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The Chemistry of Enediynes, Enyne Allenes and Related Compounds

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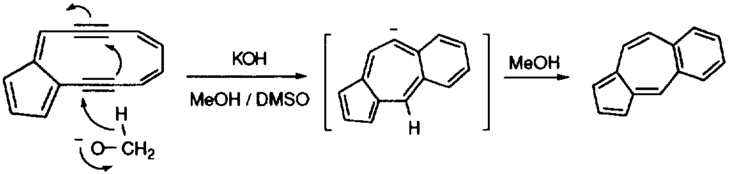
1. Introduction

The recent discovery of several potent antitumor antibiotics containing (Z)-enediynes or related systems has pushed the exploration of enediynes to the forefront of chemical and biological research.[1] In addition to their biological activity, which results in the cleavage of DNA, these compounds are also of interest because of their unique structural features. Probably the most fascinating aspect of the enediyne antitumor antibiotics is their unprecedented mechanism of activation that originates from the chemical reactivity of the enediyne moiety.

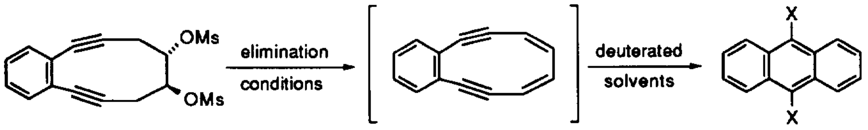
The chemistry of enediynes dates back to the mid-1960s. The first report related to enediynes appeared in 1966, in which Sondheimer reported the reaction **1.1A** → **1.1B** and proposed an ionic mechanism for the observed cyclization (Scheme 1.1).[2]



1.1A **1.1B**

Scheme 1.1

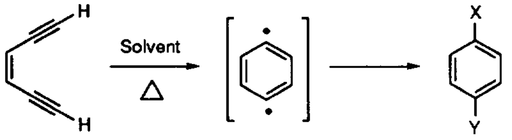
In 1971, Masamune attempted the synthesis of annulene **1.2B** from **1.2A**, but obtained anthracene (**1.2C**) as the major product (Scheme 1.2).[3] Although Masamune speculated that anthracene was derived from the expected product **1.2B** and demonstrated the incorporation of deuterium at C-9 and C-10 of anthracene to form **1.2D**, a mechanistic rationale for the observed cyclization was not proposed.



1.2A **1.2B** **1.2C** X = H
1.2D X = D

Scheme 1.2

In 1972, Bergman published a detailed study of the thermal behavior of simple acyclic (Z)-enediynes.[4] When enediyne **1.3A** was heated in solution, the products observed were benzene or its derivatives **1.3D** and **1.3E**, depending on the solvent used. Bergman invoked the intermediacy of the highly unstable 1,4-dehydrobenzene biradical **1.3B** to explain these results (Scheme 1.3).[5]



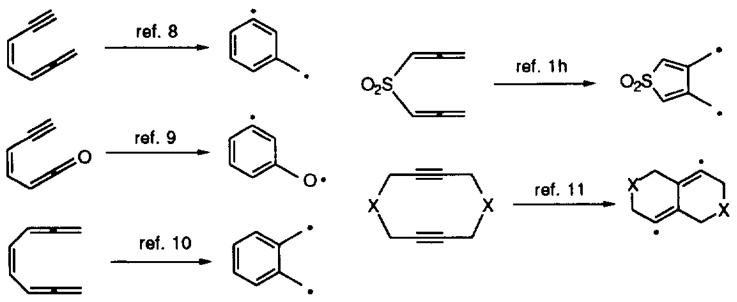
Solvent	Compound	X	Y
hydrocarbon	1.3C	H	H
CCl_4	1.3D	Cl	Cl
CH_3OH	1.3E	CH_2OH	H

1.3A **1.3B**

Scheme 1.3

There was much interest in this unique thermal cycloaromatization of (Z)-enediynes from physical organic and theoretical chemists. However, the attention given to this reaction exponentially increased in 1987 with the reports of two novel antitumor antibiotics containing a cyclic enediyne structure. These two compounds were calicheamicin γ_1^I [6] and esperamicin A_1,[7a,b] as reported by scientists from the Lederle Laboratories and Bristol-Myers, respectively. These compounds contain several interesting features including a bicyclic bridged structure containing the enediyne functionality. Their biological activity stems from the cyclization of the enediynes to afford aromatic compounds through the intermediacy of 1,4-dehydrobenzene biradicals that could cleave DNA. This discovery marked the beginning of an exciting era in chemical, biochemical, and medical research toward new and potentially useful chemotherapeutic agents, with the cycloaromatization of enediynes at center stage.

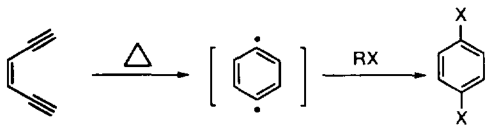
Prompted by the discovery of the enediyne antibiotics, organic chemists attempted to synthesize other unsaturated structures that could cyclize to give biradical species. Several have been discovered, some of which show promising DNA cleavage activity (Scheme 1.4).



Scheme 1.4

This report provides an overview of recent developments in the chemistry of enediynes and related systems. The emphasis is primarily on cyclization studies and on research reported after 1991, since earlier work has been amply reviewed.[1n] We reference older publications either for the sake of completeness or for historical significance. Details on the biological aspects of enediyne antitumor antibiotics are not included, although DNA cleavage experiments are discussed when reported in conjunction with chemical studies.

2. Mechanistic Aspects of the Bergman Cyclization



2.1A **2.1B** **2.1C** X = H, Cl

$\Delta H^\circ_{f,298}$ (kcal/mol)	Method	Reference
128 ± 3	experiment	16
≥136 ± 3	computation	17
138	computation	18
134	computation	13
138.0 ± 1.0	experiment	19
137.3 ± 3.3	experiment	20

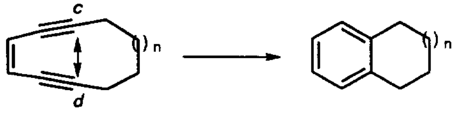
Scheme 2.1

The pioneering work on the cyclization of simple enediynes was carried out by Bergman *et al.* and suggested the intermediacy of the discrete 1,4-dehydrobenzene radical **2.1B** (Scheme 2.1).[1q,4,5,15] There are many examples in which the enediyne cyclization leads to products apparently derived from the biradical 1,4-dehydrobenzene and these will be described in a later section. Despite the large amount of this indirect evidence, direct proof for the biradical is not available. Theoretical work has appeared that challenges the universality of 1,4-dehydrobenzene as an intermediate in the Bergman cyclization. Lindh *et al.* showed by *ab initio* methods that in complex systems, such as enediyne-containing natural products, the small reduction (0.5 Å) in the distance between the terminal acetylenic carbons that occurs during activation is not sufficient for the cyclization to occur at an appreciable rate *via* a 1,4-dehydroarene.[12] Lindh has suggested that, alternatively, the reaction may involve simultaneous ring closure and hydrogen abstraction.

Calculations by Kraka and Cremer show that, in the cycloaromatization of (Z)-hex-3-ene-1,5-diyne, the transition state leading to the 1,4-dehydrobenzene biradical does not possess significant biradical character, although its geometry resembles that of biradical **2.1B**.[13] It is believed that the thermolysis of enediynes produces 1,4-dehydrobenzene biradicals exclusively in the singlet state and that intersystem crossing from the singlet to triplet state does not occur at a rate comparable to that of intermolecular radical abstraction. Grissom *et al.* attempted to raise the rate of singlet-to-triplet intersystem crossing by the application of an external magnetic field and found that the rate of spin change is insensitive to the external magnetic field.[14] Heavy atom solvent effects were also ineffective at increasing this intersystem crossing. The absence of inducible intersystem crossing as well as the lack of observable CIDNP arising directly from 1,4-dehydrobenzene[15] may also lend support to the view that discrete 1,4-dehydroarenes do not exist. The heat of formation of the 1,4-dehydrobenzene biradical from the parent enediyne has been determined both experimentally and computationally; and, as can be seen from the data in Scheme 2.1, the experimental values agree well with the calculated values.

The reactivity of (Z)-enediynes in the Bergman reaction is affected by several factors including: 1) the acetylene *cd* distance, which is the distance between the two terminal acetylenic carbon atoms; 2) the difference in strain energy between the enediyne and the transition state; 3) the concentration of the trapping agent; and 4) substituent effects. Several studies have delineated these effects on enediyne reactivity.

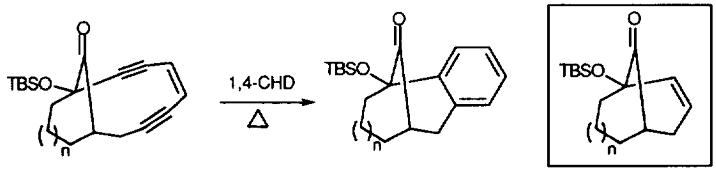
To model the 10-membered cyclic enediynes present in the calicheamicin and esperamicin antibiotics, Nicolaou and coworkers prepared several simple, relatively strain-free enediyne systems.[1h,m] At room temperature, the cyclic enediynes **2.2A** with n=1 to n=7 were found to be stable, but cyclodec-3-ene-1,5-diyne (n=1) underwent Bergman cyclization (Scheme 2.2). By comparing the observed reactivites of these compounds, Nicolaou surmised that the ease of cyclization depends upon the *cd* distance. The experimental results show that the cyclization becomes faster with decreasing *cd* separation. Nicolaou postulated the critical upper limit for the *cd* distance required for cyclization at a measurable rate at ambient temperature to be 3.2–3.3 Å.[1i] These pioneering studies showed that the 10-membered cyclic enediynes were optimal for cyclization, and subsequent studies have utilized similar models. Kraka and Cremer estimated by *ab initio* methods that the *cd* distance at which cycloaromatization becomes spontaneous at 25 °C is 3.0 Å.[13] The correlation between the *cd* gap and reactivity usually does not apply to strained enediynes such as those in bi- and polycyclic systems.[1a]



2.2A (n = 1–7) **2.2B**

Scheme 2.2

Magnus, through both qualitative and quantitative experiments, and Snyder, using *ab initio* methods, suggested independently that the critical factor that determines the reactivity of strained enediynes is not the *cd* distance but the difference in strain energy between the enediyne and the transition state leading to the biradical intermediate.[1a] Magnus and coworkers demonstrated this correlation by studying the bicyclic systems **2.3A** and **2.3B** (Scheme 2.3).[21] The data show that, although the two enediynes have similar *cd* distances, the less strained **2.3B** cyclizes faster at 71 °C than does the more strained **2.3A** at 124 °C. Based on the view that the transition state of the Bergman cyclization is product-like, Magnus demonstrated that the calculated strain energies of the simple models **2.3C** of cyclized products can be used to predict the reactivity of bicyclic enediynes; the smaller the strain energy of the model, the more reactive is the enediyne.[12,13,19,22]



2.3A, 2.3B model **2.3C**

Compound	n	r_{cd}, (Å)	SE_{model} (kcal/mol)	k, s^{-1} (T , °C)
2.3A	0	3.37	19.6	2.08×10^{-5} (124)
2.3B	1	3.39	15.1	1.07×10^{-4} (71)

Scheme 2.3

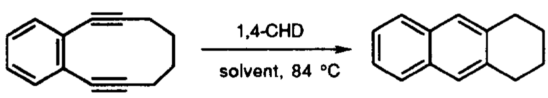
Also assuming that the transition state of the Bergman cyclization is product-like, Maier and Brandstetter used the difference in strain energies between the enediyne and the aromatic product as a measure of the reactivity of enediynes toward cyclization (Scheme 2.4).[23] Although the absolute values of the strain energy (SE) depend on the method of computation, the differences between strain energies seem to reflect adequately the observed reactivity, with less strained analogues such as **2.4B** being much more reactive than the more strained ones such as **2.4A** and **2.4D**. The advantage of this model is that it allows for structural modifications that alter the strain energy of the transition state as well as the ground state.

The dependence of the rate of disappearance of enediyne in the Bergman reaction on the concentration of trapping agent had not been recognized until recently, probably due to the prevalent observation of first-order kinetics with simple enediynes.[24] Semmelhack and coworkers found that the reactivity of **2.5A** to give **2.5B** depends on the concentration of 1,4-cyclohexadiene (1,4-CHD) (Scheme 2.5).[25a,b]

2.4A–F **2.4G–M**

Compound	n	X	SE (kJ/mol) **2.4A–2.4F**	SE (kJ/mol) **2.4G–2.4M**	ΔSE (kJ/mol)
2.4A, 2.4G	0	CH_2	51.5	82.3	30.8
2.4B, 2.4H	1	CH_2	57.8	63.8	6.0
2.4C, 2.4I	2	CH_2	67.5	91.5	24.0
2.4D, 2.4J	0	O	40.8	70.5	29.7
2.4E, 2.4K	1	O	50.2	64.6	14.4
2.4F, 2.4M	2	O	61.6	86.1	24.5

Scheme 2.4

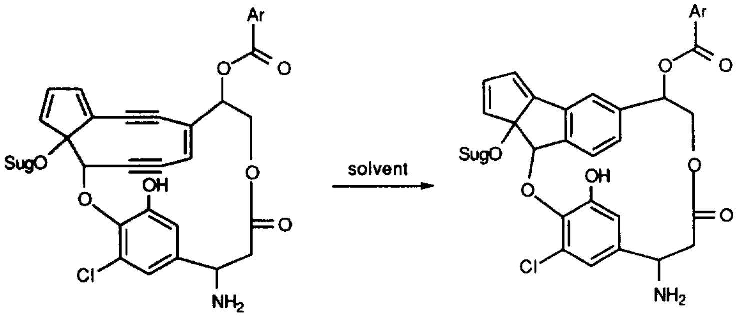


2.5A **2.5B**

conc. of 1,4-CHD (M)	Solvent	$t_{1/2}$ (h)
0.00	C_6D_6	129
0.25	C_6D_6	39
0.50	C_6D_6	24
10.50	neat	10.5

Scheme 2.5

Yoshida and collaborators studied the kinetics of the cycloaromatization of **2.6A** (the chromophore present in the natural product C-1027) in various solvents and observed a remarkable kinetic isotope effect (Scheme 2.6), suggesting that the rate of cyclization of **2.6A** is affected by the concentration of the hydrogen atom donor, and thus the hydrogen abstraction step may be rate determining.[26] The observations by Semmelhack and Yoshida demonstrate that the concentration of the H atom donor should be considered when data from different experiments are compared, unless first-order kinetics are firmly established.

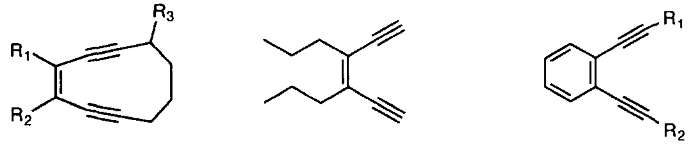


2.6A **2.6B**

Solvent	k_H / k_D
dioxane / dioxane-d_8	2.9
CH_3OH / CH_3OD	1.1
CH_3OH / CD_3OD	2.8

Scheme 2.6

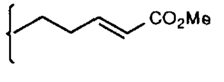
Although no complete systematic study of the effects of substituents on the reactivity of enediynes has been published, this reactivity appears to be sensitive to both electronic and steric effects of substituents. Several research groups have measured the activation energies in cyclic and acyclic systems as well as in systems containing an aromatic and simple enediyne moiety. Nicolaou and Dai determined the energy of activation for the cyclic enediyne **2.7A** (Scheme 2.7).[1n] Subsequently, Boger and Zhou reported measurements on a similar cyclic aromatic enediyne (**2.7B**) and found that the reactivity of the aromatic system was higher.[27] Bergman and coworkers had measured the energy of activation for the acyclic enediyne **2.7C**.[28] Measurements of the acyclic aromatic enediynes **2.7D**–**2.7F** by Grissom and coworkers implied that incorporation of the ene portion of the enediyne in an aromatic ring has a minimal effect on the rate of the Bergman cyclization (Scheme 2.7).[24] The Grissom group also compared the activation energies of **2.7D**–**2.7F** and found that alkyl substituents on the terminal acetylenic carbons cause a decrease in reactivity. In this instance, the observed reactivity differences cannot be attributed to strain factors, since the three substrates have comparable strain energies, as do their respective transition states.



2.7A, 2.7B **2.7C** **2.7D, 2.7E, 2.7F**

Compound	R_1	R_2	R_3	E_a (kcal/mol)	reference
2.7A	H	H	H	23.8 ± 0.04	1h
2.7B	benzo ring		OH	19.4	27
2.7C	-	-	-	27.4 ± 0.5	28
2.7D	H	H	-	25.1 ± 0.8	24
2.7E	H	X	-	28.1 ± 0.8	24
2.7F	X	X	-	34.0 ± 0.3	24

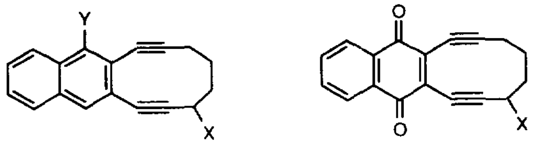
X =



Scheme 2.7

Semmelhack *et al.* found **2.8B**, in which the ene portion is part of a quinone ring, to be more reactive than **2.8A**, in which the ene is part of an aromatic ring (Scheme 2.8).[25b] This observation suggests that the olefinic/aromatic character of the ene unit of enediynes does significantly affect the reactivity of enediynes; this view is in disagreement with observations made by Boger and by Grissom. The disparity could, however, arise from the opposite electronic effects of the substituents (OMe and C=O) on the ene portion of **2.8A** and **2.8B**. A comparison of **2.8C** and **2.8D** shows that, in highly reactive enediynes, the electronic effects of the ene unit on the reactivity is insignificant.

Maier and Greiner compared the reactivity of enediyne **2.9A**[29] with the unsubstituted counterpart **2.9B**[21] and found **2.9B** to be more reactive than **2.9A** (Scheme 2.9). The lower reactivity of **2.9A** has been attributed to greater stabilization of the ground state of the enediyne compared to the transition state due to electronic effects of the *p*-methoxyphenyl group.

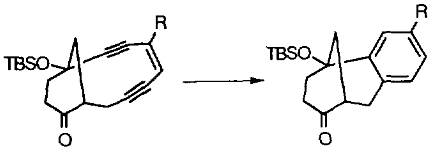


2.8A, 2.8C **2.8B, 2.8D**

Compound	X	Y	$t_{1/2}$ (h)	T (°C)
2.8A	H	MeO	>168	120
2.8B	H	-	88	40
2.8C	OH	*t*-BuOCO	2	55
2.8D	OH	-	2	55

Scheme 2.8

Other examples that illustrate how substituents affect the reactivity of enediynes in Bergman cycloaromatizations have been studied (Scheme 2.10).[25b,30] Relatively small changes in the substitution pattern result in large changes in the reactivity of the enediynes. Clearly, quinone **2.10H** is more reactive than the aromatic enediynes **2.10C** and **2.10D**. Also of interest is the fact that placing an oxygen in the ring (**2.10B**) greatly facilitates the cyclization. If the propargyl position of the enediyne is substituted with an electron-withdrawing group such as hydroxyl (**2.10D**) or especially a carbonyl (**2.10E**), the rate of cyclization is also increased. In a model of esperamicin, simply changing an alcohol (**2.10K**) to a carbonyl (**2.10J**) imparts much stability to the molecule.[29] The cyclization of many other enediyne models have been studied qualitatively; these will be discussed in a later section.

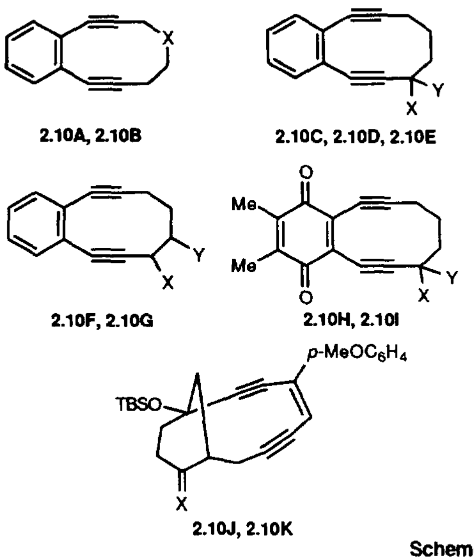


2.9A, 2.9B

Compound	R	$\Delta G^{\#}$ (kJ/mol)
2.9A	*p*-$MeOC_6H_4$	111
2.9B	H	98.7

Scheme 2.9

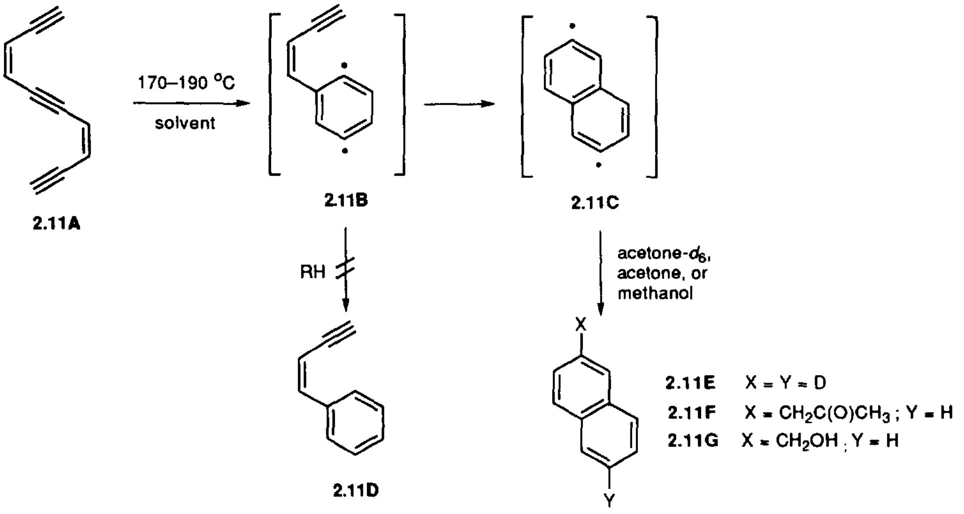
Some recent discoveries may potentially expand the knowledge of dehydroaromatic biradicals as well as the utility of enediyne cyclizations. Bergman and his group demonstrated the viability of generating the 2,6-dehydronaphthalene biradical **2.11C** by double cycloaromatization of the extended enediyne **2.11A** (Scheme 2.11).[31] When **2.11A** was heated in various radical-donor solvents, the substituted naphthalenes **2.11E**–**2.11G** were formed. The absence of product **2.11D**, derived from the 1,4-dehydrobenzene intermediate **2.11B**, suggests that either **2.11B** cyclizes very rapidly to **2.11C**, or the cyclization of **2.11A** to **2.11C** is a concerted process.



