solutions of extended solids.

Acknowledgment. This research was supported by NSF DMR 8819860.

(13) For a closely related problem, see: Albright, T. A.; Burdett, J. K.; Whangbo, M.-H. *Orbital Interactions in Chemistry*; Wiley: New York, 1985; pp 82–86.

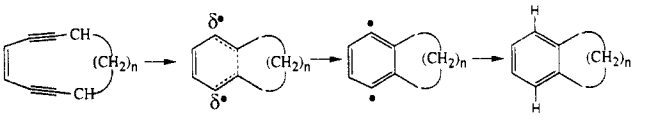
Monocyclic Enediyne Collapse to 1,4-Diyl Biradicals: A Pathway under Strain Control

James P. Snyder

Drug Design, Searle Research and Development
4901 Searle Parkway, Skokie, Illinois 60077

Received February 23, 1990

Over a decade ago Bergman and co-workers demonstrated elegantly that cyclic enediynes **1** cycloaromatize to give transient 1,4-diyl biradicals **3**.[1-3] More recently it has been discovered that microorganisms found in soil produce secondary metabolites in which the enediyne moiety is nested.[4-9] Presumably designed by evolutionary pressures in response to microbial war-making,[10] the natural products likewise cyclize to 1,4-diyls when properly triggered and subsequently deliver a lethal blow to competitors by cleavage of their DNA.[11-16] These observations have stirred a revival in enediyne chemistry[17-24] and stimulated studies to understand the factors controlling biradical formation.[25-29]

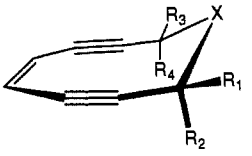


1 2 3

(1) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25-31.
(2) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082-4090.
(3) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091-4096.
(4) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Kirshnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461-3462.
(5) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Kirshnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462-3464.
(6) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464-3466.
(7) 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*, 3466-3468.
(8) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449-1452.
(9) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 68.
(10) Williams, D. H.; Stone, M. J.; Hauck, P. R.; Rahman, S. K. *J. Nat. Prod.* **1989**, *52*, 1189-1208.
(11) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697-699.
(12) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198-1201.
(13) Hawley, R. C.; Kiessling, L. L.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1105-1109.
(14) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888-6890.
(15) Kappen, L. S.; Ellenberger, T. E.; Goldberg, I. H. *Biochemistry* **1987**, *26*, 384-390.
(16) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212-7214.
(17) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247-7248.
(18) Danishefsky, S. J.; Yamashita, D. S.; Mantlo, N. B.; Schultz, G. *J. Am. Chem. Soc.* **1988**, *110*, 6980.
(19) Schreiber, S. L.; Kiessling, L. L. *Tetrahedron Lett.* **1989**, 433-436.
(20) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, 4217-4220.
(21) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, 851-854.
(22) Schoenen, F. J.; Porco, J. A.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765-3768.
(23) Haseltine, J. N.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.* **1989**, *111*, 7638.
(24) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.*, submitted.
(25) Carter, P. A.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 1626-1628.

0002-7863/90/1512-5367$02.50/0

Table I. Acetylene Proximity and MM2//PRDDO Cycloaromatization Barriers for a Series of Nine-Membered-Ring Enediynes



X	R_1	R_2	R_3	R_4	$r(C_{sp}\cdots C_{sp})$, Å	ΔE^*, kcal
CH_2	H	H	H	H	2.99	17.9
CH_2	CH_3	CH_3	CH_3	CH_3	2.95	12.5
CH_2	cyclopropyl[a]		cyclopropyl[a]		2.94	16.3
$C(CH_3)_2$	cyclopropyl[a]		cyclopropyl[a]		2.90	7.0
$C{=}CH_2$	H	H	H	H	3.00	17.4
$C{=}CH_2$	cyclopropyl[a]		cyclopropyl[a]		2.96	17.0
$C{=}CH(tBu)$	cyclopropyl[a]		cyclopropyl[a]		2.98	22.3
$C{=}C(CH_3)_2$	cyclopropyl[a]		cyclopropyl[a]		3.00	26.0
$C{=}C(CH_3)_2$					3.01	30.9

[a] Spirocyclopropyl. [b] The symmetrical F's are syn to the X flap and pointing inward. Four inward-directed F's are needed to guarantee that the high barrier is effectively probed.

Contributing to the latter question, Nicolaou and collaborators perceptively established that simple cyclic hydrocarbons are equally adept at delivering 1,4-diyl and scissoring DNA.[17,29] The investigation prompted the proposal that diacetylene proximity in **1**, $r(C_{sp}\cdots C_{sp})$, correlates with the activation barrier (E_a) for cycloreversion. Independent investigations by Magnus et al.[25,26] and ourselves[27,28] have suggested, by contrast, that differential molecular strain in the ground state and transition state (**2**), respectively, is the commanding element for closure in the more complex bicyclic situation. We have combined experiment and theory to substantiate the point.[30] The present theoretical work suggests strongly that steric strain along the closure pathway is central to condensation of the monocyclic variants as well. Two systems amenable to experimental test are presented, and quantitative predictions are made for them.

Unlike the larger ring enediynes (**1**, $n > 1$) the nine-membered ring ($n = 1$) was neither isolated nor observed,[29] consistent with its low predicted closure barrier ($\Delta E^* = 17.9$ kcal).[27b] Table I lists the same MM2//PRDDO quantities along with MM2-optimized $r(C_{sp}\cdots C_{sp})$ distances for a selection of substituted C9-cyclic enediynes. The first set of structures with tetravalent carbon on the symmetry axis (X = CH_2 or $C(CH_3)_2$) shows a diminshingly small $\Delta r = 0.09$ Å accompanied by a substantial drop of 10.9 kcal in ΔE^*. Steric compression experienced by substituents at the saturated centers confers a compensating twist on the otherwise planar enediyne moiety (Figure 1a), illustrating that ground-state strain is responsible for reducing the closure barrier.

Given the rapid cyclization of the unsubstituted parent, it will be difficult to establish relative rates for this series. However, the exomethylene variant (X = C=CR′R″) offers intriguing possibilities. With increasing steric bulk at R′ and R″ the cycloaromatization is predicted to rise by nearly 14 kcal. The final two entries in Table I should be isolable. Coincident with the extraordinary energy demands for closure, the maximum Δr is only 0.05 Å. The source of the energy differential is strain induced in the transition state analogous to the keto-embellished bicyclic systems.[25-27,30] In monocyclic cases the enediyne ground state is reasonably tolerant of the nonbonded H1-H7 and greater steric

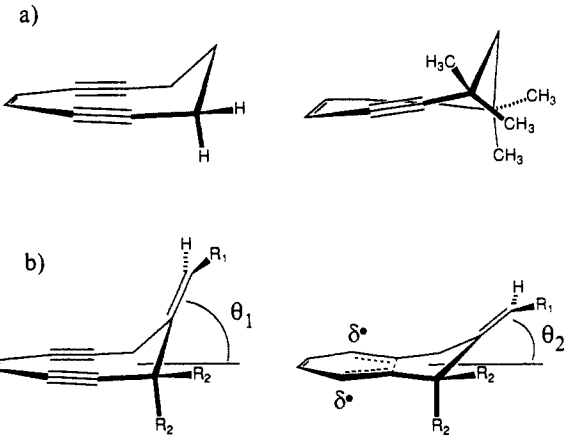
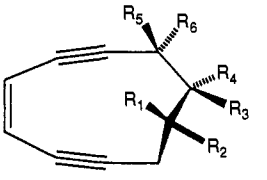


Figure 1. The origin of strain energy in the ring closures of nine-membered-ring enediynes. (a) Ground-state distortion from the flat parent to the twisted tetramethyl analogue. (b) Transition-state compression arising from ring flattening. For exomethylene structures in Table I the average $\Delta(\theta_1 - \theta_2) = 24°$.