Cmpd	X	Y	$t_{1/2}$ (h)	T (°C)	Ref.
2.10A	CH_2	-	24	84	25b
2.10B	O	-	52	37	30
2.10C	H	H	24	84	25b
2.10D	H	OH	4.5	84	25b
2.10E	O		<1	84	25b
2.10F	OH	H	4.5	84	25b
2.10G	H	OH	14	84	25b
2.10H	H	OH	2	55	25b
2.10I	O		2	55	25b

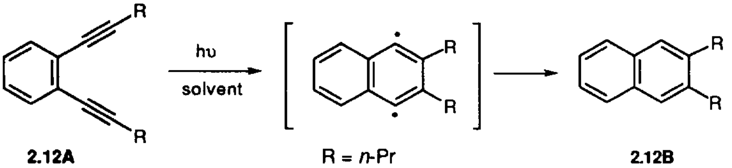
Cmpd	X	Reactivity at RT	Ref.
2.10J	O	stable	29
2.10K	H, OH	cyclizes	29

Scheme 2.10



Scheme 2.11

Probably the most significant drawback to enediyne cyclizations is that, unless the system is cyclic, high temperatures are required to promote the ring closure. Recent work by Turro and collaborators offers a mild alternative to thermolysis — namely the first direct photo-induced cycloaromatization of an enediyne.[32a] When **2.12A** was irradiated in the presence of various radical donors, the naphthalene derivative **2.12B** was formed (Scheme 2.12). A mechanism similar to that of the thermal cyclization has been proposed. A more extensive investigation of the photochemically activated Bergman cyclization was recently reported by Funk and coworkers.[32b] Buchwald *et al.* recently reported a Bergman cyclization of 1,2-*bis*(diphenylphosphinoethynyl)-benzene using palladium or platinum chlorides as catalysts.[32c]

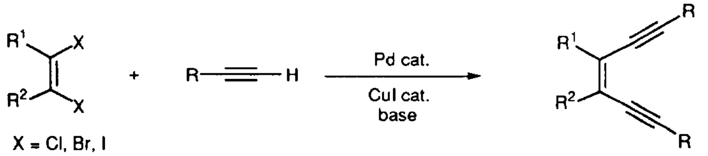


Solvent	Yield (%)
C_6H_6/benzhydrol	40
i-PrOH	0.25

Scheme 2.12

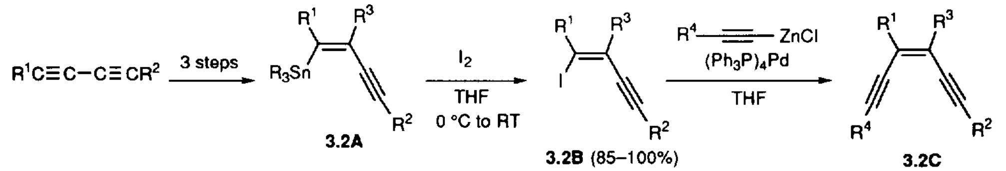
3. Synthesis of Enediynes

The greatly increased demand for structurally diverse enediynes has prompted synthetic chemists to seek novel and more efficient approaches to the enediyne functionality. Many strategies have been developed to construct or modify enediyne systems. Recent general routes to enediynes are covered here and synthetic methods involved with specific cyclic analogues that undergo cycloaromatization are discussed later in section 5. The palladium-mediated coupling of haloalkenes with acetylenes (Scheme 3.1) has been the most commonly used method for assembling enediynes.[33] A significant portion of recent developments have involved improvements or modifications of the versatile palladium-catalyzed coupling reaction.



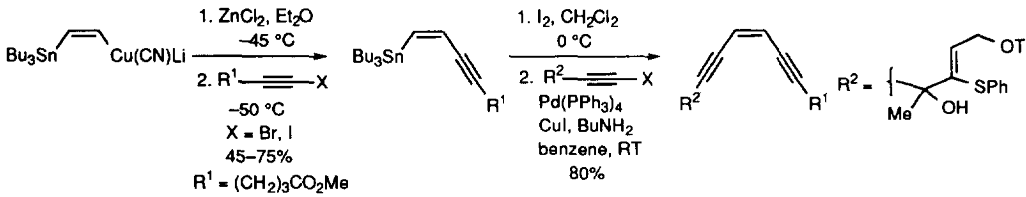
Scheme 3.1

Zweifel and Stracker reported syntheses of the di-, tri-, and tetrasubstituted (Z)-enediynes **3.2C** by palladium-catalyzed cross-coupling of the iodoenynes **3.2B**, derived from monostannylenynes **3.2A**, with alkynyl zinc reagents (Scheme 3.2).[34] A related approach has been described by Magriotis and coworkers (Scheme 3.3).[35]



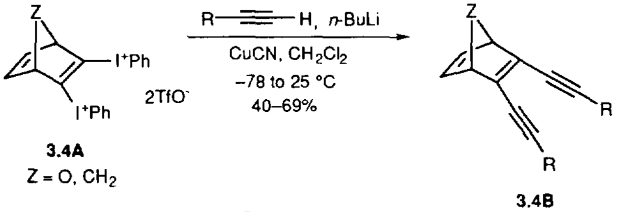
R¹, R³ = H, alkyl
R² = silyl
R⁴ = H, alkyl, aryl, silyl

Scheme 3.2



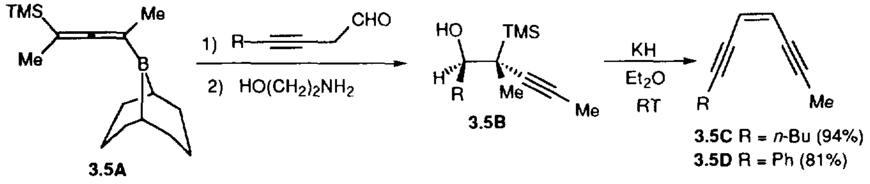
Scheme 3.3

Several reports describe the preparation of enediynes containing novel acetylenic side chains. Alami and Linstrumelle and Crousse prepared unsymmetrical (*Z*)- or (*E*)-enediynes with acetylene side chains containing sensitive functionality such as hydroxyl and amino groups by a one-pot procedure that involves two consecutive couplings and use of $Pd(PPh_3)_4$ and $PdCl_2(PhCN)_2$ as catalysts.[36] The first example of an enediyne with side chains bound to crown ethers, prepared also by standard palladium-coupling techniques, has been described by König and Rütters.[37] de Meijere and McGaffin reported the synthesis of a cyclopropyl-disubstituted enediyne by palladium-catalyzed coupling of cyclopropyl acetylene with 1,2-dibromoethylene.[38] Isobe *et al.* developed a simple method for the one-step conversion of (trimethylsilyl)acetylenes to haloacetylenes and demonstrated its utility in the synthesis of haloenediynes.[39] Stang and coworkers reported the synthesis of bicycloenediynes **3.4B** by the coupling of the iodonium salts **3.4A** with alkynyl cuprates generated *in situ* (Scheme 3.4).[40]

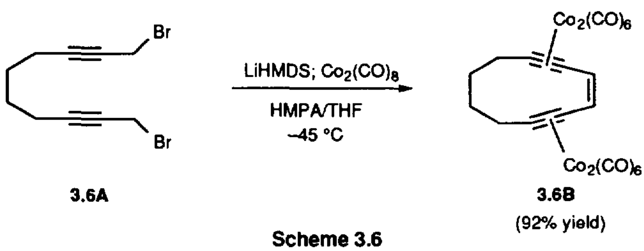


Scheme 3.4

Wang and coworkers utilized a Peterson elimination to construct nonsymmetric acyclic enediynes (Scheme 3.5).[41] The substrate alcohols **3.5B** were obtained from the reaction of acetylenic aldehydes with the δ–silyl-allenylborane **3.5A**. The 10-membered cyclic enediyne complex **3.6B** was prepared by Jones *et al.* in a one-pot procedure from the acyclic precursor **3.6A** (Scheme 3.6).[42] The HMPT/base ratio was shown to be crucial for the yield of enediyne **3.6B**.

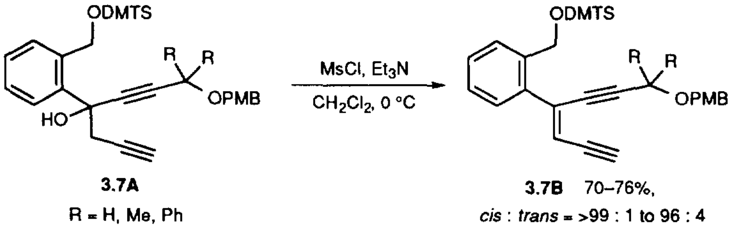


Scheme 3.5

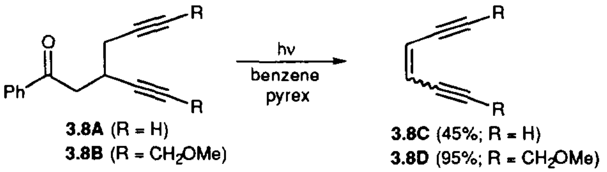


Scheme 3.6

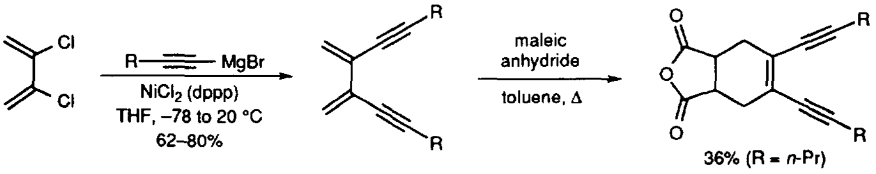
Shibuya *et al.* prepared the acyclic *cis*-enediynes **3.7B** in a highly selective manner by generating the ene unit *via* the elimination of a tertiary OH (as the mesylate) from alcohols **3.7A** (Scheme 3.7).[43] In a mild method that potentially could be used for prodrugs of enediynes, Nuss and Murphy reported the synthesis of the acyclic enediynes **3.8C** and **3.8D** by a Norrish type II photochemical fragmentation of diynes **3.8A** and **3.8B** (Scheme 3.8).[44] No selectivity (*Z*:*E* = 1:1) was observed in this reaction. Hopf and Theurig used a two-step procedure to assemble tetrasubstituted enediynes, in which the ene unit was installed by a Diels-Alder reaction (Scheme 3.9).[45]



Scheme 3.7



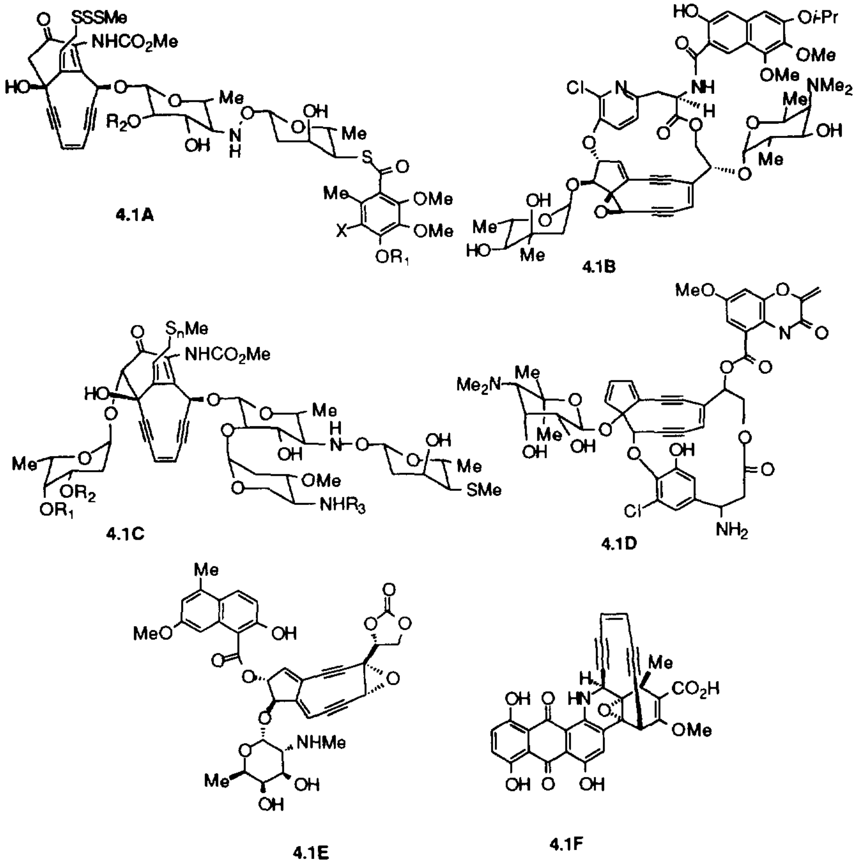
Scheme 3.8



Scheme 3.9

4. Enediyne Natural Products

Currently, five classes of enediyne-containing natural products are known: calicheamicins **4.1A**, esperamicins **4.1C**, dynemicin **4.1F**, kedarcidin chromophore **4.1B**, and C-1027 chromophore **4.1D** (Scheme 4.1).[1] The neocarzinostatin chromophore **4.1E** (Scheme 4.1) does not possess a conjugated enediyne unit, but, once activated, acts in a similar manner to the enediyne natural products. Neocarzinostatin is discussed in section 6.



Scheme 4.1

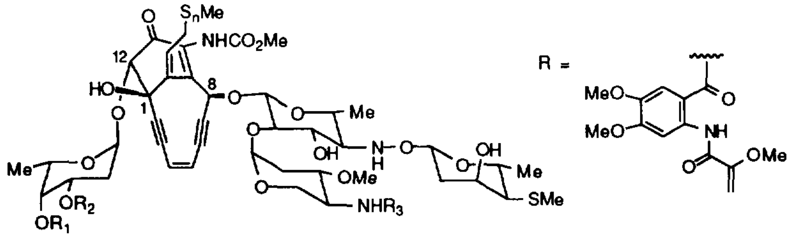
The enediyne natural products are among the most potent antitumor and antibacterial agents known.[1a,i,n] The biological activity of these compounds is attributed to their ability to cleave duplex DNA irreversibly. In general, DNA cleavage by naturally occurring enediynes occurs in four stages:

1. Recognizing and binding to DNA by a specific structural feature covalently bonded or complexed to the enediyne.
2. Activation of the enediyne toward Bergman reaction.
3. Bergman cyclization to give 1,4-dehydroarene biradicals.
4. Abstraction of hydrogen from DNA by the 1,4-dehydroarene biradicals thereby inflicting permanent damage to genetic material.

A fundamental difference between naturally occurring enediynes and synthetic models is the means of activation towards cycloaromatization. Enediynes can be activated thermally and a member that is unreactive at lower temperature can be cyclized simply by an increase in temperature. In contrast, naturally occurring enediynes that function at physiological temperature, are designed by nature to be activated chemically. In all currently known enediyne natural products, the enediyne moiety is contained within a 9- or 10-membered ring. Simple 9- and 10-membered cyclic enediynes are known to cycloaromatize at or below room temperature,[1i] but the natural enediynes are stable towards Bergman closure at physiological temperature. This distinction arises because, in natural analogues, the presence of some structural feature closely associated with the enediyne moiety raises the activation energy and thereby prevents the cyclization from occurring at an appreciable rate. Removal of this "protection" by means of a chemical reaction that occurs only after the natural product is bound to DNA, lowers the activation energy and thus facilitates the cyclization. In this context, the natural enediyne antitumor antibiotics can be regarded as prodrugs.[1a] Nicolaou compared the biological action of enediyne natural products to the workings of modern weaponry: the enediyne which is the warhead ready to explode, a molecular device that provides a mechanism to deliver the warhead to its target, and a triggering device to activate the warhead to destroy the target.[1n]

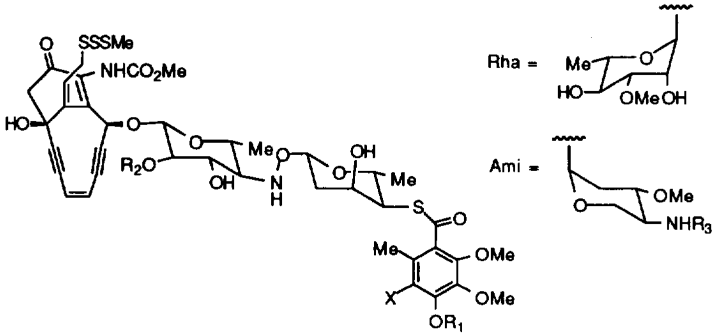
Esperamicins and Calicheamicins:

The first enediyne natural products to be identified, the esperamicins and the calicheamicins, share the same enediyne-containing bicyclic core as well as a similar mode of biological action; they differ only in the ancillary structure. The family of esperamicins, isolated from the fermentation broths of *Actinomadura verrucosospora*,[7] has now grown to seven known members with esperamicin A being the most prominent (Scheme 4.2).[1n,46] The absolute stereochemistry of the aglycone of the esperamicins has been assigned by Golik and collaborators as C-1 (*S*), C-8 (*S*), and C-12 (*S*).[47] The calicheamicin family, produced by *Micromonospora echinospora ssp. calichensis*, currently consists of 15–20 members (Scheme 4.3).[1n,6,48]



Esperamicin	n	R_1	R_2	R_3
A_1	3	H	R	*i*-Pr
A_{1b}	3	H	R	Et
A_{1c}	3	H	R	Me
P	4	H	R	*i*-Pr
A_2	3	R	H	*i*-Pr
A_{2b}	3	R	H	Et
A_{2c}	3	R	H	Me

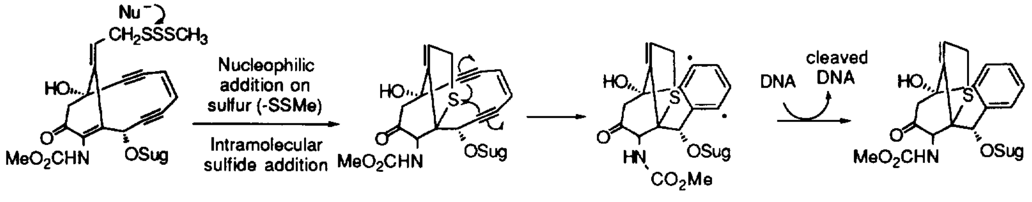
Scheme 4.2



Calicheamicin X		R_1	R_2	R_3
β_1^{Br}	Br	Rha	Ami	*i*-Pr
γ_1^{Br}	Br	Rha	Ami	Et
α_2^{I}	I	H	Ami	Et
α_3^{I}	I	Rha	H	
β_1^{I}	I	Rha	Ami	*i*-Pr
γ_1^{I}	I	Rha	Ami	Et
δ_1^{I}	I	Rha	Ami	Me

Scheme 4.3

The chemical events responsible for the biological activity of the esperamicins and calicheamicins are shown in Scheme 4.4, as demonstrated for calicheamicin γ_1^I, the most thoroughly studied member of the calicheamicin family.[1n,o] The rate determining step for activation of calicheamicin γ_1^I was found to be the generation of an allylic thiolate. Townsend and coworkers showed that neither the basicity of the aminosugar nor the binding to DNA has a catalytic effect on the activation of calicheamicin γ_1^I.[49a,b]



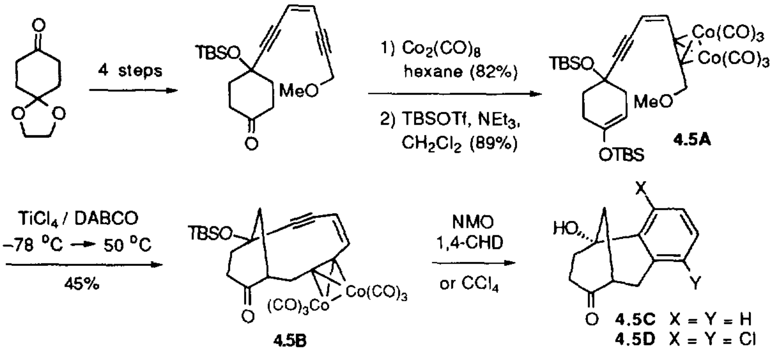
Scheme 4.4

There has been considerable work on the identification, properties, and synthesis of the esperamicins and calicheamicins.[1d,g,h,i,o] Synthetic effort has been directed toward both the enediyne core and the polysaccharide fragments of these molecules. Detailed biosynthetic studies on esperamicin A were carried out by Lam *et al.*, who examined the incorporation of labeled compounds fed to cultures of *Actinomadura verrucosospora*.[50]

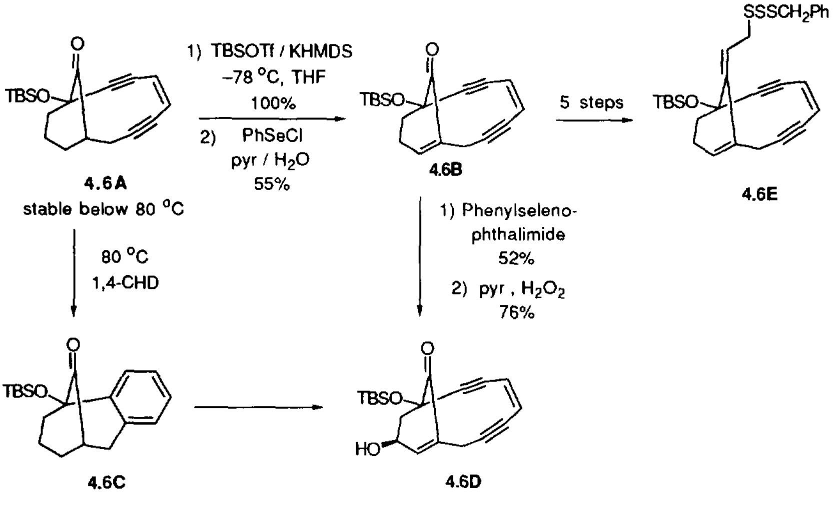
In addition to contributions involving the enediyne core, several significant reports have appeared on the preparation of the sugar moieties. Golik *et al.*, based on both chemical and spectroscopic studies, assigned the β–D–glucohexopyranose configuration to the hydroxylamino sugar fragment of esperamicin A_1.[51] Kahne and his group studied the influence of the hydroxylamine glycosidic linkage on the shape of the calicheamicin oligosaccharide both experimentally and computationally.[52] The results suggest that this unusual N-O bond organizes the two halves of the molecule into a shape that complements the shape of the minor groove of DNA. Kahne also developed a general method to introduce the N-O linkage to oligosaccharides and applied it to the stereoselective construction of the trisaccharide of calicheamicin.[53a,b] Roush and coworkers reported the asymmetric synthesis of the thiosugar of esperamicin A_1 and the 4-hydroxylamino sugar of the calicheamicins.[54] Mash and Nimkar synthesized the 4-ethylaminopentapyranose unit of the calicheamicins and esperamicins stereoconvergently from 2-deoxy-D-ribose.[55] Scharf and Claßen described the synthesis of the thiosugar unit of the calicheamicins and esperamicins from methyl α-D-galactopyranoside.[56] The first total synthesis of the trisaccharide of the esperamicins was accomplished by Danishefsky and his group,[57] who also described the first total synthesis of the aryltetrasaccharide system of the calicheamicins and demonstrated its coupling to aglycone intermediates by a Schmidt reaction.[58] Nicolaou and Clark synthesized both carbohydrate fragments of esperamicin A_1 in optically active form.[59]

There have been extensive efforts toward the synthesis of the enediyne core of the esperamicins and calicheamicins as well as toward their total synthesis. Since Danishefsky's pioneering work describing the synthesis of calicheamicinone in both racemic and enantiomerically pure form,[1n,60a–c] various syntheses have been reported. Many of these syntheses have been covered in an earlier review[1n] and only recent contributions will be summarized here.

Magnus *et al.* introduced a general strategy for the construction of the bicyclo[7.3.1]tridecenediyne core of the esperamicins and calicheamicins, based on the ability of acetylenes to form a complex with η^2-$Co_2(CO)_6$ (Scheme 4.5).[1d,e,21] The dicobalt hexacarbonyl adduct **4.5B** was synthesized through cyclization of **4.5A** *via* η^2-dicobalt hexacarbonyl propargyl cation alkylation. Decomplexation of **4.5B** in 1,4-CHD or CCl_4 yielded the cycloaromatized product **4.5C** and **4.5D**, respectively, without isolation of the intermediate enediyne. Enediyne **4.6A**, prepared in a similar manner, was found to be stable below 80 °C and to undergo cyclization at higher temperature (Scheme 4.6). The enediyne core structure **4.6A** could also be functionalized by oxidative methods to introduce the 1,2-alkene and 3-oxygen substituent (**4.6D**) (Scheme 4.6). The allylic trisulfide could be installed *via* Wittig reaction on the 13-keto group (**4.6E**).[61]

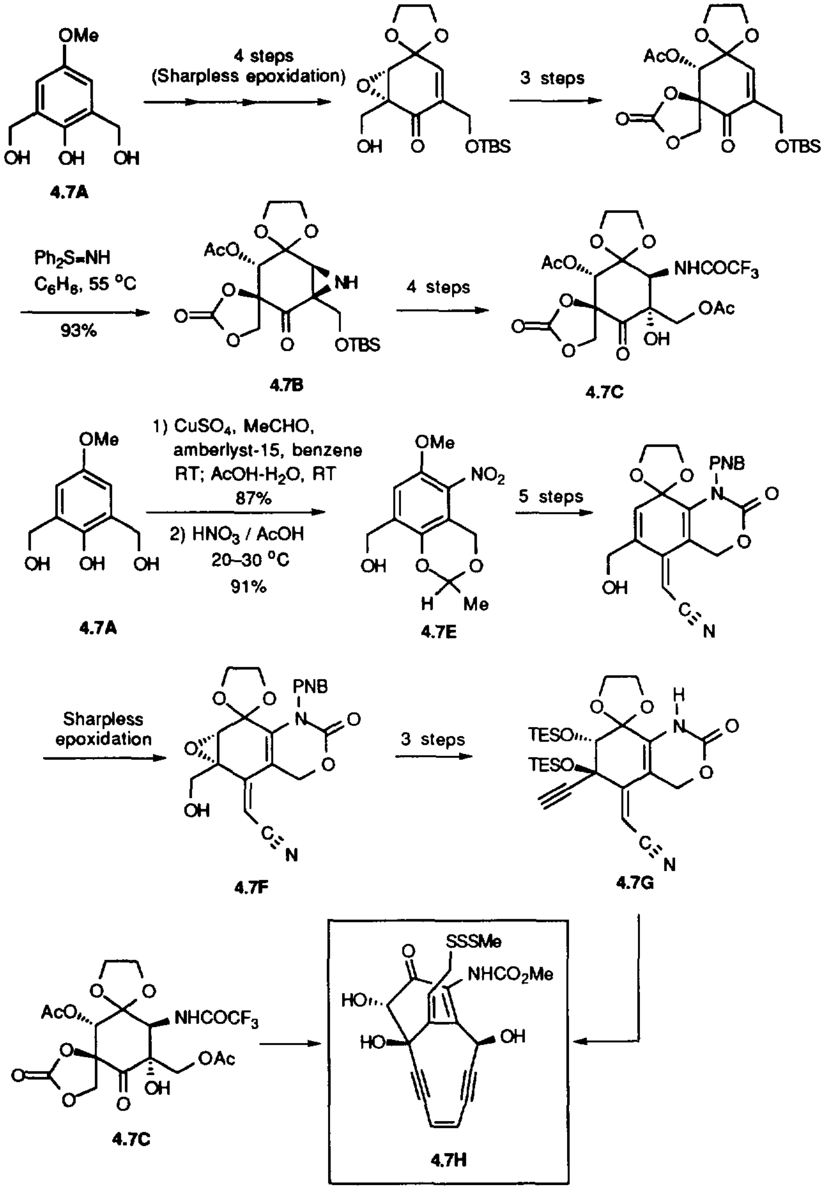


Scheme 4.5



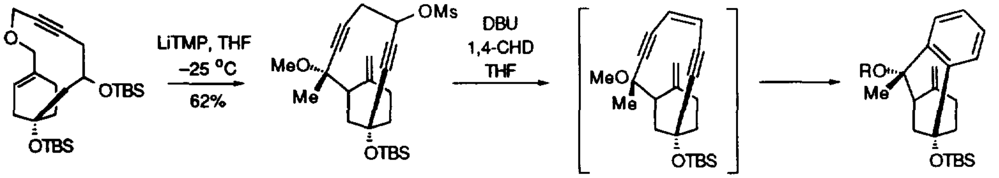
Scheme 4.6

Nicolaou *et al.* described the synthesis of a variety of highly functionalized intermediates suitable for further elaboration to esperamicinone **4.7H**, the aglycone of esperamicin A_1, starting from the readily available arene **4.7A** (Scheme 4.7).[62] The strategy is based on an asymmetric epoxidation of a quinone monoketal. Two approaches for the introduction of the vinylogous urethane were demonstrated; in one, the nitrogen atom was introduced at a later stage of the synthesis (**4.7A** → **4.7C** → **4.7H**); in the other, the task was accomplished at an earlier stage (**4.7A** → **4.7G** → **4.7H**).



Scheme 4.7

Grierson and coworkers developed a novel approach to the bicyclic core structure of calicheamicin γ_1^I and esperamicin A_1 based on a [2,3]-Wittig rearrangement (Scheme 4.8).[63a,b] Treatment of **4.8A** with LiTMP yielded enediyne precursor **4.8B**. This compound, when treated with DBU in the presence of 1,4-CHD, presumably reacted to form enediyne **4.8C**, which was not stable and spontaneously cyclized to give the aromatic products **4.8D–4.8F**. Product **4.8D** is consistent with a quenching of the 1,4-dehydroaromatic intermediate; the formation of the two unexpected products **4.8E** and **4.8F** apparently involves 1,5-hydrogen transfer from the methoxy group in the biradical intermediate.

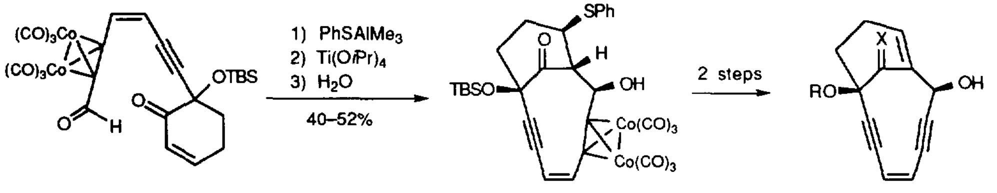


4.8A **4.8B** **4.8C**

4.8D R = Me
4.8E R = CHO
4.8F R = H

Scheme 4.8

The approach of Kadow and coworkers toward the core structure of the esperamicins and calicheamicins was based on the conjugate addition of $PhSAlMe_2$ to enone **4.9A** followed by an *in situ* aldol reaction and decomplexation to give the stable bicyclic enediyne **4.9C** stereoselectively (Scheme 4.9).[64] Although this simple model lacked a DNA recognition appendage, it underwent cycloaromatization in the presence of 2-mercaptoethanol and showed substantial *in vivo* antitumor activity. Kadow *et al.* also synthesized the core structure **4.9D** and developed methods for a selective functionalization thereof (Scheme 4.9).[65a,b]

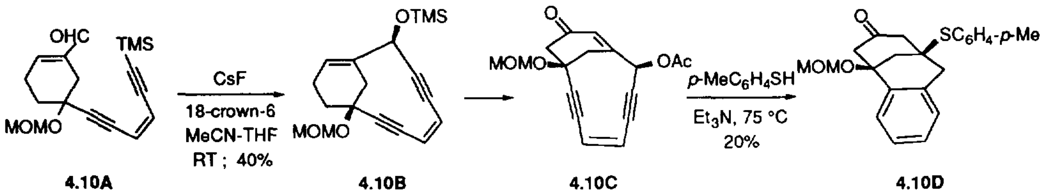


4.9A **4.9B**

4.9C R = H ; X = O
4.9D R = TBS ; X = H, H

Scheme 4.9

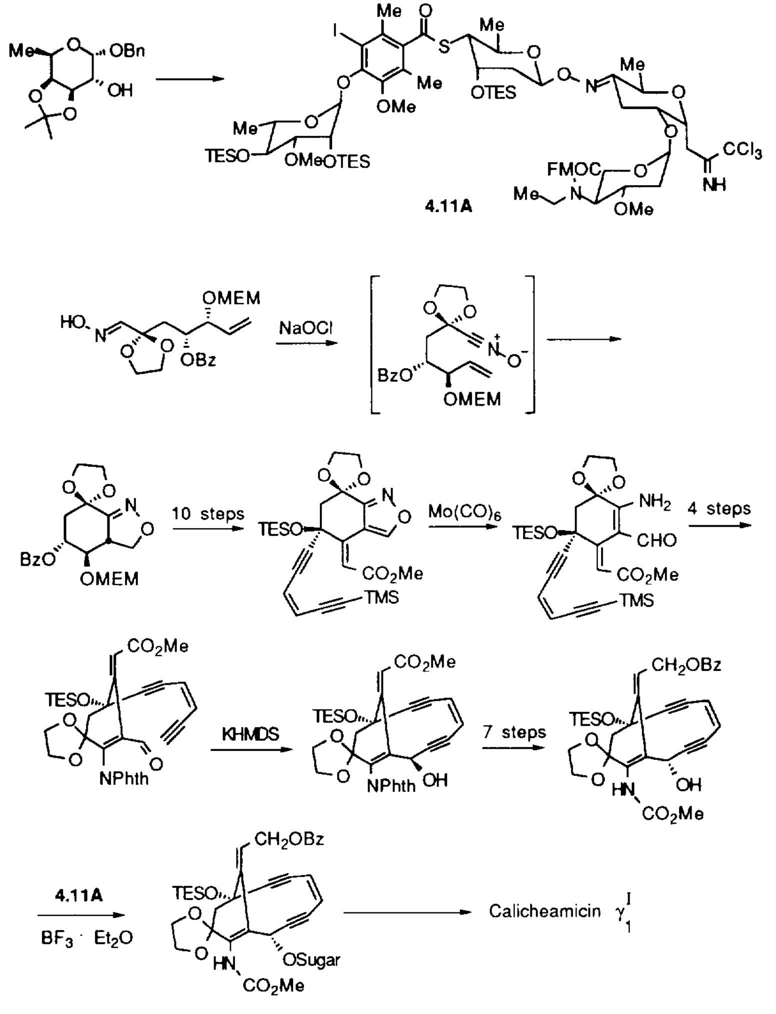
Isobe and coworkers synthesized the esperamicin/calicheamicin core **4.10C**[66a] (related closely to Kadow's model **4.9C**) using as the key step a CsF-promoted intramolecular desilylative condensation procedure developed by Wender and Zercher (Scheme 4.10).[67] Enediyne **4.10C** required higher temperatures to cyclize under thiol activation than did **4.9C**. Mastalerz *et al.* recently reported a similar approach to esperamicin analogues.[66b]



4.10A **4.10B** **4.10C** **4.10D**

Scheme 4.10

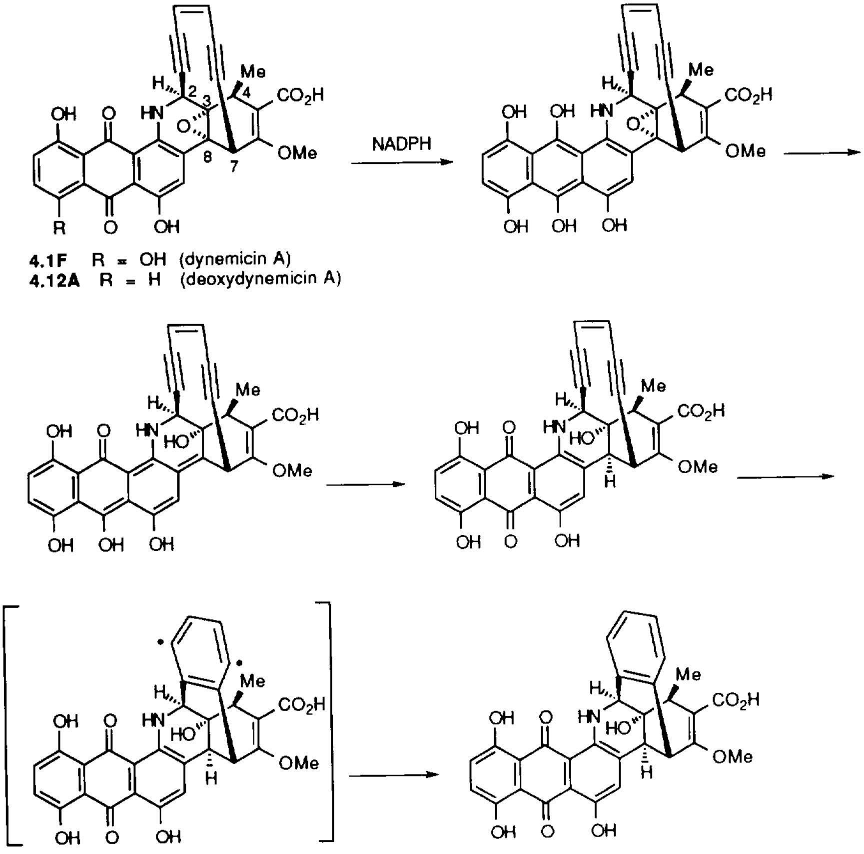
The first total synthesis of calicheamicin γ_1^{I} was accomplished by Nicolaou and his group.[1g,68a–e] The convergent approach (Scheme 4.11) includes assembly of the oligosaccharide fragment, enantioselective synthesis of an aglycone precursor and coupling of the oligosaccharide fragment to the aglycone precursor. Further elaboration of the aglycone precursor gave calicheamicin γ_1^{I} in enantiomerically pure form. Danishefsky *et al.* employed a similar strategy for the coupling of the oligosaccharide to the aglycone in his recent report of the total synthesis of calicheamicin γ_1^{I}.[68f]



Scheme 4.11

Dynemicins:

The dynemicin family of enediyne antitumor antibiotics currently includes two members (Scheme 4.12).[1n] The better known member, dynemicin A (**4.1F**), was isolated from the fermentation broth of *Micromonospora chersina*.[69] The more recently identified deoxydynemicin A (**4.12A**) is produced by *Micromonospora globosa* MG331-HF6.[70] The dynemicins feature structural characteristics of both the anthracycline and the enediyne families and hence are representative of a unique class of natural antitumor agents. Dynemicin A is also less toxic than are the esperamicins and calicheamicins. Myers and coworkers recently showed the absolute stereochemistry of the natural (+)-enantiomer of dynemicin A to be C-3 (*S*), C-4 (*S*), C-7 (*R*), C-8 (*R*).^{71} The proposed mechanism for the cycloaromatization of dynemicin A (**4.1F**) is given in Scheme 4.12.^{71,72}



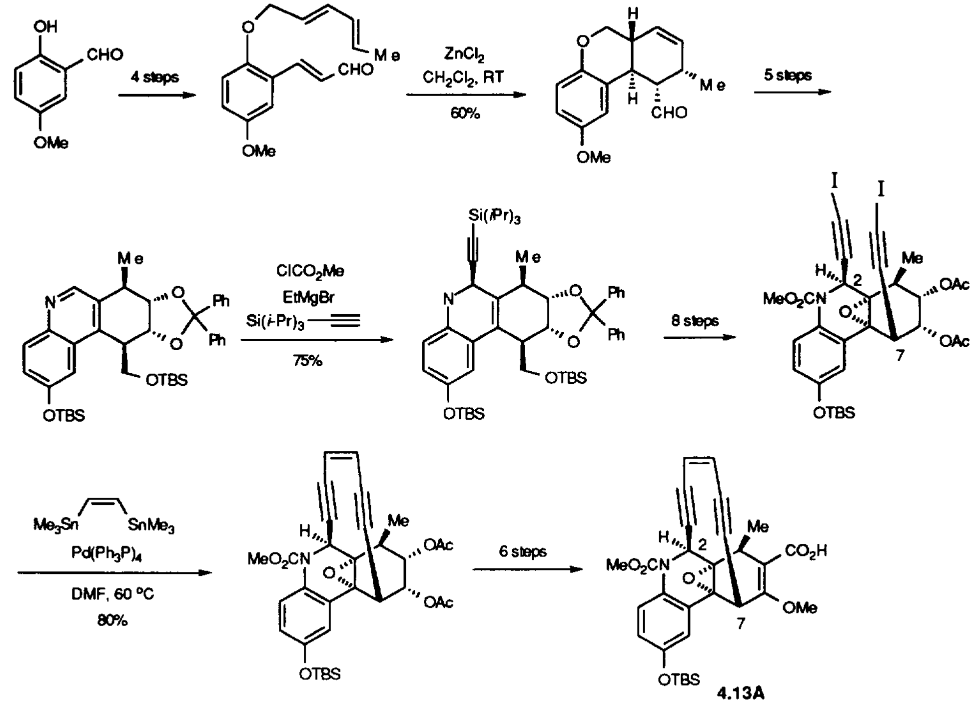
4.1F R = OH (dynemicin A)
4.12A R = H (deoxydynemicin A)

Scheme 4.12

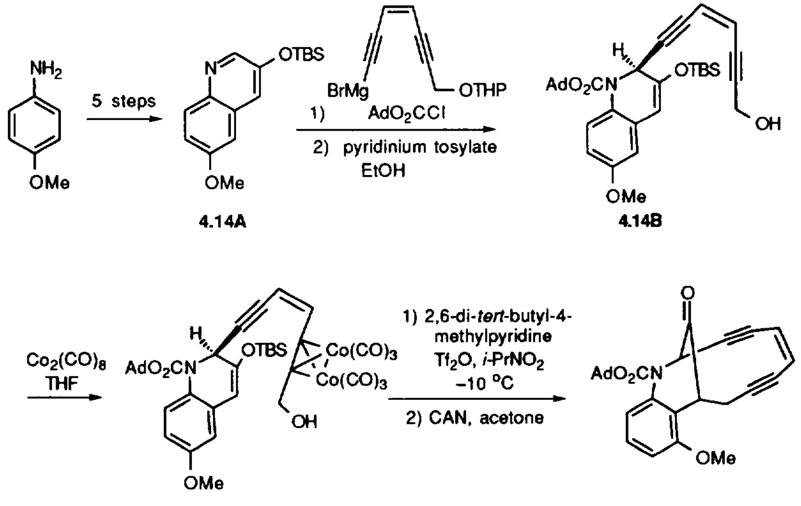
The dynemicins, like the esperamicins and calicheamicins, have been intensively investigated by synthetic chemists. Efforts have been directed toward both the pentacyclic framework and the enediyne core. Nicolaou^{73} and Isobe^{74} prepared the pentacyclic quinone of dynemicin A. Syntheses of the tetracyclic anthraquinone subunit of dynemicin A were described by Magnus^{75} and by Schreiber.^{76} Danishefsky reported a route to the deprotected ABC ring system **4.13A** of dynemicin A, which addressed one of the crucial stereochemical challenges in the total synthesis of dynemicin A, namely introduction of the *cis* relationship at C-2 and C-7 (Scheme 4.13).^{77a,b} Takahashi *et al.* used a related approach towards the synthesis of dynemicin analogues.^{77c}

Magnus assembled the bicyclic enediyne core **4.14D** of the dynemicins using the η^2–$Co_2(CO)_6$-propargyl cation cyclization strategy as the key step (Scheme 4.14).^{1d,e,78} The overall yield from quinoline **4.14A** was 15%. Schreiber reported the total syntheses of di- and tri-*O*-methyl dynemicin A (**4.15A**) featuring a trans-annular Diels-Alder reaction and an anthraquinone annulation sequence as key processes (Scheme 4.15).^{79}

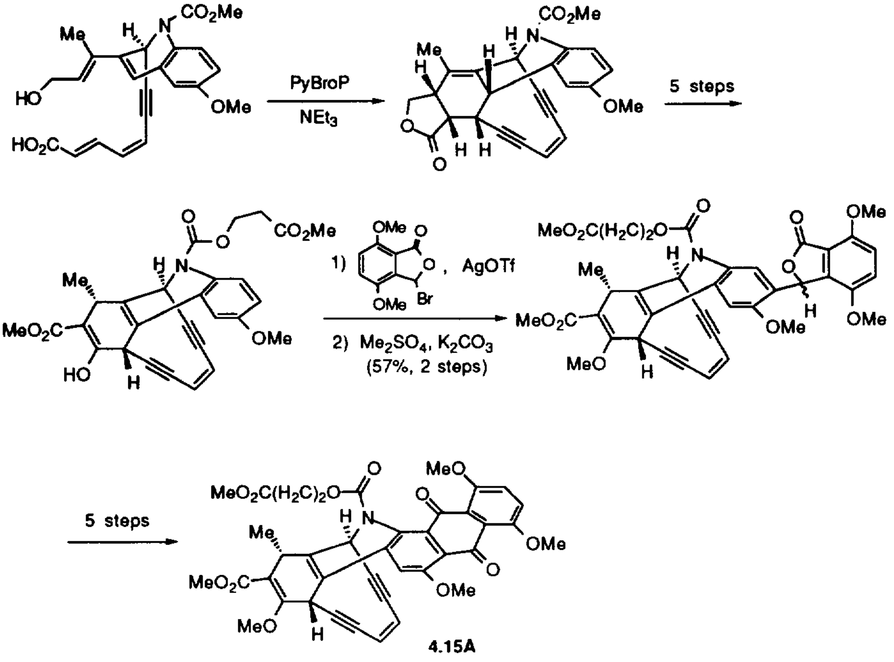
Myers *et al.* accomplished the first total synthesis of (+)-dynemicin A (**4.1F**).^{71,80a} Enantioselective and highly convergent, Myers' route (Scheme 4.16) includes enantioselective construction of the quinone imine precursor **4.16A**, annulation of the anthraquinone skeleton by a Diels-Alder reaction to form **4.16B**, and then oxidation to afford dynemicin A (**4.1F**). The Myers group recently used this methodology for the preparation of several dynemicin analogues.[80b]



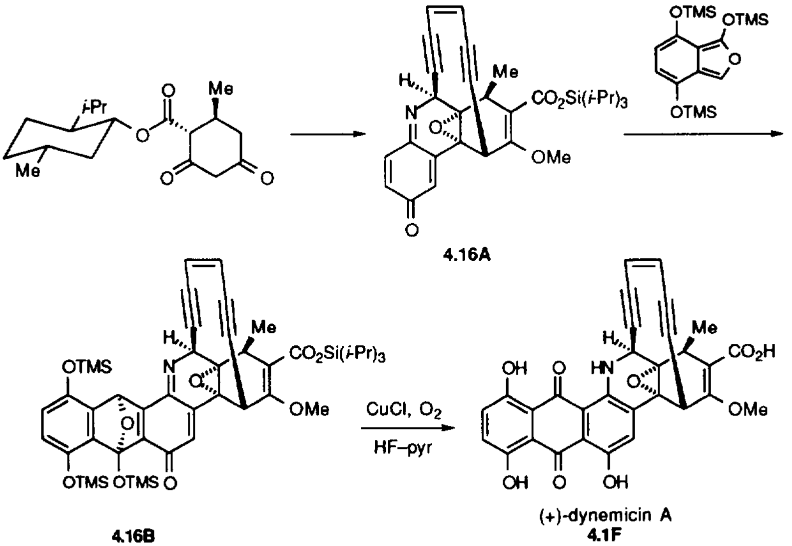
Scheme 4.13



Scheme 4.14



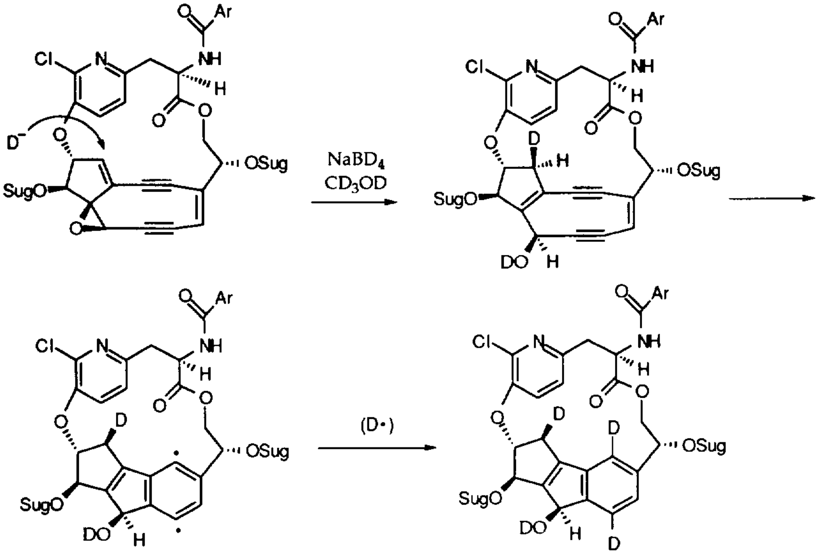
Scheme 4.15



Scheme 4.16

Kedarcidin:

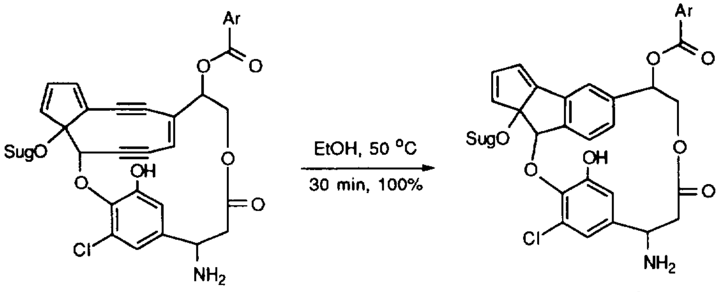
Produced by an *actinomycete* strain, kedarcidin is a chromoprotein consisting of a water-soluble apoprotein and a highly unstable enediyne-containing chromophore (**4.1B**), the latter which is responsible for its DNA cleaving activity (Scheme 4.17).[81] The apoprotein is believed to play a role in the stabilization and transport of the chromophore. Zein *et al.* showed that the kedarcidin apoprotein can cleave proteins *in vitro*, behaving like a protease.[82] Leet and coworkers elucidated the structure, including absolute stereochemistry, of the kedarcidin chromophore using a combination of chemical, spectroscopic, and molecular modeling methods. They also proposed a mechanism for its mode of action based on the products observed from its reduction by $NaBD_4$ (Scheme 4.17).[83] Due to its relatively recent discovery, the kedarcidin chromophore has not yet received much attention from synthetic chemists. Sztaricskai *et al.*[84] as well as Kihlberg, Somfai, and Vuljanic[85] have reported syntheses of the amino sugar component of the kedarcidin chromophore as its methyl glycoside.