Table II. Acetylene Proximity and MM2//PRDDO Cycloaromatization Barriers for a Series of 10-Membered-Ring Enediynes



R_1	R_2	R_3	R_4	R_5	R_6	$r(C_{sp}\cdots C_{sp})$, Å	ΔE^*, kcal
H	H	H	H	H	H	3.46	24.7
CH_3	H	CH_3	H	H	H	3.32	23.8[b]
CH_3	H	H	CH_3	H	H	3.23	23.6[c]
H	CH_3	CH_3	H	H	H	3.53	23.8[d]
H	H	CH_3	CH_3	CH_3	CH_3	3.23	20.8
CH_3	CH_3	CH_3	CH_3	H	H	3.14	18.9

[a] The lowest energy ring conformations for both ground and transition states (ref 27) were used in this study. [b] Cis; the bis-CH_2OH derivative cyclizes with an $E_a = 23.6$ kcal/mol (ref 17). [c] Trans-diequatorial. [d] Trans-diaxial.

interactions as a result of the comparatively large angle between the average planes of the two halves of the molecule (Figure 1b). At the transition state, however, the greater substituent buttressing in the flatter structure drives the energy upward.

The 10-membered enediyne (**1**, $n = 2$) can be manipulated similarly. The parent compound cyclizes to 1,4-diyl with $E_a = 23.8$ kcal[29] ($\Delta E^* = 24.7$ kcal).[27] Cis and trans methylation about the symmetry axis (entries 2-4, Table II) is predicted to reduce ΔE^* by just 0.9-1.1 kcal, yet Δr ranges from -0.23 to +0.07 Å. Diminished acetylene proximity is not expected to yield significantly enhanced closure rates in these cases. Unfavorable gauche interactions are introduced equally into both the ground state and the transition state with compensating ring relaxation. The distance criterion appears at first glance to be manifested in the two tetramethyl substitutions (entries 5 or 6, Table II). Careful analysis of conformation and geometric distortion shows that steric strain is not only concomitant with contracted $r(C_{sp}\cdots C_{sp})$ but most likely the cause of it.

In conclusion, the design of novel enediynes is underway in a number of laboratories both to provide new drug entities[14,31-33]

(26) Magnus, P.; Kewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921-6923.
(27) (a) Snyder, J. P. *J. Am. Chem. Soc.* **1989**, *111*, 7630-7632. (b) ΔE^* = E(transition state; GVB) - E(ground state; SCF).
(28) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, *112*, 4040-4042.
(29) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866-4868.
(30) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986-4987.
(31) Nicolaou, K. C.; Zuccarello, G.; Caulfield, T.; Stylianides, N.; Skokolas, G.; Wendeborn, S.; Maligres, P.; Schweiger, E.; Kataoka, H.; Toshima, K.; Lopez, J. M. P. *Int. Chem. Congr. Pacific Basin Soc. (Honolulu)* **1989**, Organic Chemistry, Abstract 387.
(32) Isobe, M.; Nishikawa, T.; Goto, T. *Int. Chem. Congr. Pacific Basin Soc. (Honolulu)* **1989**, Organic Chemistry, Abstract 183.
(33) Magnus, P. (University of Texas at Austin), private communication.

and to explore questions of mechanism.[27,30,34,35] Those that depend on a prior estimate of the energy requirements for cyclization to biradical are advised to consider together both extremes of the potential energy surface rather than either alone.

Acknowledgment. I am grateful to Professor Kosta Steliou (University of Montreal) and Professor K. C. Nicolaou (UCSF and Scripps) for their interest in and continuing influence on the work.

(34) Bergman, R. G. (University of California, Berkeley), private communication.
(35) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *31*, 1521-1522.