Scheme 4.17

C-1027:

The latest entry to the growing class of enediyne antitumor antibiotics, C-1027 (**4.1D**), is a chromoprotein isolated from *Streptomyces globisporus* C-1027.[86a] The chromophore of C-1027 is highly labile and, once separated from the apoprotein, undergoes cycloaromatization without any activation.[86] Minami, Yoshida and coworkers[87,88] jointly elucidated the structures of C-1027 chromophore and its cycloaromatized product **4.18A** (Scheme 4.18). Hirama *et al.* described the synthesis and absolute stereochemistry of the aminosugar moiety of C-1027.[89]



C-1027 chromophore (4.1D)

4.18A

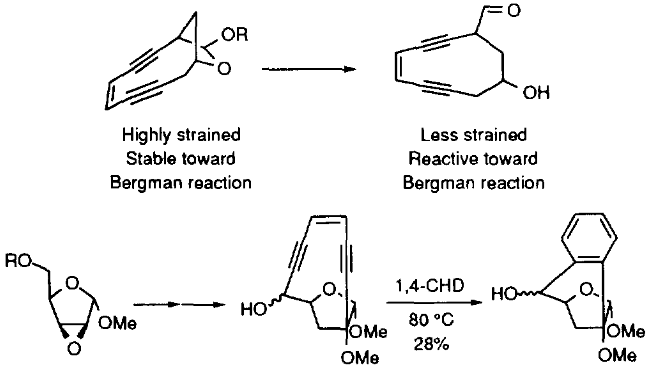
Scheme 4.18

5. Analogues and Models of Enediyne Natural Products

Despite their remarkable potency as antitumor antibiotics, enediyne natural products have found limited use in clinical applications owing to their toxicity and instability. Organic chemists have therefore sought to develop analogues and models of enediyne natural products that are more selective and stable and still retain or even exceed the efficacy of the natural counterparts. Nicolaou[90] listed several desirable characteristics of analogues that would allow such compounds to be clinically useful agents: 1) chemically stable under neutral conditions but able to undergo cycloaromatization upon suitable activation; 2) structurally simple, thus easily synthesized; 3) attachable to appropriate delivery systems and to other desirable moieties through proper functionality; and 4) equipped with suitable initiators that may be activated under mild or biological conditions.

Kadow pointed out that reactive but non-essential functional groups should be absent from analogues to achieve greater chemical stability.[65b] In the past few years, there have been many reports of potential mimics of enediyne natural products that span a broad range in terms of design logic and sophistication. Some of these compounds are merely novel cyclic enediynes with the capacity to undergo Bergman aromatization upon suitable activation, whereas others are refinements of the natural products themselves.

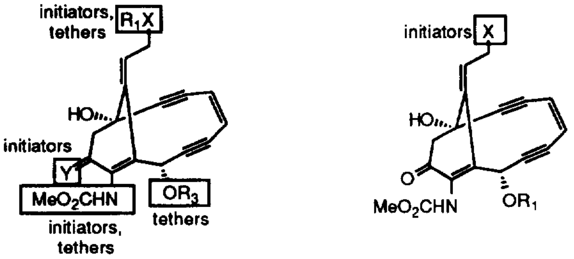
A cyclic enediyne may or may not cycloaromatize efficiently at physiological temperature depending on the activation energy involved, which, in turn, is controlled by the combined electronic and steric effects of the structural features. A general strategy toward model systems for enediyne natural products would be to assemble a 10-membered cyclic enediyne with a specific structural feature that precludes a Bergman closure at physiological temperature. Then removal of the blocking device by chemical or physical means would activate the system toward cycloaromatization. Maier proposed an activation mechanism using the scission of a stable bicyclo[7.2.1]-enediyne to form a reactive 10-membered monocyclic enediyne.[91] He proposed the model system **5.1A** containing an acetal, which would afford an activated enediyne upon removal (Scheme 5.1). As expected, **5.1A** proved to be stable at room temperature in solution and remained intact after 2 h at 60 °C; however, cyclization occurred readily at 80 °C. The stability of enediyne 5.1A to hydrolysis conditions was not reported.



5.1A

Scheme 5.1

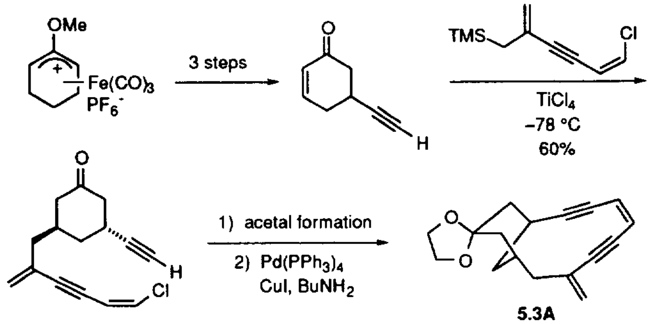
Various studies have shown that sparsely functionalized analogues of natural enediynes can nevertheless exhibit promising DNA cleaving activity, and counterparts to all of the enediyne antibiotics have been prepared. Nicolaou and coworkers synthesized a series of calicheamicin mimics (e.g.: **5.2B–F**) based on the core **5.2A** that allows for the attachment of delivery systems, triggers, etc. (Scheme 5.2).[90] In the case of calicheamicin δ_1^I, the successful development of a total synthetic route (Section 4) by Nicolaou opened up the possibility of improving upon the biological activity of the natural product itself.[92] Following a variation of the scheme for calicheamicin δ_1^I, Nicolaou *et al.* synthesized the non-natural analogue calicheamicin θ_1^I (**5.2F**) (Scheme 5.2).[90] Equipped with a thioacetyl group instead of the trisulfide present in calicheamicin δ_1^I, **5.2F** was designed to be activated by interaction with oxygen nucleophiles. Calicheamicin θ_1^I exhibits both double and single-stranded DNA cleavage at very low concentrations in neutral or basic medium in the absence of any additives. Calicheamicin δ_1^I was essentially inactive under similar conditions.



5.2B X = $O_2CC_6H_4$-*p*-NO_2 ; R_1 = H
5.2C X = SC(O)Me R_1 = H
5.2D X = SSMe R_1 = H
5.2E X = NHC(O)Me R_1 = H
5.2F X = SC(O)Me ; R_1 = sugar

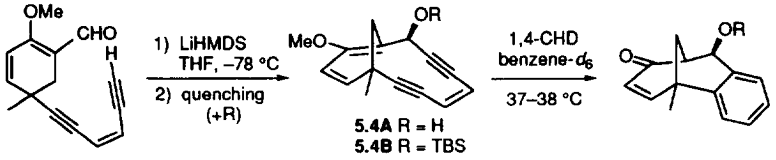
Scheme 5.2

Schinzer and Kabbara prepared the calicheamicin model **5.3A** using an allylsilane conjugate addition and an intramolecular palladium-catalyzed coupling as the key steps (Scheme 5.3).[93] Enediyne **5.3A** was found to be stable at room temperature. Semmelhack *et al.* designed the calicheamicin/esperamicin analogues **5.4A** and **5.4B** based on a keto/enol trigger (Scheme 5.4).[94]



5.3A

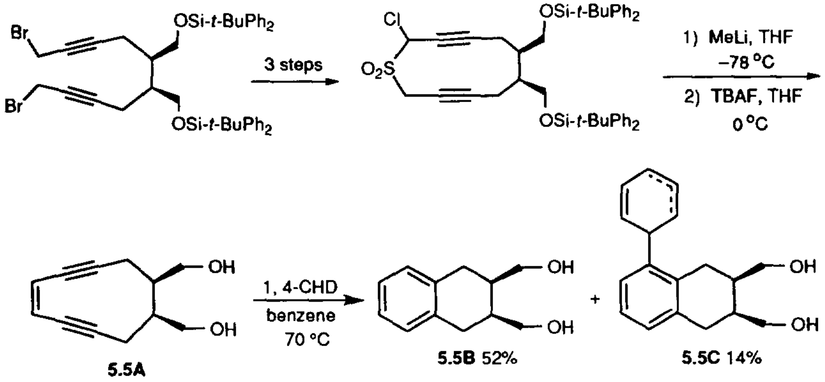
Scheme 5.3



5.4A R = H
5.4B R = TBS

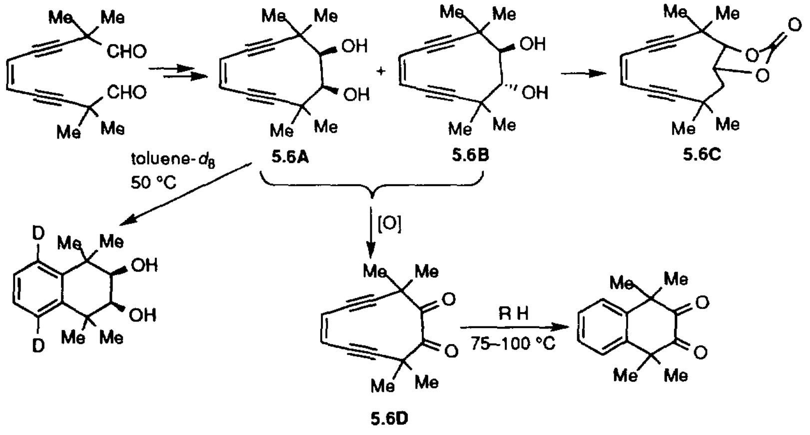
Scheme 5.4

Many simple cyclic enediynes have been prepared in an effort to improve the DNA cleaving activity while retaining synthetic simplicity of the enediynes. Nicolaou and coworkers have developed a general route to monocyclic enediynes, employing the Ramberg-Bäcklund reaction as the key process to install the ene unit.[95] The water-soluble enediyne **5.5A**, obtained by this methodology, cycloaromatized at and above 37 °C to form products **5.5B** and **5.5C** and caused cleavage of double-stranded DNA in the absence of any additives (Scheme 5.5).



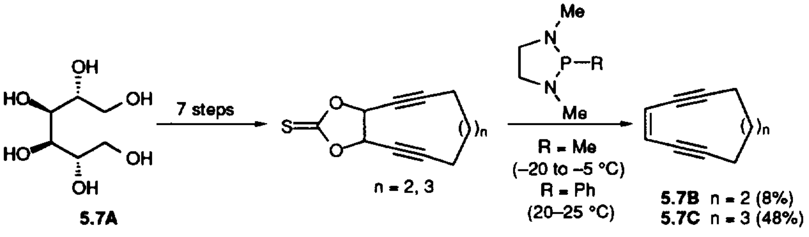
Scheme 5.5

The Nicolaou and Bergman groups also prepared a series of 10-membered monocyclic analogues differing in substitution pattern and compared their reactivity toward ring closure (Scheme 5.6).[96] In toluene-d_8, *cis*-diol **5.6A** cyclized faster ($t_{1/2}$ = 4 h at 50 °C) than the *trans* isomer **5.6B** ($t_{1/2}$ ≈ 22 h at 50 °C). Diketone **5.6D** required significantly higher temperatures for cyclization. Carbonate **5.6C** was found to be stable at 100 °C for several hours, providing an effective locking device for diol **5.6B** when the cyclizations were carried out in the presence of DNA. Diols **5.6A** and **5.6B** caused significant DNA cleavage, whereas dione **5.6D** was less effective under similar conditions.

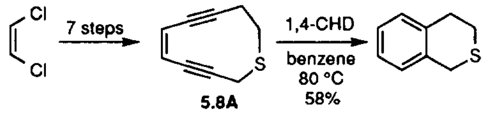


Scheme 5.6

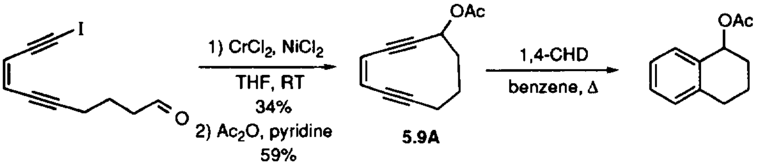
Using the sugar dulcitol (**5.7A**) as the common substrate, Semmelhack and Gallagher have introduced a general approach to the monocyclic enediyne systems **5.7B** and **5.7C**, in which the ene unit is introduced under mild conditions *via* a Corey-Winter reaction (Scheme 5.7).[97] Shibuya and coworkers synthesized the 10-membered cyclic thioenediyne model system **5.8A**, which, in sharp contrast to the carbocyclic analogue **5.7B**, was found to be stable at room temperature but underwent cyclization at 80 °C (Scheme 5.8).[98] The carbocyclic analogue **5.9A**, substituted at a propargylic position, was synthesized by Beau and Crévisy *via* an intramolecular, transition metal-catalyzed condensation.[99] Unlike the corresponding unsubstituted compound **5.7B**, **5.9A** proved to be stable at room temperature but at elevated temperatures underwent cyclization (Scheme 5.9).



Scheme 5.7

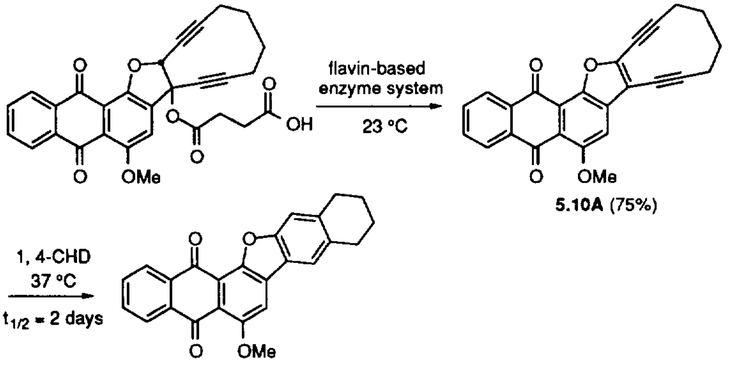


Scheme 5.8

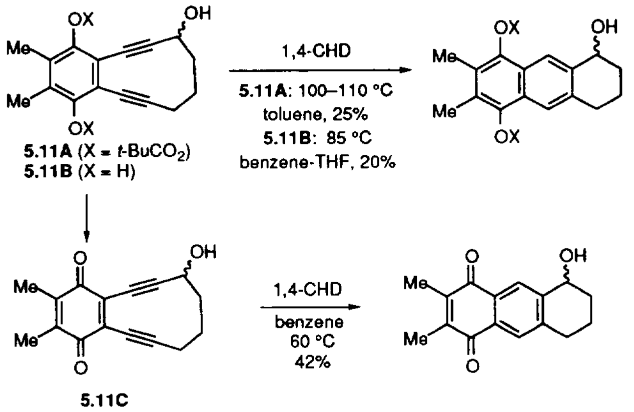


Scheme 5.9

In a mild method that potentially could be used for prodrugs of enediynes, Myers and Dragovich used the enzyme-catalyzed reductive elimination of succinic acid to introduce the ene portion of the anthraquinone enediyne **5.10A**.[100] At 37 °C, this enediyne cyclized only slowly ($t_{1/2}$ ≈ 2 days) (Scheme 5.10). Nicolaou *et al.* utilized the redox system hydroquinone/quinone as the activation mechanism for models based on arene enediynes (Scheme 5.11).[101] The protected hydroquinone **5.11A** underwent cycloaromatization sluggishly even at high temperatures ($t_{1/2}$ = 74 h at 110 °C); and hydroquinone **5.11B**, although air sensitive, was also



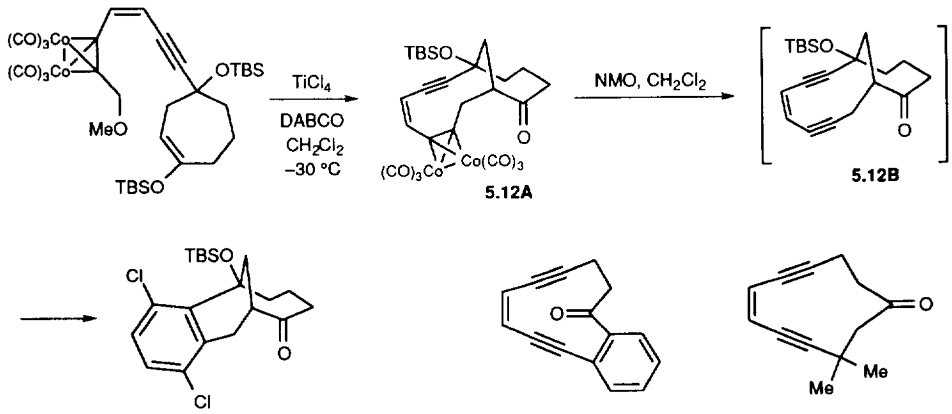
Scheme 5.10



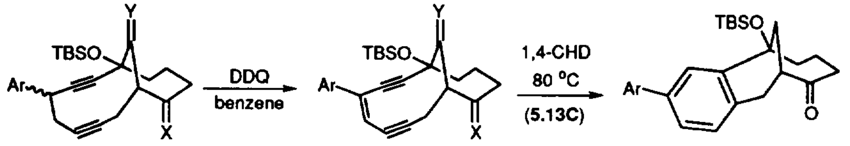
Scheme 5.11

quite stable toward Bergman reaction. Quinone **5.11C**, on the other hand, was highly reactive toward cyclization. While enediyne **5.11A** exhibited no DNA-cleaving activity, **5.11B** and **5.11C** showed significant DNA-damaging properties. Semmelhack also observed hydroquinone enediynes to be less reactive compared to quinone analogues.[25b]

Maier and coworkers employed an intramolecular η^2–dicobalt hexacarbonyl propargyl cation alkylation (Nicholas reaction) to prepare a number of mono- and bicyclic 11-membered enediynes (Scheme 5.12).[102] Enediyne **5.12B** proved to be reactive at room temperature, and afforded the cyclized product **5.12C** when the protected alkyne in **5.12A** was unmasked. The monocyclic enediynes **5.12D** and **5.12E**, each containing an 11-membered ring, were prepared by a similar approach and were stable at room temperature (Scheme 5.12). In related studies, Maier utilized the intramolecular Nicholas procedure to construct substrates **5.13A** and **5.13B** and subsequently introduced the ene unit by oxidation using DDQ to form enediyne **5.13C** and **5.13D** (Scheme 5.13).[29] Enediyne **5.13C**, stable at room temperature, underwent cycloaromatization at 80 °C in the presence of 1.4-CHD to form **5.13E**.



Scheme 5.12



5.13A, 5.13B
Ar = p-MeOC$_6$H$_4$

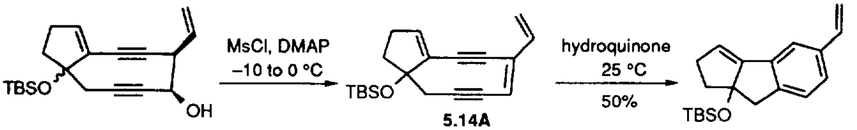
5.13C, 5.13D

5.13E

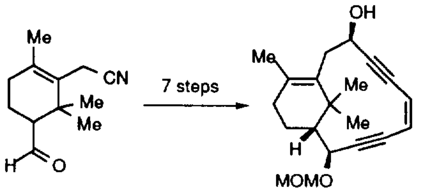
Compound	X	Y	Yield (%) from α-Ar	Yield (%) from β-Ar
5.13C	O	H, H	68	74
5.13D	H, H	O	81	88

Scheme 5.13

Takahashi and Doi prepared the activated enediyne analogue **5.14A**,[103] which is structurally similar to neocarzinostatin and which underwent cycloaromatization upon standing at 25 °C (Scheme 5.14). Fallis *et al.* proposed a new family of biologically active agents, named taxamycins, that incorporates an enediyne unit into the taxane ring skeleton, and they reported the synthesis of the first model **5.15A** (Scheme 5.15).[104] The thermolysis products of **5.15A** have not been identified satisfactorily, although aromatization of some kind was evident.



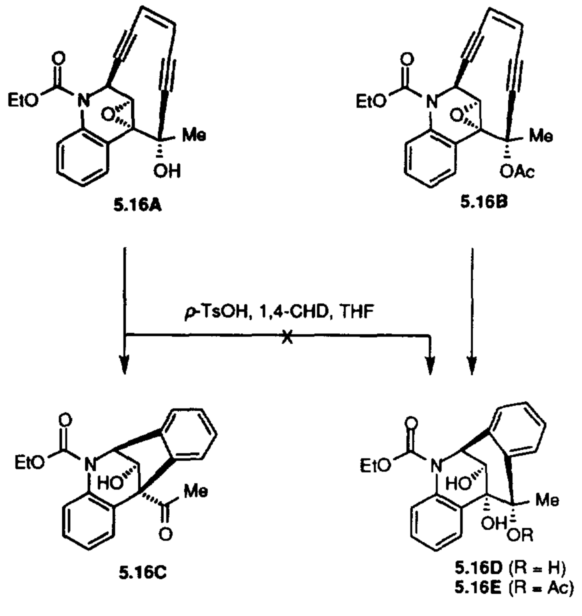
Scheme 5.14



5.15A

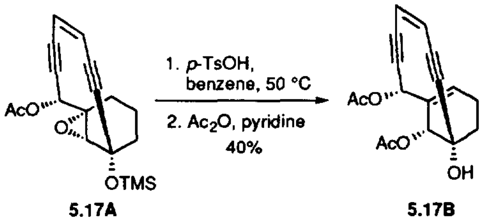
Scheme 5.15

Since the recent discovery of dynemicin A, there has been much work describing the preparation of dynemicin analogues. Isobe and coworkers reported the dynemicin model **5.17A** that lacks the propargylic and aromatic nitrogen believed to participate in the activation process (Scheme 5.17).[105] Attempted activation of **5.17A** by acid-catalyzed epoxide opening led to the formation of enediyne **5.17B**, which was found to be stable at room temperature, suggesting that the aromatic ring and, perhaps, also the nitrogen should be present to ensure ring opening with the desired regioselectivity. In order to increase the reactivity of **5.17A**, Isobe *et al.* synthesized the dynemicin models **5.16A** and **5.16B** containing both the nitrogen and the aromatic ring (Scheme 5.16).[106] Upon acid activation, the enediyne unit of **5.16A** was consumed to give a benzene derivative, which, however, was not triol **5.16D**, the expected product from Bergman closure, but ketone **5.16C**. This outcome suggested that a pinacol-pinacolone rearrangement had preceded or, more likely, had followed the cycloaromatization. Acetate **5.16B**, when treated with acid, gave cyclized product **5.16E** consistent with a Bergman cycloaromatization. Models **5.16A** and **5.16B**, despite the protected nitrogen, showed significant cleaving activity toward supercoiled DNA. Isobe recently discussed synthetic work directed toward improvements of these models.[107]

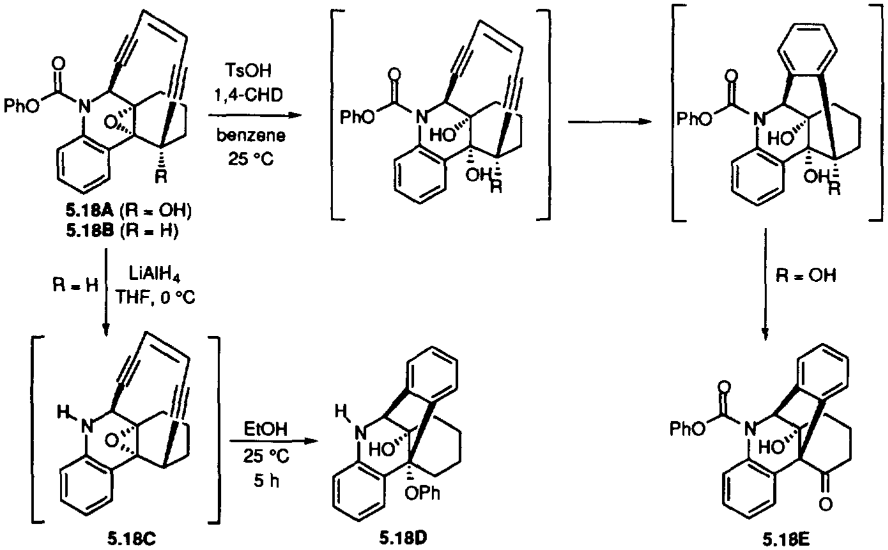


Scheme 5.16

Nicolaou and coworkers have made numerous contributions to the synthesis of novel dynemicin models. In one study, a series of dynemicin models (e.g. **5.18A** and **5.18B**) was designed that could be activated either by acid treatment or by nitrogen deprotection (Scheme 5.18).[108] In the case of acid treatment of **5.18A**, the isolated product **5.18E** was consistent with a pinacol-pinacolone rearrangement prior to or following the cycloaromatization, similar to the reaction of **5.16A**. The free amine **5.18C** was unstable at room temperature and, when stored crude in ethanol, gave the cycloaromatized product **5.18D** (Scheme 5.18). Only the unprotected nitrogen model **5.18C** displayed DNA cleavage activity.

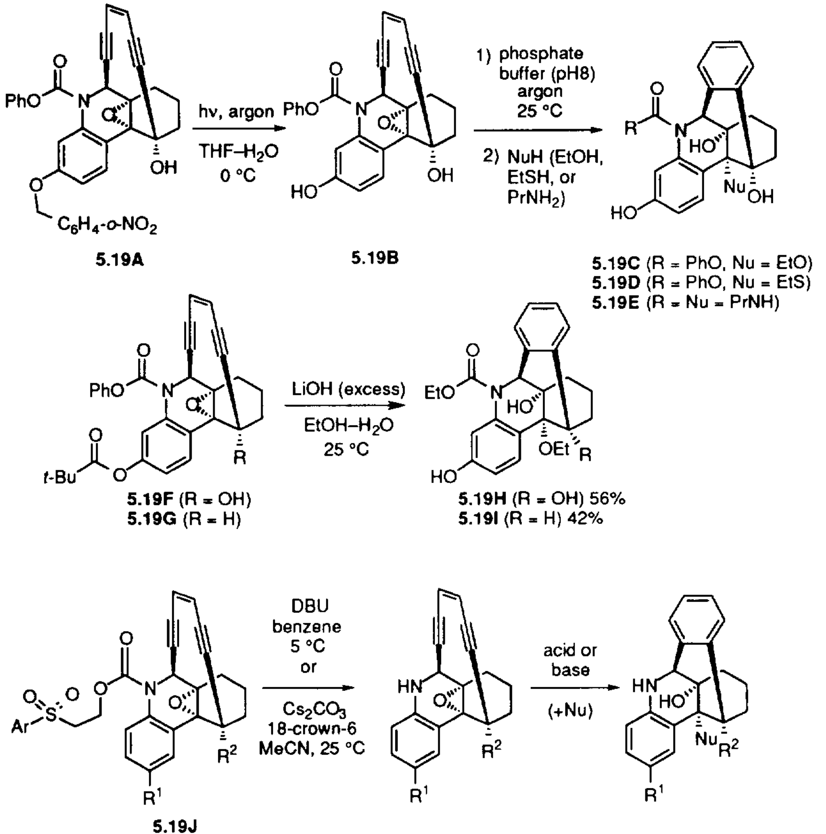


Scheme 5.17



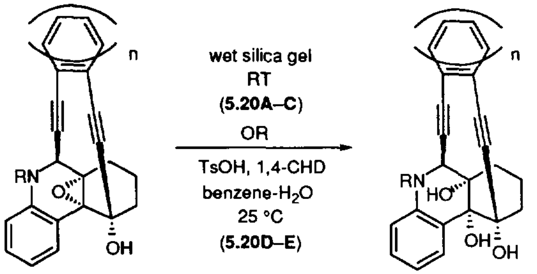
Scheme 5.18

Nicolaou and his group have also investigated several triggers for the cycloaromatization of dynemicin analogues. They designed dynemicin model **5.19A** to be activated photochemically under neutral conditions (Scheme 5.19).[109a] Phenol **5.19B**, unstable at room temperature, cycloaromatized in a pH 8.0-buffer in the presence of suitable nucleophiles to give **5.19C–E**. Nicolaou also designed the dynemicin model systems **5.19F** and **5.19G** equipped with triggering devices at C-3 of the aromatic nucleus (Scheme 5.19).[109b] Cycloaromatization occurred when **5.19F** and **5.19G** were treated with a weak base. Nicolaou synthesized a series of dynemicin model systems (**5.19J**), carrying an (arylsulfonyl)ethoxycarbonyl group on the nitrogen as the triggering device, which could be removed under basic conditions *via* a β-elimination/CO_2-extrusion process (Scheme 5.19).[110] The resultant free amines underwent cycloaromatization under basic or acidic conditions and displayed potent DNA-damaging activities.



Scheme 5.19

Nicolaou and coworkers also examined the dynemicin models **5.20B** and **5.20C**, which, although labile, were found to be more stable than the parent **5.20A** (Scheme 5.20).[111] *cis*-Diol **5.20F**, which resulted from wet silica gel treatment of **5.20B**, was stable enough to be observed by TLC and by ^1H NMR spectroscopy, but cyclized readily upon standing at room temperature. *cis*-Diol **5.20G**, obtained in a similar manner, was stable enough to be purified by chromatography and to be characterized. These diols were the first isolable *cis*-diol models of the dynemicin A cascade. The models **5.20B** and **5.20C** also exhibited significant DNA cleaving ability. The N-protected models **5.20D** and **5.20E**, in sharp contrast to the free amines **5.20B** and **5.20C**, underwent cycloaromatization directly upon acid treatment with no isolable diol intermediates.[112]



5.20A (R = H; n = 0)
5.20B (R = H; n = 1)
5.20C (R = H; n = 2)
5.20D (R = C(O)OPh; n = 1)
5.20E (R = C(O)OPh; n = 2)

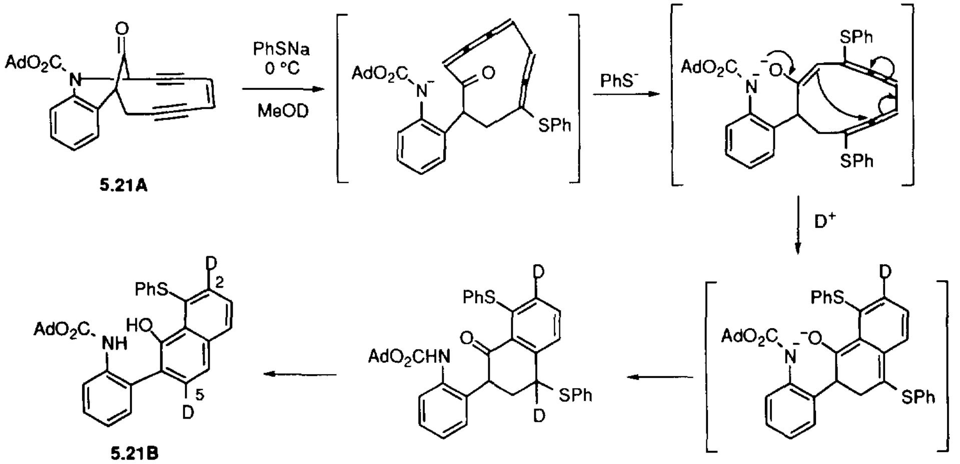
5.20F (n = 1)
5.20G (n = 2)
5.20H (n = 1) 79%
5.20J (n = 2) 49%

Scheme 5.20

Magnus and coworkers synthesized a series of simple azabicyclo[7.3.1]-enediyne dynemicin core analogues such as **5.21A**. This compound underwent cycloaromatization in MeOD *via* a non-radical pathway to afford product **5.21B** (Scheme 5.21).[113] A polar ionic mechanism was proposed, which is consistent with the observation that, in MeOD, two deuterium atoms were incorporated into the product at C-2 and C-5 of the naphthyl ring (**5.21B**). Since these analogues exhibited both *in vitro* and *in vivo* antitumor activity, Magnus concluded that biradical formation is not a prerequisite for biological activity. His team also found that the series of dynemicin models **5.22A–G** underwent radical-mediated cycloaromatization without the assistance of nucleophiles at dramatically different rates despite similar *cd* distances (Scheme 5.22).[114] The cyclizations can be greatly accelerated either by replacement of the carbonyl oxygen with a carbon (**5.22D** and **5.22E**) or by a change in the hybridization at the one-carbon bridge (**5.22F** and **5.22G**).

In addition to their significant work in the synthesis of calicheamicin/esperamicin analogues, Danishefsky *et al.* also prepared the dynemicin analogue **5.23C** *via* the unstable hydroquinone **5.23B**.[115] Interestingly, **5.23B** is also thought to be an intermediate in the reductive activation process of **5.23C** toward Bergman reaction (Scheme 5.23). The analogue **5.23C** displayed cytotoxicity against a variety of tumor cells.

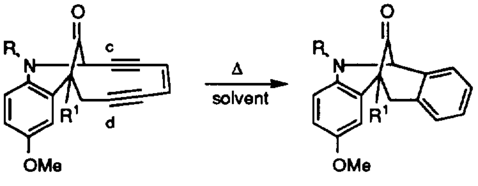
Schreiber and his researchers examined the cycloaromatization of the series of enediynes **5.24A–K** related to the dynemicins, some of which are *trans*-substituted and the others *cis*-substituted (Scheme 5.24).[116] The *trans* isomers **5.24B–F** underwent facile Bergman closure at 80–110 °C in toluene, whereas the corresponding *cis* isomers **5.24G–K** were unreactive under similar conditions. They therefore inferred that the stereochemistry at C-10a and C-11 determined the reactivity of these models equipped with an *exo*-epoxide. Based on theoretical work, Schreiber attributed the observed reactivity difference to unfavorable steric interactions that develop as the α-substituted compounds undergo conformational changes necessary for the Bergman reaction.



5.21A

5.21B

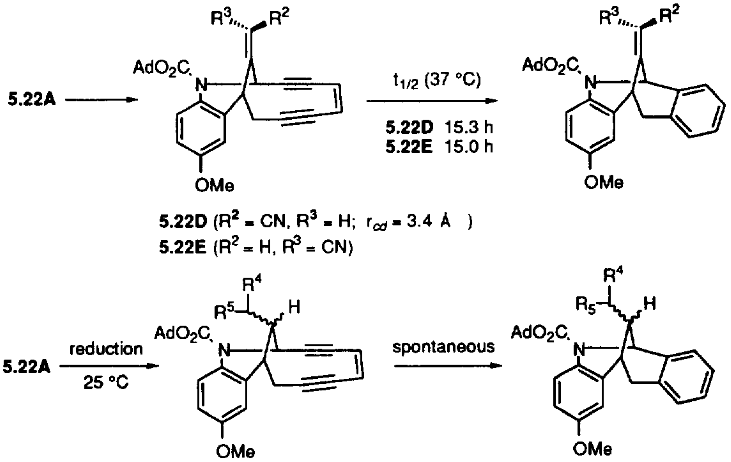
Scheme 5.21



5.22A-C

Compound	R	R¹	$t_{1/2}$ (37 °C)[a]
5.22A	CO_2Ad	H	325 d
5.22B	CO_2Ad	CH_2OMe	6.28 yr
5.22C	H	H	196 d

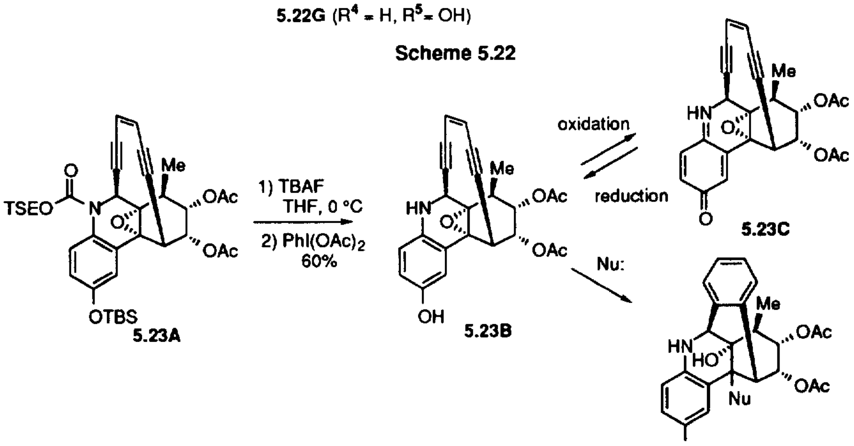
[a] Half-lives are reported disregarding the modest solvent effect observed. r_{cd} (**5.22A**) = 3.4 Å



5.22D (R^2 = CN, R^3 = H; r_{cd} = 3.4 Å)
5.22E (R^2 = H, R^3 = CN)

5.22F (R^4= OH, R^5= H)
5.22G (R^4 = H, R^5= OH)

Scheme 5.22

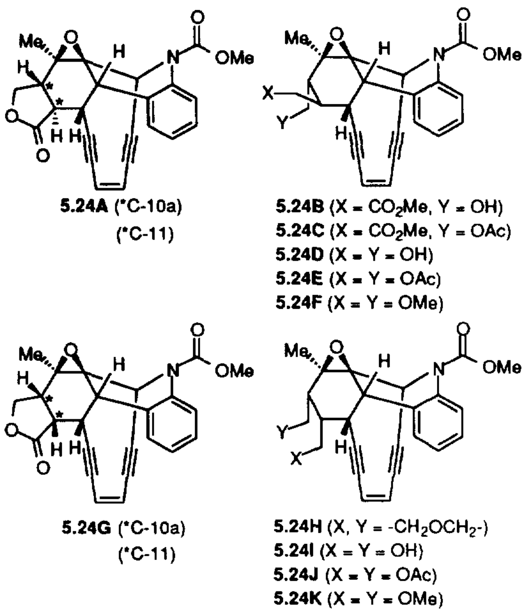


5.23A

5.23B

5.23C

Scheme 5.23



5.24A (*C-10a) (*C-11)

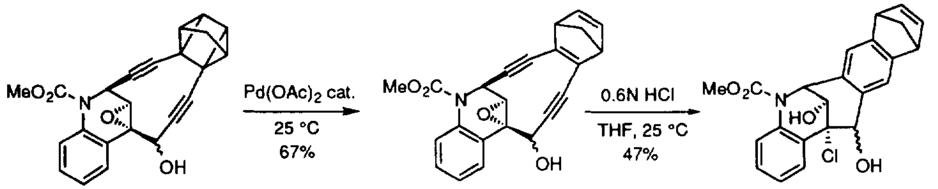
5.24B (X = CO_2Me, Y = OH)
5.24C (X = CO_2Me, Y = OAc)
5.24D (X = Y = OH)
5.24E (X = Y = OAc)
5.24F (X = Y = OMe)

5.24G (*C-10a) (*C-11)

5.24H (X, Y = $-CH_2OCH_2-$)
5.24I (X = Y = OH)
5.24J (X = Y = OAc)
5.24K (X = Y = OMe)

Scheme 5.24

Wender and coworkers contributed significantly to the synthesis of dynemicin analogues with novel triggers. In one study, they prepared the dynemicin analogue **5.25A** with a masked ene unit (Scheme 5.25).[117] Treatment with Pd(II) effected the retro [2+2]-process to produce the enediyne **5.25B**. Acid hydrolysis led to the cyclized product **5.25C**. In another study, Wender *et al.* utilized an intramolecular desilylative condensation procedure to prepare the various dynemicin analogues **5.26C–F**, thereby avoiding the use of harsh acidic or basic conditions in the critical core-ring closure step.[103b] The analogues **5.26C** and **5.26D** can be activated toward cycloaromatization by treatment with acid at room temperature (Scheme 5.26).[67] The Wender group also described the dynemicin analogues **5.26E** and **5.26F**, which are activated photochemically (Scheme 5.26).[118,119] The deprotection of the nitrogen by irradiation activates **5.26E** and **5.26F** under neutral conditions without the use of any additives leading to compounds **5.26K** and **5.26L**. Photoactivation of these analogues in the presence of DNA leads to DNA cleavage.

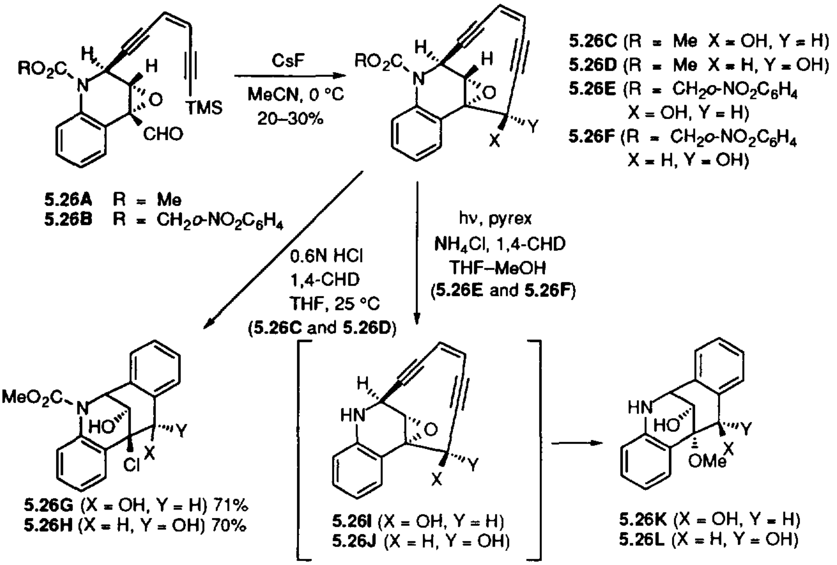


5.25A **5.25B** **5.25C**

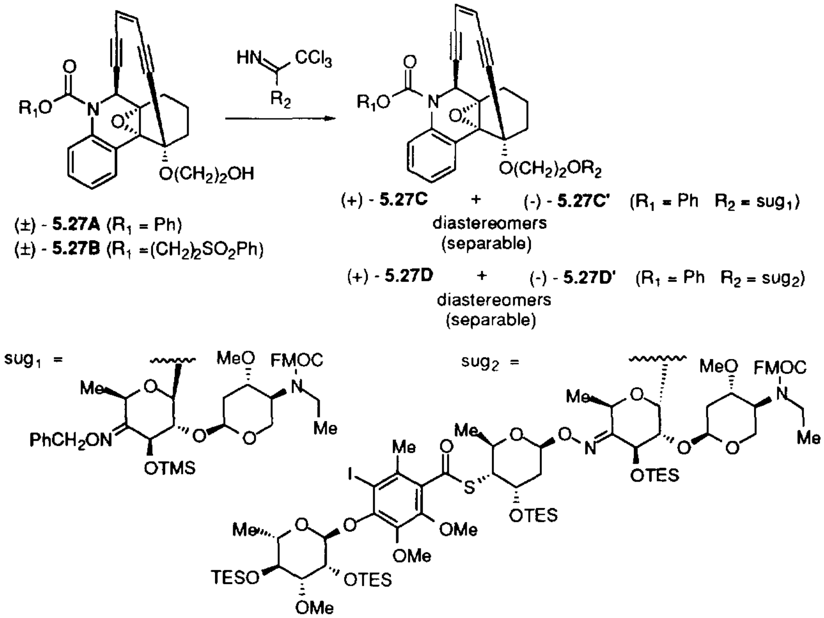
Scheme 5.25

Other dynemicin models were described by Maier and Abel,[120] who prepared dynemicin analogues that lack the aromatic nitrogen and, based on NMR studies, proposed that the role of nitrogen is to restrain rotation of the *anti*-anthraquinone moiety thereby providing a stereochemically favored conformation for epoxide opening. Braña and coworkers prepared dynemicin A models containing a bicyclic tetrahydropyridine system.[121] Danishefsky *et al.*[122] and also Dai *et al.*[123] described new synthetic methods useful in the preparation of dynemicin models.

A novel approach to new analogues is to combine subunits, or their models, of different enediyne natural products. Another strategy is to incorporate structural features of other biologically active natural compounds into synthetic mimics of enediynes. Nicolaou and coworkers coupled an oligosaccharide portion of calicheamicin δ_1^I with the dynemicin A core model **5.27A** to give hybrid analogues **5.27C** and **5.27C'**, which could be separated to obtain optically active analogues (Scheme 5.27).[124] Nicolaou also synthesized the hybrid molecules **5.27D** and **5.27D'**, which combine the intact oligosaccharide fragment of calicheamicin δ_1^I with the enediyne core model **5.27B** of dynemicin A carrying a triggering device on the nitrogen (Scheme 5.27).[125] The analogues **5.27D** and **5.27D'** possess the correct stereochemistry at all stereocenters and exhibit significant antitumor activity.

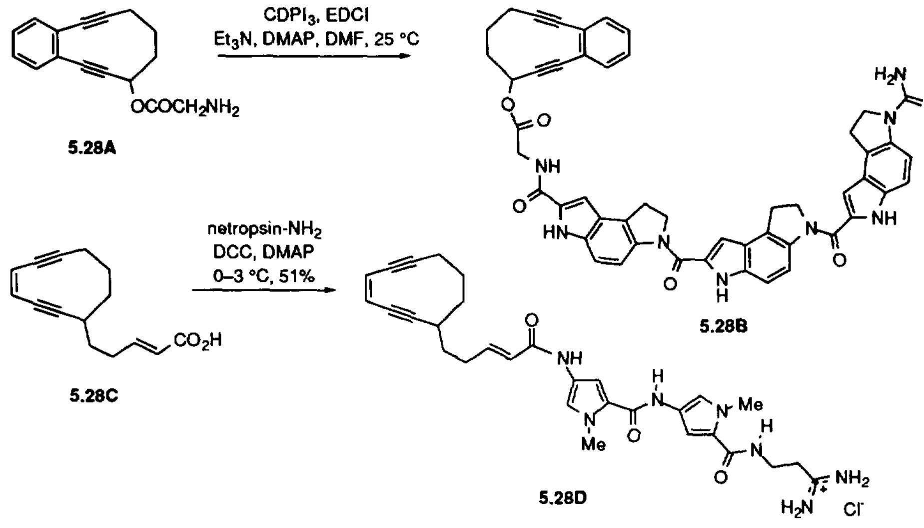


Scheme 5.26



Scheme 5.27

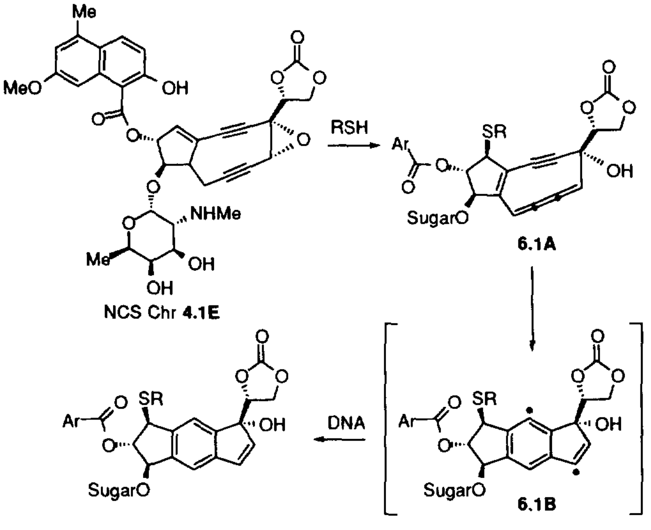
Several efforts have been made to attach enediyne models to molecules that are known to interact with DNA. Boger and Zhou described the analogue **5.28B** that links a simple cyclic arene enediyne **5.28A** with CDPI$_3$, a synthetic and effective non-covalent minor-groove DNA binding agent based on the structure of CC-1065 (Scheme 5.28).[27] The hybrid compound **5.28B** was found to cleave single-stranded DNA efficiently at 40 °C. Semmelhack and coworkers prepared compound **5.28D** by tethering the simple cyclic enediyne **5.28C** to an analogue of netropsin, a minor-groove DNA binding agent (Scheme 5.28).[126] DNA cleavage analysis showed that **5.28D** was 2000-fold more potent than the precursor **5.28C** and only 40-fold less potent than calicheamicin.