General Methodology for the Synthesis of Neocarzinostatin Chromophore Analogues: Intramolecular Chromium-Mediated Closures for Strained-Ring Synthesis

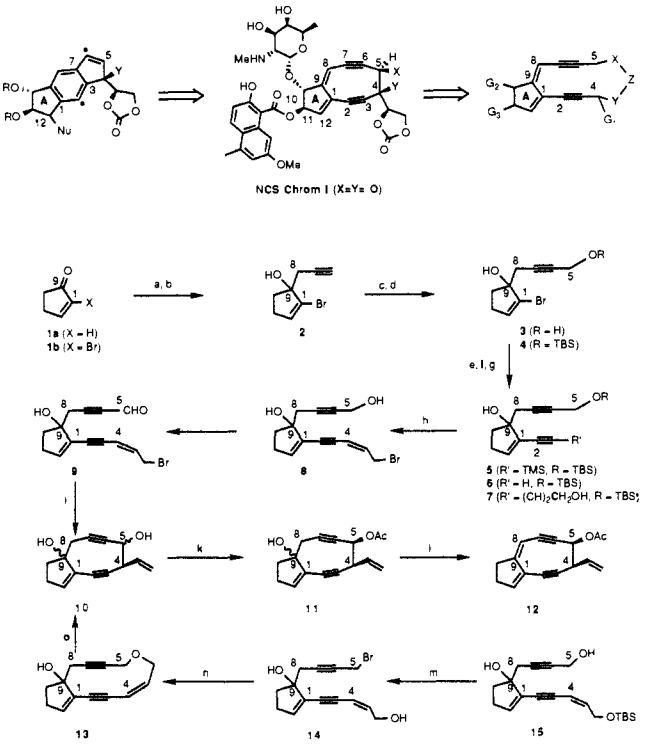
Paul A. Wender,* Jeffrey A. McKinney,[1] and Chisato Mukai[2]

Department of Chemistry, Stanford University Stanford, California 94305
Received March 23, 1990
Revised Manuscript Received May 2, 1990

Neocarzinostatin (NCS) is an antitumor antibiotic that has been used for the treatment of pancreatic cancer, gastric cancer, and leukemia in humans.[3] The drug consists of a structurally unprecedented, non-protein chromophore (NCS Chr I)[4] stabilized through noncovalent association with a single-chain polypeptide (MW = 10 700). NCS is proposed to function through the selective cleavage of DNA, involving deoxyribosyl hydrogen abstractions[5a,b] by a diyl formed upon thiol addition to NCS Chr I.[5c] Mechanistic studies[5] and the finding that NCS Chr I and its halohydrin analogue NCS Chr II exhibit similar biological activity[6] suggest that the bicyclic diene–diyne subunit and a leaving group at C5 are essential for diyl formation. Thus far, only one synthetic route to the bicyclic core of NCS Chr I has been reported,[7] while a less strained, homologous ring system has recently been elegantly assembled by Hirama and co-workers.[8] As part of our continuing effort to explore the fundamental utility and chemotherapeutic potential of this novel system for DNA cleavage, we have developed as described herein a convergent route to NCS Chr I analogues that possess the complete bicyclic core and functionality array required for diyl generation.

Our synthetic plan for bicyclic NCS Chr analogues involves three stages: attachment of appendages to the C1 and C9 positions of a preformed a ring, closure of the termini of these appendages by a ring-contraction strategy, and introduction of the C8–C9 double bond. This design allows for the attachment of various DNA recognition elements to the A ring, the segregation of the entropic and enthalpic problems associated with formation of the strained nine-membered B ring, and the installation of the unstable diyl progenitor functionality at a late synthetic stage. Central to the success of this plan is the construction of the strained cyclononadiyne subunit, which we have efficiently achieved through an internal chromium-mediated condensation.[9]

Scheme I[a]