Scheme 5.28

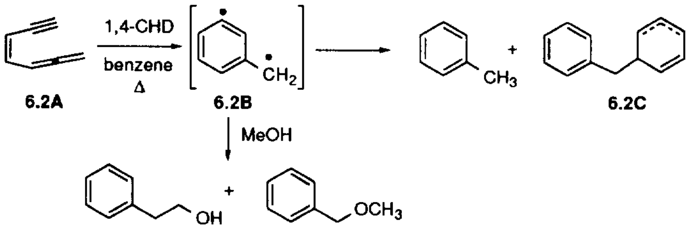
6. Enyne-allenes, -cumulenes, and -ketenes

The biological activity of the natural antitumor antibiotic neocarzinostatin chromophore (NCS Chr) **4.1E** has been known since 1965,[127] however, its structure and mechanism of action was elucidated much later.[128] The activation of NCS Chr includes the cyclization of the (Z)-cumulene-enyne **6.1A** to form the biradical intermediate **6.1B** (Scheme 6.1). The resemblance of this cycloaromatization pathway to the Bergman reaction has resulted in a search for other conjugated unsaturated systems able to cyclize *via* a biradical mechanism.



Scheme 6.1

Myers *et al.* studied the feasibility of the rearrangement of the acyclic enyne allene **6.2A** to the biradical intermediate **6.2B** (Scheme 6.2).[8] Although the cyclizations **6.2A** → **6.2B** and **1.3A** → **1.3B** are related, the ground state of **6.2B** is most likely a σ,π-biradical, whereas that of **1.3B** is constrained to be a σ,σ-biradical. Despite the difference, the cycloaromatization of **6.2A** was found to be facile; heating **6.2A** in deoxygenated benzene in the presence of 1,4-CHD gave toluene and the 1,4-CHD adduct **6.2C** as the only detectable volatile products (Scheme 6.2). They showed that, whereas the Bergman reaction is modestly endothermic, formation of α,3-dehydrotoluene from **6.2A** is strongly exothermic ($\Delta H_r \approx -15 \pm 3$ kcal/mol). Theoretical work by Morokuma and Koga confirmed that the biradical formation from **6.2A** is more exothermic and requires a lower activation energy than that from (*Z*)-hex-3-ene-1,5-diyne.[129] Myers observed substantial polar character in the cyclization when it was carried out in the presence of polar reagents (Scheme 6.2).[8] This result is in contrast to the biradical reactivity shown by the σ,σ–biradicals generated in the Bergman reaction (although some evidence for non-radical pathways has also been presented).[113] Squires and coworkers presented both experimental and theoretical evidence for the singlet multiplicity of the ground state of **6.2B**.[130] Mitra and Capitani, based on a PM3 study, suggested that 3.49 Å represents an upper limit to the critical distance between the bonding termini (*cd* distance) in the cyclization of enyne allenes and cumulenes.[131]

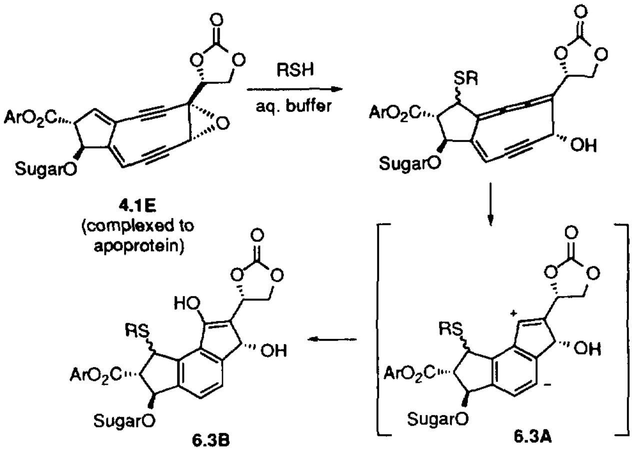


Scheme 6.2

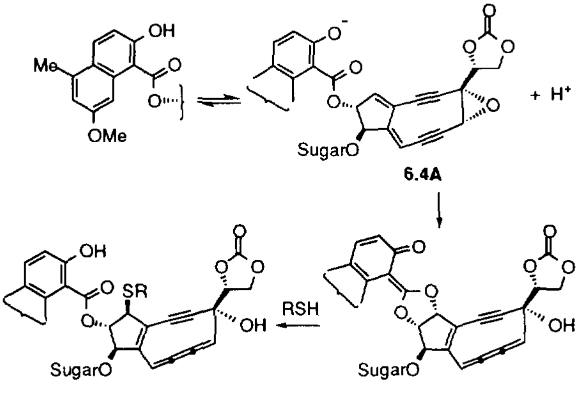
Neocarzinostatin, isolated from *Streptomyces carzinostaticus*, consists of a heat, light, and base labile chromophore bound to a 113-amino acid apoprotein. The crystal structure of neocarzinostatin complex was reported by Myers *et al.*[132] and proton NMR studies on the binding of the chromophore to the apoprotein have been reported by Hirama and coworkers.[133] Hirama also studied the binding of simple NCS Chr analogues to the apoprotein and concluded that the naphthoate moiety of the NCS Chr is essential for the binding.[134] Several groups have reported recent efforts toward the synthesis of NCS Chr.[103,135]

The Myers group, who first elucidated the mechanism of cycloaromatization of NCS Chr (Scheme 6.1), also provided evidence that thiol activation of NCS Chr is facilitated dramatically by participation of the sugar amino group as an internal base.[135g,i] Sugiyama, Saito, and coworkers found that the NCS Chr complexed to apoprotein reacts differently from the free NCS Chr upon thiol activation to give **6.3B** as the major cyclization product (Scheme 6.3).[136] The intermediacy of zwitterion **6.3A** was proposed, and the greater stability of the apoprotein - **6.3A** complex was suggested to explain the preference for this path.

Fuchs and Lamothe discussed experimental evidence for the proposal that the α–hydroxy naphthoate moiety in NCS provides anchimeric assistance during the epoxide opening reaction (Scheme 6.4).[137] Hensens, Goldberg and coworkers elucidated the structures of the major and the minor base-catalyzed degradation products of NCS Chr that are formed in the absence of DNA.[138] These studies showed that the conjugate addition of the enolate ion generated from the α-hydroxy naphthoate functionality **6.4A** leading to the spirolactone cumulene intermediate is stereoselective.

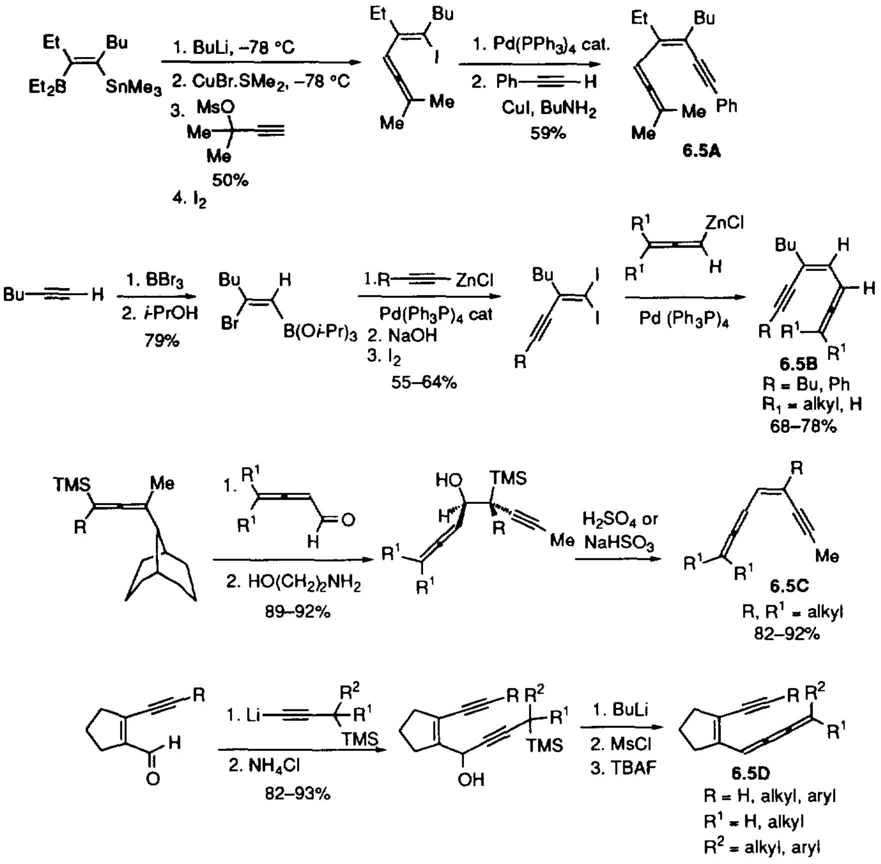


Scheme 6.3



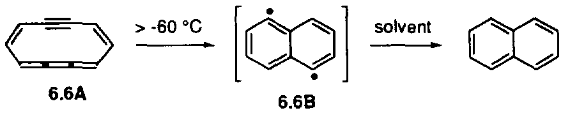
Scheme 6.4

Due to the involvement of enyne cumulenes in the DNA cleavage process by neocarzinostatin, the development of efficient synthetic routes to enyne cumulenes and related systems has received much attention. Wang and his group have developed several useful approaches to enyne allenes (Scheme 6.5). One method described a two-step preparation of the enyne allenes **6.5A** having a tetrasubstituted central alkene, where boron chemistry was utilized to introduce the allene unit.[139] Another method involved the synthesis of the enyne allenes **6.5B** by bromoboration of a terminal alkyne followed by consecutive Pd(0)-catalyzed coupling reactions with organozinc chlorides derived from terminal alkynes and allenes.[140] Similar to their method for the preparation of enediynes, the Wang group has employed a Peterson olefination approach to the preparation of enyne allenes **6.5C**. Wang also described the synthesis of the enyne[3]cumulenes **6.5D** *via* 1,4-elimination of hydroxytrimethylsilane from 4-(trimethylsilyl)-2-butyn-1-ols obtained from condensation of terminal propargylic silanes with conjugated enynyl aldehydes.[141]



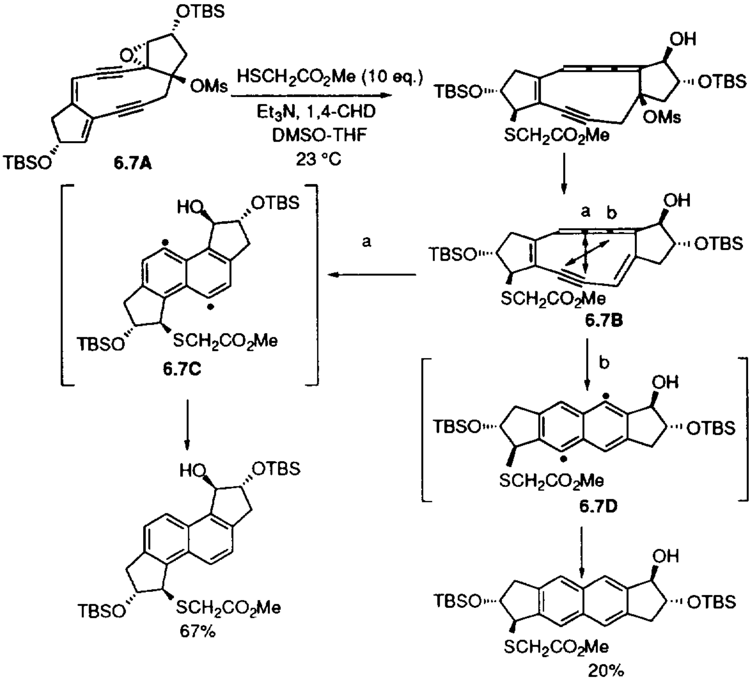
Scheme 6.5

Various cyclic as well as open-chain unsaturated systems related to NCS Chr have been assembled in an effort to develop novel DNA cleaving agents. Myers and Finney prepared and characterized the elusive hydrocarbon **6.6A** at low temperature (Scheme 6.6).[142] This compound was found to undergo rapid cyclization above –60 °C ($t_{1/2} \approx 25$ min at –51 °C) to form naphthalene *via* the biradical 1,5-dehydronaphthalene **6.6B**. Since NCS Chr is activated physiologically by thiols, there have been attempts to design novel enyne allene precursors that could be activated by thiols. Myers and Dragovich designed the epoxy dienediyne **6.7A** as a thiol-activatable precursor to enyne cumulene **6.7B**.[143] This compound can cyclize in one of two modes (a or b) to give the 1,5-dehydronaphthalene biradical intermediate **6.7C** or **6.7D** (Scheme 6.7). Brückner and Suffert synthesized the cyclic NCS Chr analogue **6.8A**, which, upon treatment with thiols in acidic medium, gave the phenanthrene derivatives **6.8B** and **6.8C** (Scheme 6.8).[144a] The Brückner group also prepared cyclic NCS Chr analogues containing a six-membered ring rather than the five-membered ring present in NCS Chr.[144b]

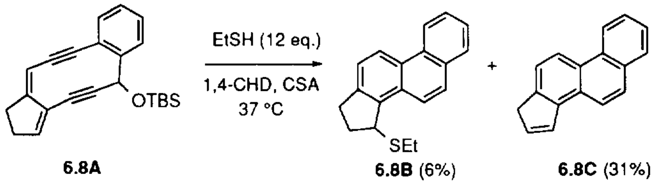


6.6A 6.6B

Scheme 6.6

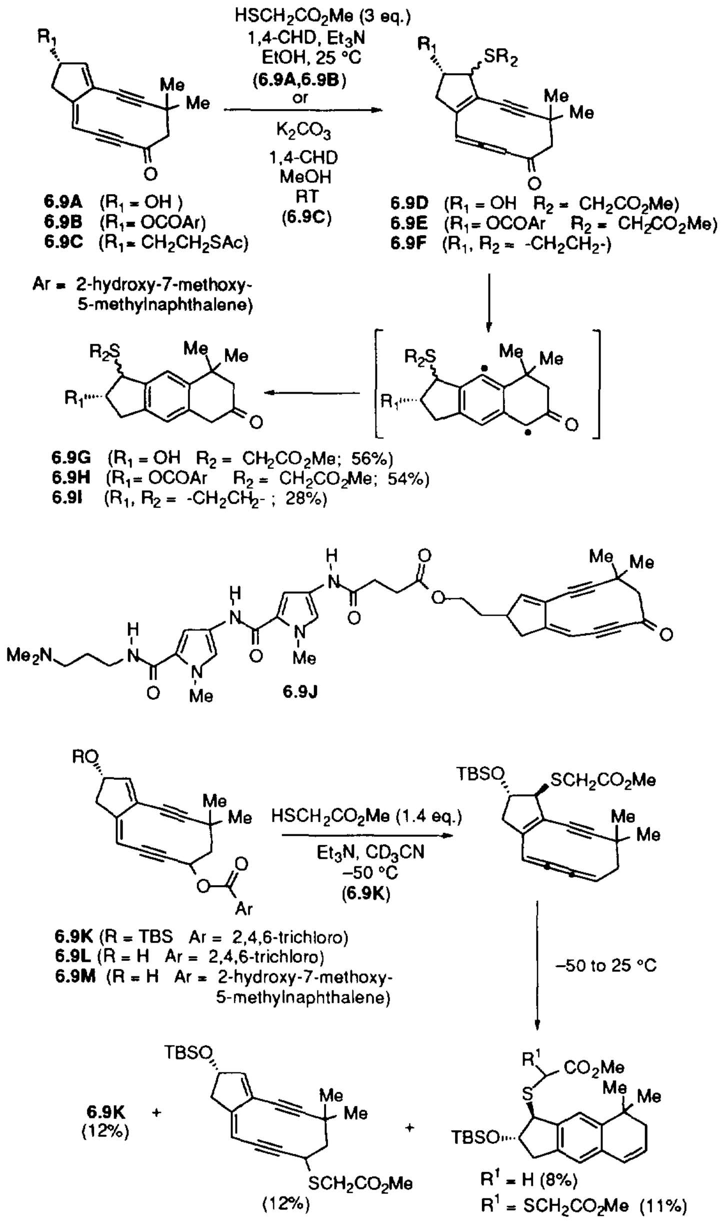


Scheme 6.7



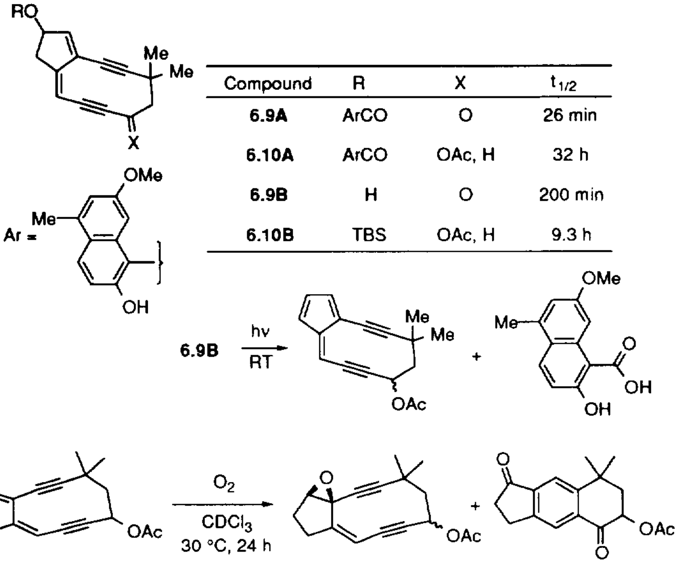
Scheme 6.8

Hirama and collaborators designed the NCS Chr models alcohol **6.9A** and naphthoate **6.9B** and found that these compounds underwent thiol-triggered cycloaromatization smoothly *via* the enyne cumulene intermediates **6.9D** and **6.9E**, respectively (Scheme 6.9).[145] Alcohol **6.9A** was shown to possess high guanine selective DNA cleavage activity. They prepared the NCS Chr analogue **6.9C** strategically equipped with an intramolecular acetylthioethane tether and found it to undergo cycloaromatization under weakly basic conditions, initiated by intramolecular conjugate addition of the thiolate anion (Scheme 6.9).[146] Hirama *et al.* described the hybrid system **6.9J** combining an NCS Chr analogue with a netropsin type minor groove binder.[147] The thiol-triggered smooth cycloaromatization of **6.9J** cleaved supercoiled DNA more efficiently than did alcohol **6.9A** and thioacetate **6.9C** (Scheme 6.9). Hirama's team also synthesized the related NCS Chr analogues **6.9K–M**, which underwent cycloaromatization upon thiol activation (Scheme 6.9).[148] The DNA cleaving ability of hybrid **6.9M** was observed to be 50-fold greater than that of **6.9L**.



Scheme 6.9

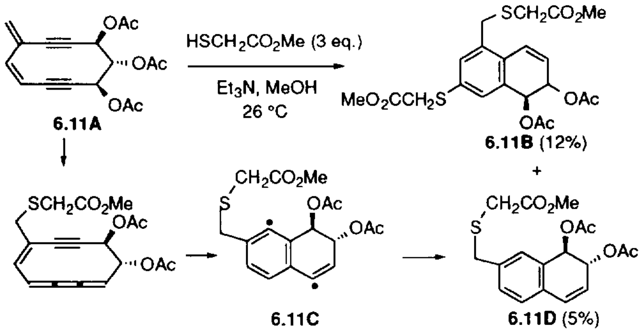
On the assumption that the naphthoate moiety is responsible for the UV-light sensitivity of NCS Chr, Hirama *et al.* studied the photoreactivity of the NCS Chr analogues **6.9A** and **6.10A** bearing the naphthoate moiety and **6.9B** and **6.10B** which lack an aromatic chromophore (Scheme 6.10).[149] Upon irradiation with 340-380 nm light, the naphthoate analogues **6.9A** and **6.10A** decayed much faster than **6.9B** and **6.10B**. The central pathway of photochemical decomposition of **6.9A** proved to be a fragmentation reaction of the naphthoate ester, analogous to a Norrish type II cleavage. Hirama *et al.* also studied the sensitivity of the related NCS Chr analogue **6.10C** to molecular oxygen, which converted it to a mixture of the labile epoxide **6.10D** and the oxygenated cycloaromatized product **6.10E** (Scheme 6.10).[150] This observation sharply contrasts the behavior of NCS Chr itself, which showed no distinct difference in the rates of decomposition between the degassed and the oxygenated AcOH/MeOH solutions in the dark.



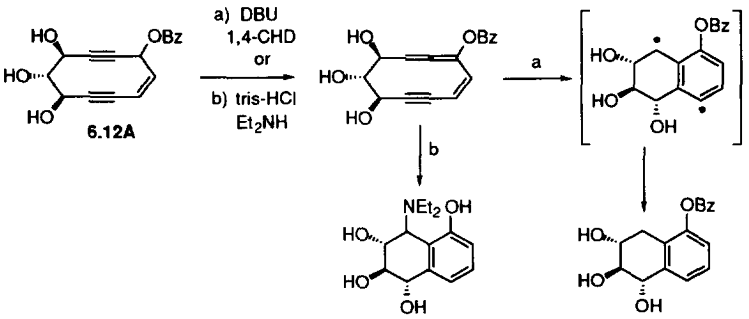
Compound	R	X	$t_{1/2}$
6.9A	ArCO	O	26 min
6.10A	ArCO	OAc, H	32 h
6.9B	H	O	200 min
6.10B	TBS	OAc, H	9.3 h

Scheme 6.10

Toshima and coworkers synthesized and cyclized the thiol activatable NCS Chr analogue **6.11A** (Scheme 6.11).[151] Product **6.11D** is consistent with the intermediacy of biradical **6.11C**, but the mechanism leading to the major product **6.11B** is not clear. Toshima *et al.* also prepared the related analogue **6.12A**, which was found to cycloaromatize *via* both radical (a) and polar (b) pathways depending on the reaction conditions (Scheme 6.12).[152] Enediyne **6.12A** exhibited guanine-selective DNA cleavage in basic medium without the aid of additives.

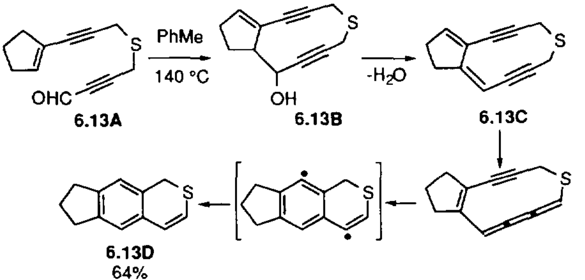


Scheme 6.11

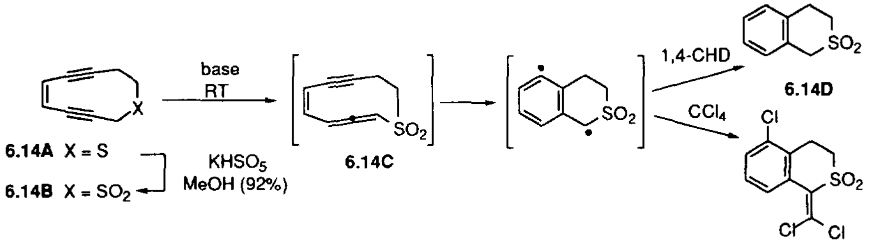


Scheme 6.12

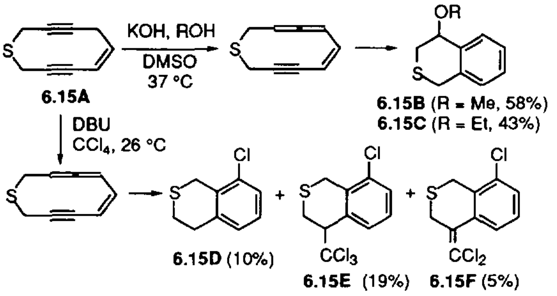
Several research groups have designed sulfur-containing NCS Chr analogues. Mikami *et al.* synthesized **6.13B** from the ene reaction of **6.13A** at 140 °C (Scheme 6.13).[135a] At this temperature, **6.13B** underwent spontaneous elimination of water to form **6.13C** and cycloaromatization to form **6.13D** without thiol activation. Shibuya and his group prepared sulfone **6.14B** from the corresponding sulfide **6.14A** and investigated its cycloaromatization (Scheme 6.14).[153] When treated with a base (Et_3N, *t*-BuOK, or DBU) at room temperature in the presence of 1,4-CHD, **6.14B** reacted rapidly to afford benzylsulfone **6.14D** as the major product. The fact that sulfide **6.14A** does not cyclize in basic medium at room temperature as well as the fact that the major product is **6.14E**, when CCl_4 is used as the solvent, suggests the involvement of enyne allene intermediate **6.14C** as opposed to the Bergman reaction of enediyne **6.14B**. Sulfone **6.14B** exhibited potent single-stranded DNA cleavage activity. Tatsuta and coworkers prepared the cyclic enediyne **6.15A**, which showed two different modes of cyclization depending on the reaction conditions (Scheme 6.15).[154] When the cyclization is carried out in a polar solvent, a polar mechanism leading to products **6.15B** and **6.15C** is observed. In contrast, using a non-polar solvent in the reaction affords products **6.15D**, **6.15E**, and **6.15F**, which suggest the intermediacy of a biradical.



Scheme 6.13

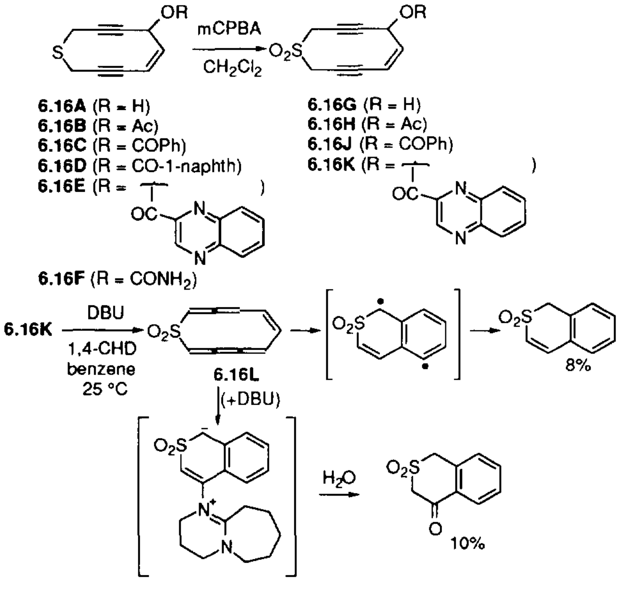


Scheme 6.14



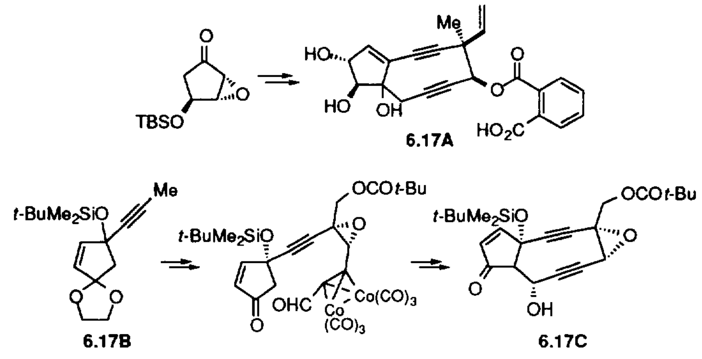
Scheme 6.15

Toshima *et al.* prepared a series of derivatives of **6.16A** (**6.16B–F**) and found that their behavior in the presence of DBU in CCl_4 is similar to that of **6.15A**.[155] Compounds **6.16C–E** with aromatic side chains showed high DNA cleaving potency under similar conditions. Toshima also synthesized the enyne allene sulfones **6.16G–K** by oxidation of the corresponding sulfides (Scheme 6.16).[156] Sulfones **6.16H–K** bearing a leaving group at the allylic position cycloaromatized *via* the allene ene cumulene intermediate **6.16L** following both ionic and free radical paths (as shown for **6.16K**). These compounds also showed DNA cleaving activity under basic conditions.



Scheme 6.16

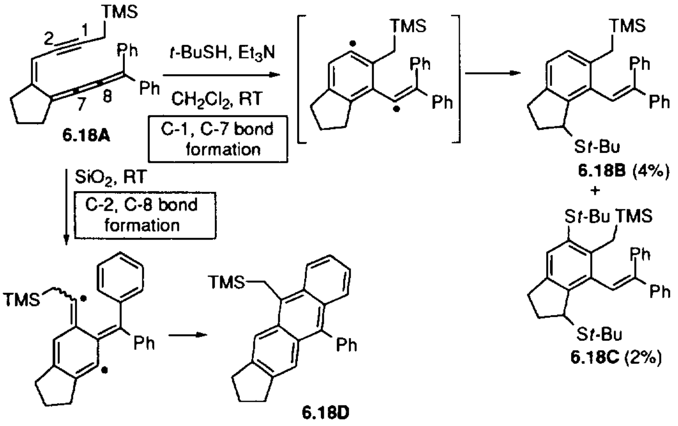
Several groups have reported the preparation of highly functionalized NCS Chr analogues. Takahashi and collaborators synthesized analogue **6.17A**, which was found to be stable at ambient temperature (Scheme 6.17).[157] Triol **6.17A** showed strong DNA cleaving activity in the presence of methyl thioglycolate. Magnus and Davies synthesized the highly functionalized NCS Chr analogue **6.17C** from the protected enynone **6.17B** using the hexacarbonyldicobalt aldol methodology (Scheme 6.17).[158] Compound **6.17C** was found to be stable at room temperature both in solution and in neat form.



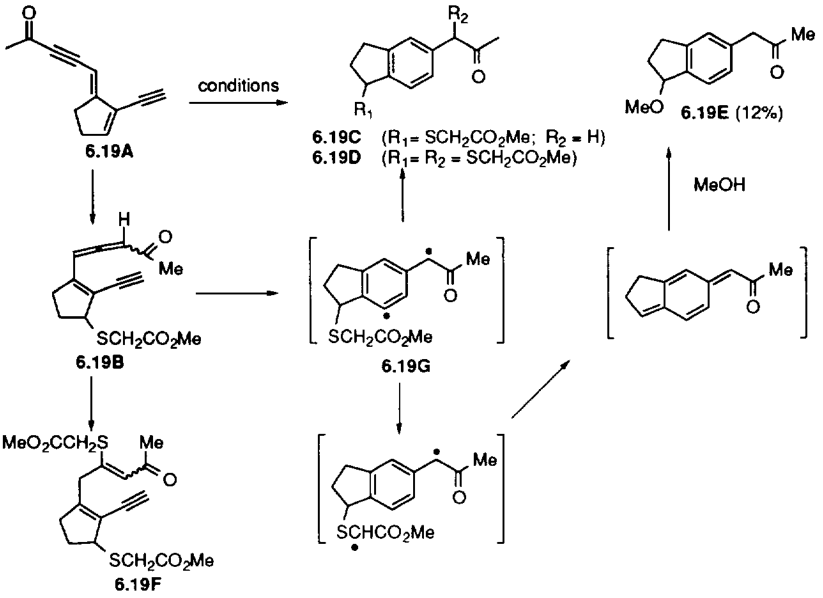
Scheme 6.17

Open-chain analogues of NCS Chr have been described by several research groups. Brückner and coworkers reported the NCS Chr model **6.18A**, which, upon treatment with thiol in basic medium, gave the cycloaromatized products **6.18B** and **6.18C** (Scheme 6.18).[159] However, when subjected to silica gel chromatography, **6.18A** underwent cyclization *via* a regiochemically different mode followed by cycloisomerization to give anthracene **6.18D**. Wender and Tebbe synthesized analogue **6.19A**, in which the carbonyl group was expected to serve as a functional equivalent of the epoxide, allowing for an activation process based on conjugate addition of thiols (Scheme 6.19).[160] Under acidic conditions, **6.19A** cycloaromatized to give products **6.19C**, **6.19D**, and **6.19E**. The major product **6.19E** was proposed to arise from an internal hydrogen abstraction process by biradical **6.19G**. In a basic medium at low temperature, the enyne allene intermediate **6.19B** could be isolated; when **6.19B** was subjected to acid treatment, the selectivity of the cycloaromatization was markedly improved over the direct acid activation of **6.19A** (Scheme 6.19).[160b]

Hirama *et al.* described the cross-conjugated dienediyne system **6.20A**, which gave the isolable enyne[3]-cumulene **6.20B** when treated with thiols (Scheme 6.20).[161] Thermolysis of **6.20B** produced the styrene derivative **6.20D** *via* a free-radical cycloaromatization and benzocyclobutane **6.20C** *via* [2+2]-cycloaddition. Wu and coworkers generated the acyclic enyne allene sulfone **6.21B** by base-catalyzed isomerization of propargylic sulfone **6.21A** (Scheme 6.21).[162]

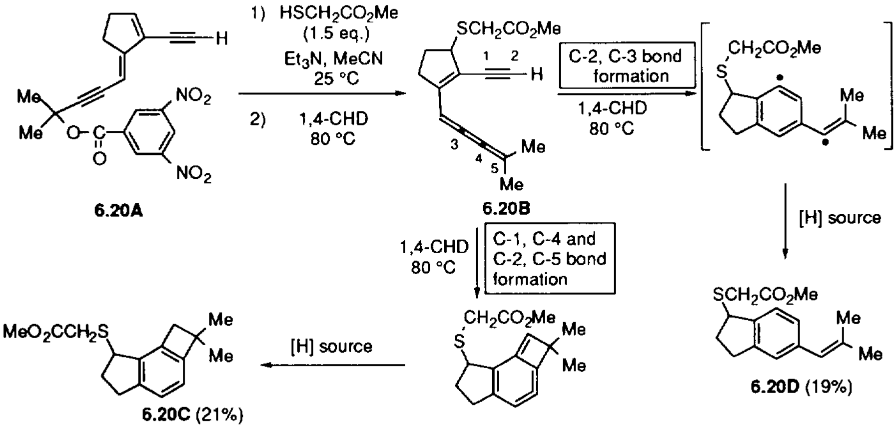


Scheme 6.18

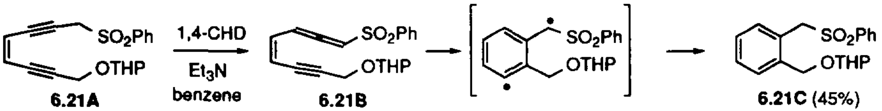


Starting material	Conditions	Yields (%)					
		6.19A	6.19B	6.19C	6.19D	6.19E	6.19F
6.19A	$HSCH_2CO_2Me$ (10 eq.) HOAc, MeOH, 70 °C	0	0	2	3	12	0
6.19A	$HSCH_2CO_2Me$ (0.6 eq.) Et_3N, MeCN	43	14	0	0	0	8
6.19B	HOAc, MeOH, 40 °C	-	0	1	0	85	0

Scheme 6.19



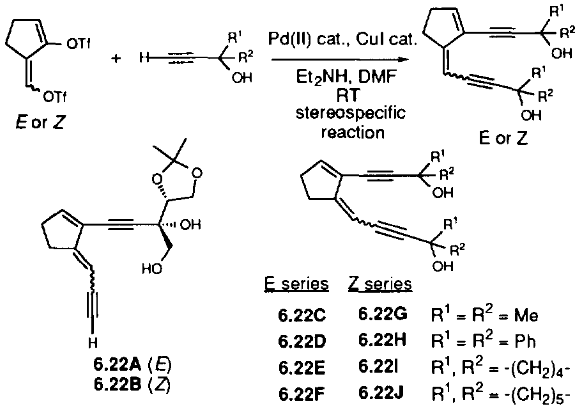
Scheme 6.20



6.21A **6.21B** **6.21C** (45%)

Scheme 6.21

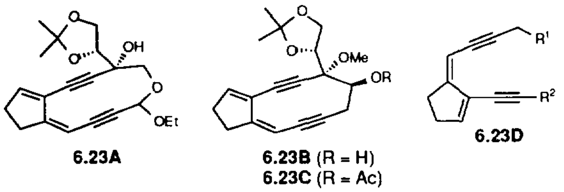
Terashima and collaborators synthesized the open-chain (*E*)- and (*Z*)-dienediyne systems **6.22A** and **6.22B** by palladium-mediated coupling of corresponding dienolditriflates with propargyl alcohols (Scheme 6.22).[163] Compounds **6.22A** and **6.22B** exhibited different *in vitro* cytotoxicity with **6.22B** being at least 10 times more potent than **6.22A**. However, in the (*E*)-series **6.22C–F** and in the (*Z*)-series **6.22G–J** prepared in a similar manner, each pair of geometric enediynes with the exception of **6.22E** and **6.22I** showed comparable cytotoxicity.[164] This similarity in cytotoxicity behavior between both (*E*) and (*Z*) isomers has been attributed to the hydroxyl groups at both ends of the propargylic side chains overriding the effect of the stereochemistry of the exocyclic olefin. Terashima *et al.* also synthesized the cyclic NCS Chr analogues **6.23A–C** using similar palladium catalyzed coupling reactions of enol triflates and propargyl alcohols (Scheme 6.23).[164,165] Brückner, Suffert, and coworkers also utilized the enol triflate-alkyne coupling strategy using two different alkynes to assemble open-chain dienediynes of the type **6.23D** related to NCS Chr (Scheme 6.23).[166]



6.22A (*E*)
6.22B (*Z*)

E series	Z series	
6.22C	6.22G	$R^1 = R^2 = Me$
6.22D	6.22H	$R^1 = R^2 = Ph$
6.22E	6.22I	$R^1, R^2 = -(CH_2)_4-$
6.22F	6.22J	$R^1, R^2 = -(CH_2)_5-$

Scheme 6.22



6.23A

6.23B (R = H)
6.23C (R = Ac)

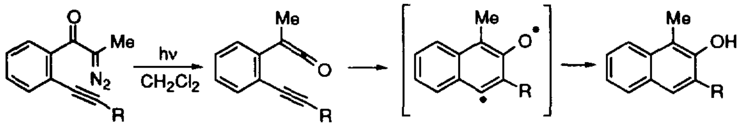
6.23D

R^1 = OTHP, $OSiPh_2Me$, CH_2OH, $(CH_2)_2OH$, CH_2TMS
R^2 = TMS, CH_2TMS, *n*-Bu, $(CH_2)_2OH$

Scheme 6.23

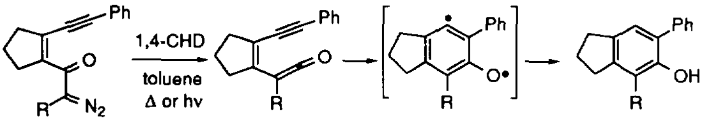
Prompted by the success of enyne cumulenes as potential DNA damaging agents, researchers have recently paid considerable attention to cycloaromatization of the isoelectronic enyne ketenes. Padwa *et al.* reported the synthesis of β-naphthols **6.24C** from cycloaromatization of enyneketenes **6.24B** generated by photolysis of 2-diazoacetophenones **6.24A** (Scheme 6.24).[167] Nakatani, Saito, and coworkers showed that thermolysis or photolysis of diazoketones **6.25A** and **6.25B** in the presence of 1,4-CHD gave the cycloaromatized products

6.25D and **6.25E**, respectively, *via* the enyne ketene intermediate **6.25C** (Scheme 6.25).[9] Upon irradiation in the presence of DNA, **6.25A** effectively caused single-strand cleavage.



6.24A **6.24B** **6.24C** good yields

Scheme 6.24



6.25A (R = Me)
6.25B (R = H)

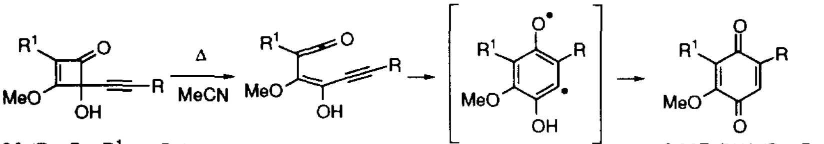
6.25C

6.25D (R = Me; 51%, 140 °C, 30 min; 36%, hv, 0 °C, 30 min)

6.25E (R = H; very slow, 140 °C; 38%, 170 °C, 30 min; complex mixture, hv, 0 °C, 30 min)

Scheme 6.25

Moore and his group used the thermolysis of 4-alkynyl-4-hydroxycyclobutenones **6.26A–E** to generate enyne ketenes, which cycloaromatized to give *p*-quinones **6.26F** (Scheme 6.26).[1k,168] All members of the series of cyclobutenones **6.26A–E** exhibited DNA cleaving capability, and those bearing alkyl groups at C-2 (**6.26A**) showed greater efficiency than the 2-alkoxy analogues (**6.26B** and **6.26C**).



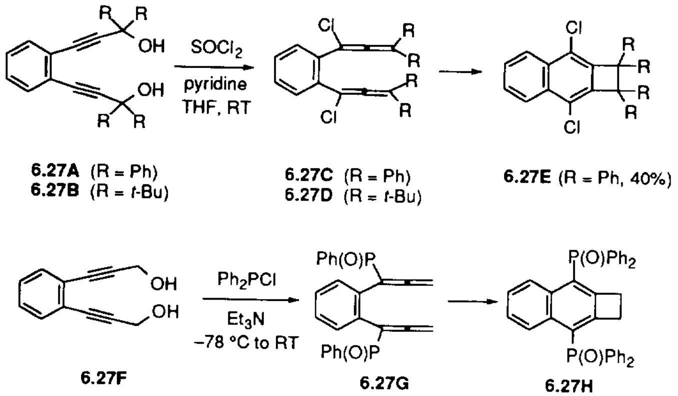
6.26A (R = Bn, R^1 = *n*-Bu)
6.26B (R = Bn, R^1 = MeO)
6.26C (R = Ph, R^1 = MeO)
6.26D (R = Bn, R^1 = CH_2CH_2S-9-Anth)
6.26E (R = $CH_2C_6H_4$-*p*-$NHMe_2$, R^1 = CH_2CH_2S-2-Py)

6.26F 71% (R = Bn, R^1 = CH_2CH_2S-9-Anth)

Scheme 6.26

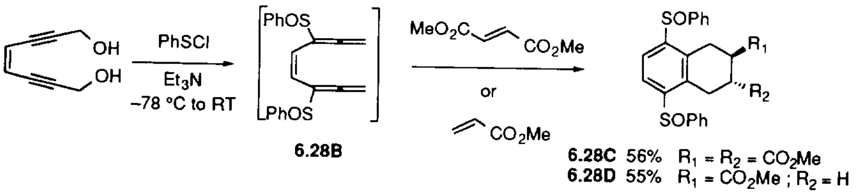
There have also been reports on the cyclization of ene diallenes and ene cumulenes. Toda and coworkers described an approach to benzocyclobutene derivative **6.27E** from enediyne diol **6.27A** *via* cycloaromatization of the diallene intermediate **6.27C** (Scheme 6.27).[10] The cyclization appears to depend on the steric bulk of the allene substituent R, since the corresponding intact diallene **6.27D** was isolated when a *t*-Bu group was used as the substituent. Grissom's team generated the ene diallene **6.27G** from a *bis*-[2,3]-sigmatropic shift and found that the only observed product was benzocyclobutene **6.27H** (Scheme 6.27).[169] A *bis*-[2,3] sigmatropic shift utilizing sulfur rather than phosphorus led to enediallenes **6.28B**, which reacted with dienophiles in a [4+2]-fashion to give aromatic products (**6.28C**, **6.28D**) in good yields (Scheme 6.28).[169]

Kerwin synthesized the sulfone crown ether diyne **6.29A**, which cleaved supercoiled DNA in alkaline aqueous buffer presumably *via* the diallenyl sulfone intermediate **6.29B** (Scheme 6.29).[170] However, the involvement of a biradical intermediate was excluded since neither the addition of a radical scavenger nor the exclusion of oxygen from the reaction inhibited the ability of compound **6.29A** to cleave DNA.



6.27A (R = Ph)
6.27B (R = *t*-Bu)
6.27C (R = Ph)
6.27D (R = *t*-Bu)
6.27E (R = Ph, 40%)
6.27F
6.27G
6.27H

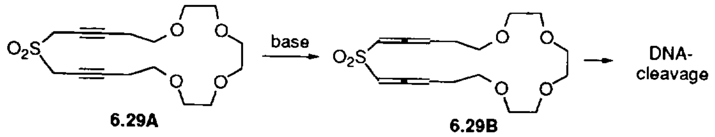
Scheme 6.27



6.28B

6.28C 56% $R_1 = R_2 = CO_2Me$
6.28D 55% $R_1 = CO_2Me$; $R_2 = H$

Scheme 6.28

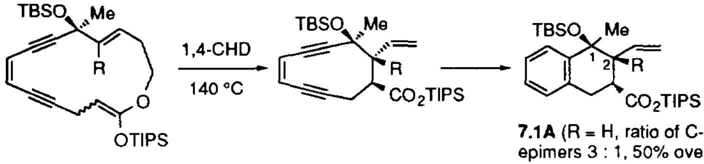


6.29A
6.29B

Scheme 6.29

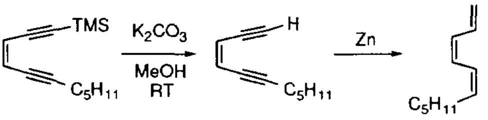
7. Synthetic Utility of Enediynes and Related Systems

The majority of the research in the area of enediynes and related systems has focused on the DNA cleaving ability of the natural products and synthetic analogues. The application of Bergman and related cyclizations to other synthetic targets has received less attention; nevertheless, some major advances have been made. Several publications have appeared describing the use of enediynes to access other useful synthetic targets. Magriotis and Kim described a stereocontrolled route to the highly substituted tetrahydronaphthalene systems **7.1A** and **7.1B** based on a tandem Ireland/Claisen and Bergman cyclization procedure (Scheme 7.1).[171] Linstrumelle and coworkers described the synthesis of (*Z,Z*)-conjugated trienes **7.2A** from trimethylsilyl enediynes *via* a desilylation/reduction process (Scheme 7.2).[172]



7.1A (R = H, ratio of C-2 epimers 3 : 1, 50% overall)
7.1B (R = SPh, ratio of C-1 epimers 7 : 1, 45%)

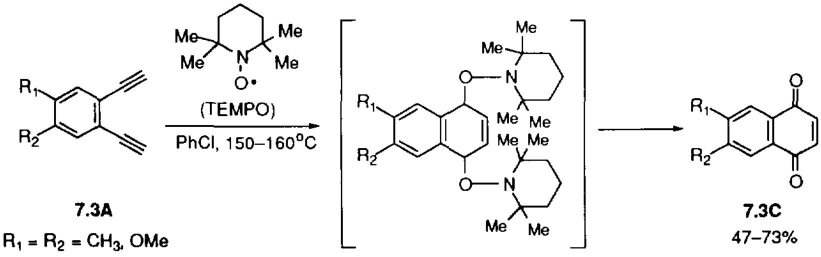
Scheme 7.1



7.2A (58% overall)

Scheme 7.2

Although there is no direct proof for biradical intermediates in the Bergman cyclization (see Section 2), much indirect evidence suggests that the reaction proceeds through intermediates that are radical in character. Recently, Grissom and Gunawardena showed that, upon thermolysis, enediyne arenes **7.3A** react with the well-known radical trapping agent TEMPO to give the intermediate **7.3B**, which then undergoes spontaneous homolysis to form napthoquinone **7.3C** (Scheme 7.3).[173] This result provides further evidence for the involvement of a biradical intermediate in the initial ring closure.