[a] (a) Br_2, Et_3N, CH_2Cl_2, 0 °C to room temperature; (b) $HCCCH_2MgBr$, Et_2O, room temperature; (c) EtMgBr, HMPA, Et_2O, 50 °C, $(CH_2O)_n$, Et_2O, room temperature; (d) TBSCl, DMF, imidazole, 0 °C to room temperature; (e) $PdCl_2(PPh_3)_2$, CuI, $(i\text{-}Pr)_2NH$, HCCTMS, THF, room temperature; (f) K_2CO_3, CH_3OH, room temperature; (g) $PdCl_2(PPh_3)_2$, CuI, $(i\text{-}Pr)_2NH$, $ICHCHCH_2OH$, THF, room temperature; (h) Et_3N, MsCl, -78 °C; LiBr, $(CH_3)_2CO$, room temperature; 3:1:1 HOAc/THF/H_2O, room temperature; (i) MnO_2, room temperature; (j) $CrCl_2$, THF; (k) Ac_2O, Et_3N, DMAP, room temperature; (l) DMAP, MsCl, Et_3N, 0 °C; (m) MsCl, Et_3N, -50 °C to room temperature; LiBr, $(CH_3)_2CO$, room temperature; *n*-Bu_4NF, room temperature (47%); (n) NaH, HMPA, THF, reflux (52%); (o) *n*-BuLi, HMPA, -78 °C (<29%).

2-Bromocyclopentenone (**1b**) (Scheme I), prepared in one operation from cyclopentenone (**1a**),[10] served in the first stage of our plan as an excellent preformed A ring, possessing differentiated functionality for sequential bond formation to vicinally related centers C9 and C1. Addition of propargylmagnesium bromide to **1b** allowed for the formation of the C8–C9 bond, providing alcohol **2** (93% yield), from which diol **3** (80%) was obtained through a metalation and paraformaldehyde condensation se-

(1) NIH Postdoctoral Fellow, 1990–1991 (GM 13575-01).
(2) Young Scientist Fellow on leave of absence from the Department of Pharmaceutical Sciences, Kanazawa University, Japan, 1986–1988.
(3) Kitajima, K. *Nippon Ketsueki Gakkai Zasshi* **1974**, *37*, 767. Takahashi, M.; Toriyama, K.; Maeda, H.; Kikuchi, M.; Kumagai, K.; Ishida, N. *Tohuku J. Exp. Med.* **1969**, *98*, 273. Ishii, K.; Nakamura, K. *Cancer Chemother.* **1972**, *1*, 433. Knobf, M. K. T.; Fischer, D. S.; Welch-McCaffrey, D. *Cancer Chemotherapy, Treatment and Care*; Year Book Medical: Chicago, 1984; p 77.
(4) For references on the determination of NCS Chr I structure, see: Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331. Napier, M. A.; Goldberg, I. H.; Hensens, O. D.; Dewey, R. S.; Liesch, J. M.f Albers-Schoenberg, G. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 1073. Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212.
(5) (a) Kappen, L. S.; Ellenberger, T. E.; Goldberg, I. H. *Biochemistry* **1987**, *26*, 384. Kappen, L. S.; Goldberg, I. H. *Biochemistry* **1989**, *28*, 1027 and references cited therein. (b) For a model of NCS Chr I-DNA interactions, see: Hawley, R. C.; Kiessling, L. L.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 1105. (c) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146 and references cited therein.
(6) Kappen, L. S.; Napier, M. A.; Goldberg, I. H. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1970 and ref 4b.
(7) Wender, P. A.; Harmata, M.; Jeffrey, D.; Mukai, C.; Suffert, J. *Tetrahedron Lett.* **1988**, *29*, 909.
(8) Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120.
(9) For pioneering studies in this field, see: Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. At the outset of our work, only three examples of the intramolecular version of this reaction were reported: Still, W. C.; Mobilo, D. J. *J. Org. Chem.* **1983**, *48*, 4785. Okuda, Y.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 481. Shibuya, H.; Ohashi, K.; Kawashimo, K.; Hori, K.; Murakauri, N.; Kitagawa, J. *Chem. Lett.* **1986**, 85. More recent examples include the following: Kato, N.; Tanaka, S.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3231. Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. Kishi, Y.; Rowley, M. *Tetrahedron Lett.* **1988**, *29*, 4909. The utility of this reaction in the synthesis of strained rings has not been previously explored.
(10) Smith, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth.* **1983**, *61*, 65.

0002-7863/90/1512-5369$02.50/0