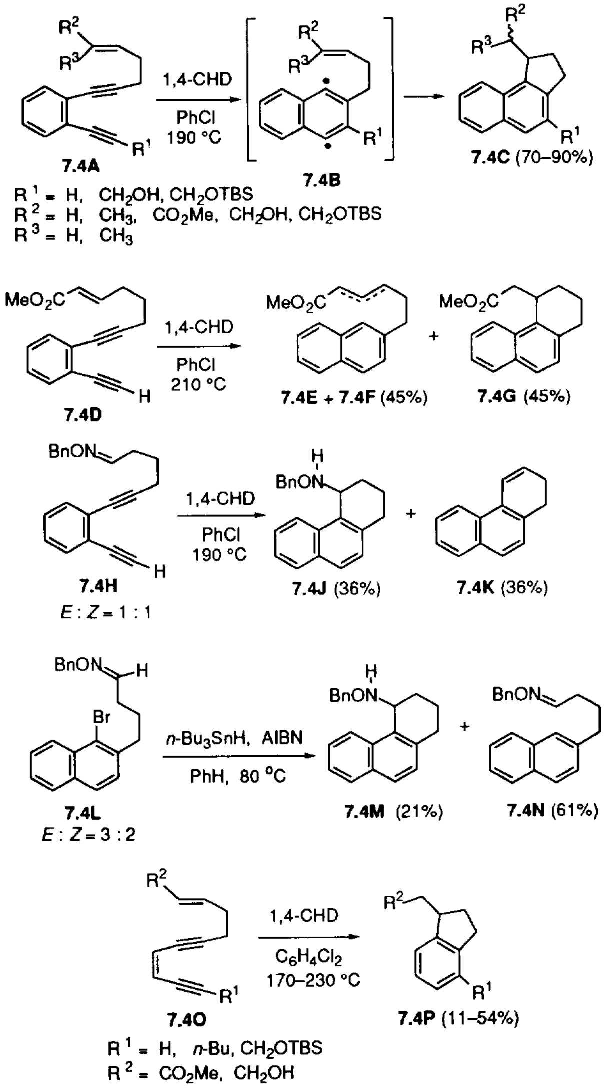
7.3A
R$_1$ = R$_2$ = CH$_3$, OMe
-OCH$_2$CH$_2$O-

7.3B

7.3C
47–73%

Scheme 7.3

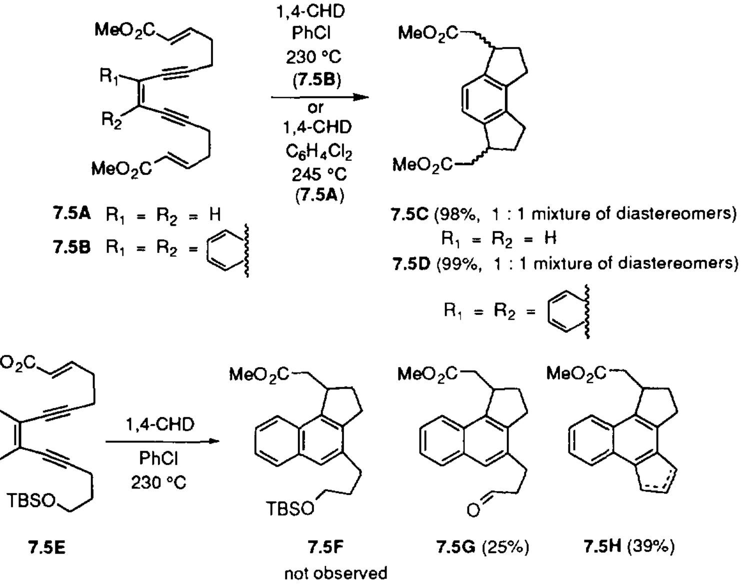
Extensive evidence for biradical intermediates in the enediyne and enyne allene cyclizations has been presented by Grissom, by Wang, and by Moore, who all showed that the intermediates can undergo subsequent chemistry characteristic of radical reactions. Grissom, Calkins, and Egan prepared the dihydrobenzindene derivatives **7.4C** by trapping the 1,4-dehydroarene intermediates **7.4B** (generated by Bergman cyclization) with reactive, strategically placed (5-*exo*-trig) intramolecular radical acceptors (Scheme 7.4).[174] The tandem cyclization of the 6-*exo* substrate **7.4D** required higher temperatures and was complicated by competing 1,5-hydrogen abstractions resulting in three products, **7.4 E–G**. Grissom, Klingberg, and coworkers also demonstrated the viability of non-olefin radical acceptors to trap 1,4-dehydroarene radicals generated by Bergman cyclization of arene enediynes (Scheme 7.4).[175] The thermolysis of oxime ether **7.4H** gave tricyclic compounds **7.4J** and **7.4K** as major products *via* a tandem enediyne-radical cyclization. The structures of these products were compared with those arising from simple cyclization of aromatic radicals generated from tributyltin hydride treatment of aryl halides (**7.4L** → **7.4M** and **7.4N**). These results suggest that the tandem enediyne-radical cyclization proceeds through a radical intermediate. Non-aromatic enediynes **7.4O** undergo similar tandem cyclizations to afford dihydroindenes **7.4P**, although the yields are not as good as those with the aromatic enediynes **7.4A** (Scheme 7.4).[176]



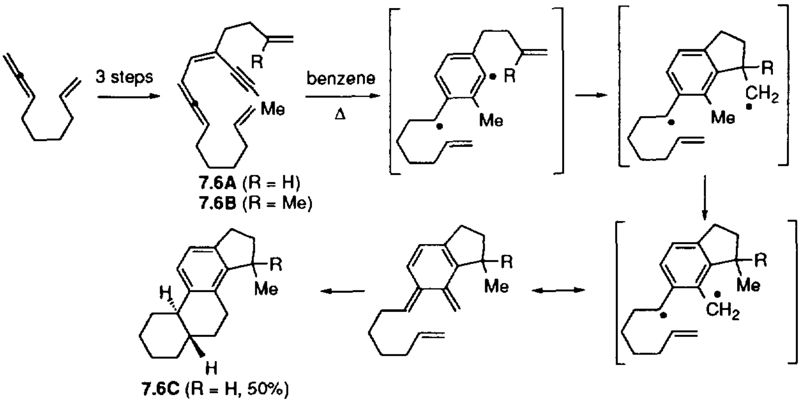
Scheme 7.4

Grissom and coworkers reported that the thermolysis of **7.5B** carrying radical-accepting tethers at both ends of the enediyne gave the tetracyclic product **7.5D** *via* a tandem enediyne-*bis*-radical cyclization (Scheme 7.5). The non-aromatic enediyne **7.5A** also readily underwent this tandem cyclization in excellent yield.[177] Grissom also described examples of the tandem enediyne-*bis*-radical cyclizations in which non-radical accepting tethers underwent cyclizations onto aromatic rings (Scheme 7.5).[177] Enediyne **7.5E** did not lead to product **7.5F** expected from a single radical cyclization but instead gave a mixture of **7.5G** and **7.5H**.

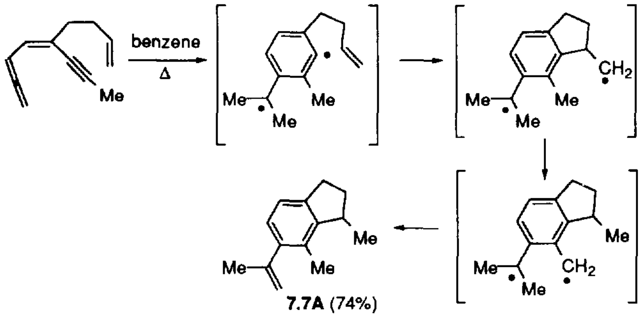
Wang *et al.* initially reported that the intermediates of enyne allene cyclizations would undergo subsequent radical reactions. They developed a procedure for one-step construction of the tetracyclic steroidal skeleton by thermolysis of enyne allenes **7.6A** and **7.6B** (Scheme 7.6).[178] The process involves enyne allene cycloaromatization, radical cyclization, 1,5-hydrogen transfer, and intramolecular Diels-Alder reaction. Wang also reported a related approach to the 2,3-dihydroindene derivative **7.7A** (Scheme 7.7).[179]



Scheme 7.5

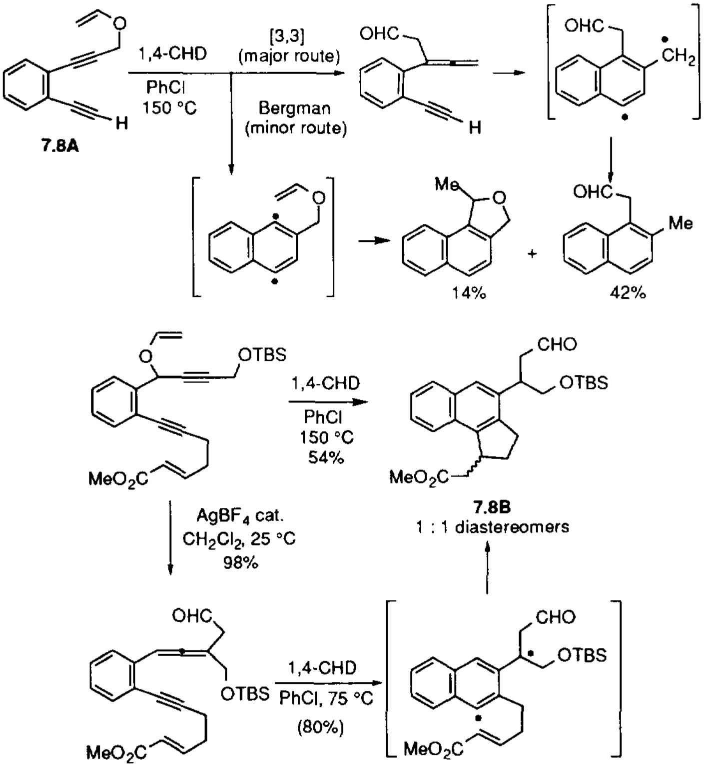


Scheme 7.6

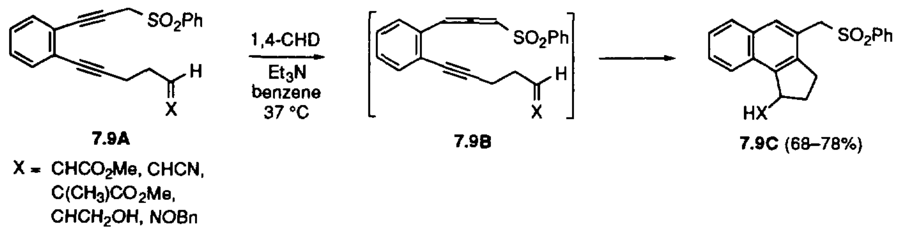


Scheme 7.7

Grissom and coworkers were also able to intercept radical intermediates from enyne allene cyclizations. In one study, Grissom and Huang found that arene enediynes of the general structure **7.8A** undergo a sequential [3,3] sigmatropic shift-enyne allene cyclization at lower temperatures than those normally required for simple Bergman cyclization (Scheme 7.8).[180] A modification of the reaction can be applied to the synthesis of 2,3-dihydrobenz[*e*]indene derivatives **7.8B** in a single step or at lower temperature in two steps (Scheme 7.8). An alternative route to 2,3-dihydrobenz[*e*]indenes **7.9C** described by Grissom and Klingberg constitutes the base-catalyzed isomerization of enediyne sulfones **7.9A** to enyne allenes **7.9B** followed by tandem enyne allene-radical cyclization at 37 °C (Scheme 7.9).[181]

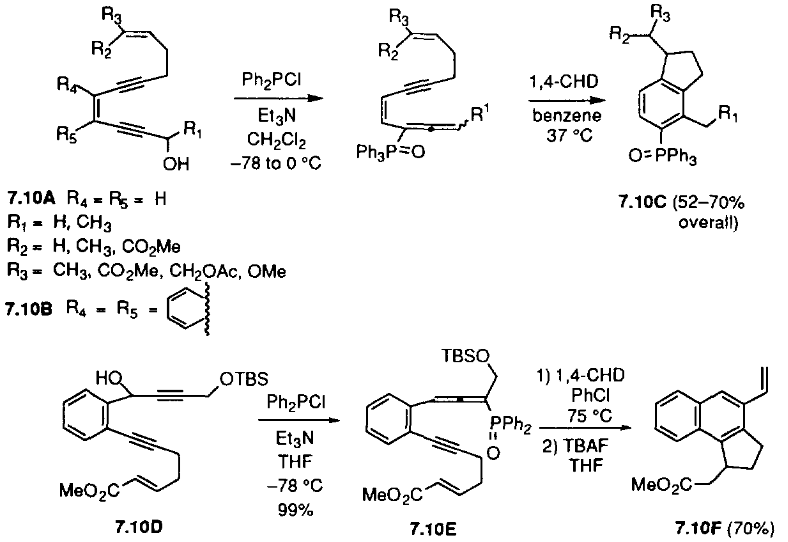


Scheme 7.8



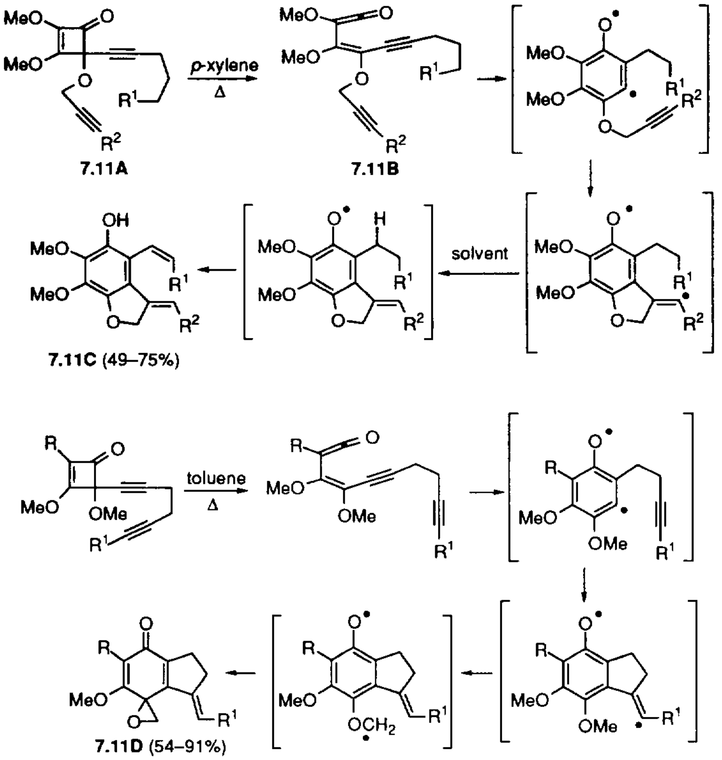
Scheme 7.9

Grissom *et al.* found that the 2,3-dihydroindene derivatives **7.10C** can be synthesized efficiently under mild conditions from enediyne alcohols **7.10A** by a two-step procedure, which involves an enyne allene cycloaromatization that occurs at 37 °C (Scheme 7.10).[182] The procedure is not amenable to the corresponding arene enediyne alcohols **7.10B**.[183] However, the enyne allene **7.10E** derived from propargyl alcohol **7.10D** undergoes an efficient tandem enyne allene cycloaromatization-radical cyclization process at 75 °C to give a tricyclic compound, which was isolated and identified as the Wittig elimination product **7.10F**.[183]

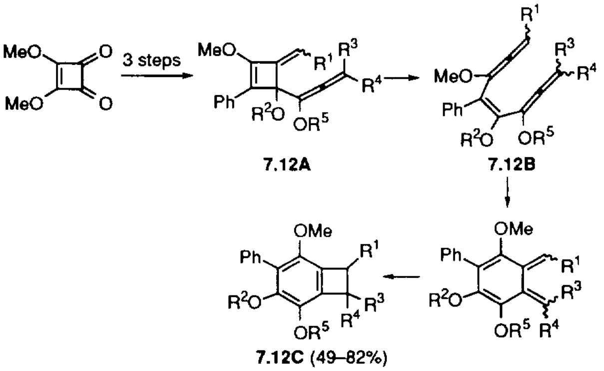


Scheme 7.10

Moore and coworkers described a procedure for the synthesis of the highly substituted benzofurans **7.11C** from 4-alkynyl-4-propargyloxy cyclobutenones **7.11A** (Scheme 7.11).[184] The reaction proceeds through cyclization of the intermediate enyne ketene **7.11B**. In a related study, Moore's laboratory also described a route to the annulated spiroepoxycyclohexadienones **7.11D** from similar substrates (Scheme 7.11).[185] They also synthesized benzocyclobutenes **7.12C** from 3-alkylidene or benzylidene-4-allenylcyclobutenes **7.12A** *via* cyclization of the ene diallene intermediate **7.12B** (Scheme 7.12).[186]



Scheme 7.11



Scheme 7.12

8. Conclusion

Enediynes, enyne allenes, and structurally related compounds have attracted an immense amount of attention from the biological and chemical communities since the initial report of the enediyne antitumor antibiotics esperamicins and calicheamicins in 1987.[7] Much work has been directed toward synthesis of the naturally occurring enediyne antibiotics (esperamicins, calicheamicins, dynemicins and neocarzinostatin chromophore); and with the recent discovery of the kedarcidin and C-1027 chromophore structures, the excitement over the synthesis of these compounds is certain to continue. It is fascinating to wonder why microorganisms make such unusual compounds, and it is likely that additional enyne antibiotics will be discovered.

Given the structural complexity of the naturally occurring enediyne antibiotics, significant progress has been made toward the preparation of comparably potent synthetic compounds which are architecturally less daunting, thus easier to synthesize. Much work continues toward the development of novel structures that cyclize through biradical mechanisms but have yet to be discovered in nature. There is much excitement over enyne compounds that may cyclize and cleave DNA through bifurcated mechanisms involving both radical and ionic pathways. In fact, the fire continues to build as to whether true biradical intermediates are involved at all in the cyclizations of these structures. However, some of these compounds do appear to cyclize through radical intermediates as shown by the flurry of attention given to carrying out additional radical chemistry subsequent to the formation of these purported biradical species. This chemistry promises to be another tool added to the growing arsenal available to the synthetic organic chemist for the preparation of biologically active organic molecules.

Although it has been only about 10 years since the initial report of the structure of the enediyne antitumor antibiotic neocarzinostatin chromophore, literally thousands of papers have appeared describing the chemistry and biology of these unique enediyne compounds. It is mindboggling to imagine where this field may be in another 10 years. Science has been in search of the "magic bullet" for the cure of cancer. Could an elegantly designed enyne possibly offer a solution?

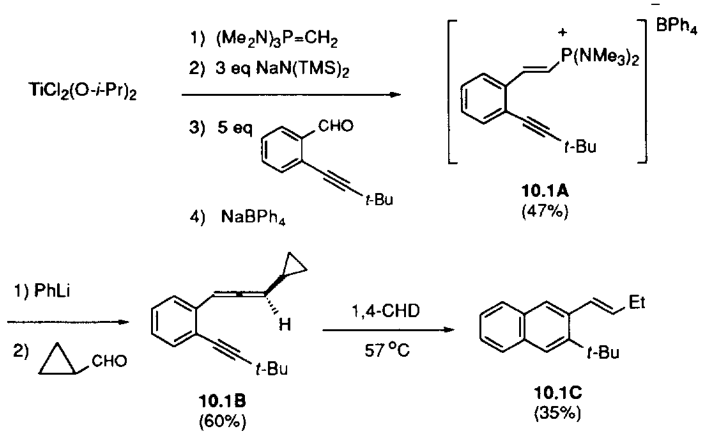
9. List of Abbreviations

Ac	acetyl
Ad	adamantyl
AIBN	azo-bisisobutyronitrile
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
1,4-CHD	1,4-cyclohexadiene
*m*CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulphonic acid
Δ	heat
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMAP	4-(*N*,*N*-dimethyl)aminopyridine
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Et	ethyl
FMOC	9-fluorenylmethyl carbonate
hv	light
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTS	dimethyl(1,1,2,2-tetramethyl)ethylsilyl
dppp	1,3-bis(diphenylphosphino)propane
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoric triamide
LDA	lithium diisopropylamide
Me	methyl
MEM	methoxyethoxymethyl
MOM	methoxymethyl
Ms	methanesulfonyl
NMO	*N*-methylmorpholine *N*-oxide
Ph	phenyl
Phth	phthaloyl
PMB	*p*-methoxybenzyl
Pr	propyl
PyBroP	bromo-*tris*-pyrrolidino-phosphonium hexafluorophosphate
pyr	pyridine
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
THF	tetrahyrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidide
Ts	toluenesulfonyl

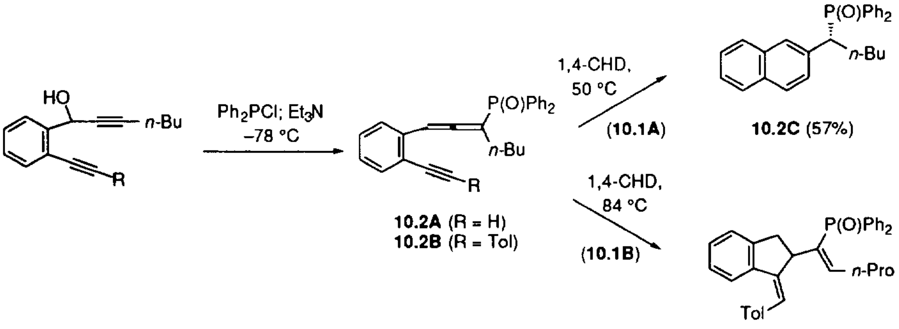
10. Addendum

After this review was completed, several additional studies were published.

Section 6: Finn and Dopico synthesized enyne allenes such as **10.1B** by treating the phosphonium ylides (derived from base treatment of salt **10.1A**) with aldehydes (Scheme 10.1).[187] The thermal cyclization of this enyne allene **10.1B** at 57 °C proceeds through a radical mechanism as evidenced by the formation of naphthalene **10.1C**. Schmittel and coworkers also reported an unusual difference between the reactions of the enyne allenes **10.2A** and **10.2B**.[188] The thermal cyclization of **10.2A** gave the expected cyclization product **10.2C** whereas the reaction of **10.2B** afforded product **10.2D** through a different mode of cyclization.

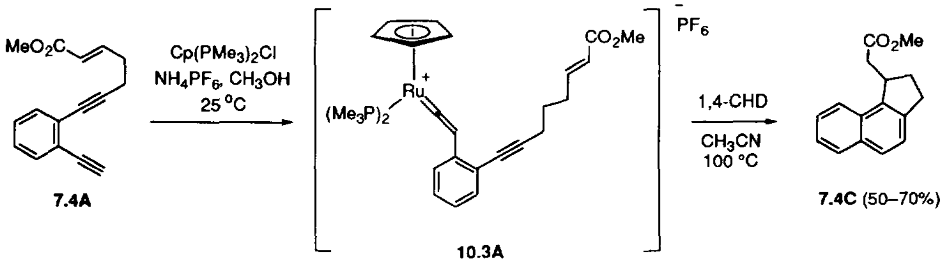


Scheme 10.1



Scheme 10.2

Section 7: Finn and Wang described the metal-promoted tandem cyclization of enediyne **7.4A** at 100 °C to give the dihydrobenzindene system **7.4C**.[189] This reaction proceeds at lower temperatures than the corresponding thermolysis in the absence of metals,[174] because the intermediate vinylidene complex **10.3A** cyclizes more readily than the enediyne **7.4A**.



Scheme 10.3

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