## CONTROLLING THE REACTIVITY OF BERGMAN AND MYERS-SAITO CYCLIZATIONS

Reported by Daniel A. Ryan November 4, 2002

### INTRODUCTION

Enediyne compounds have captured the imagination of chemists since the discovery of calicheamicin (**1**) and neocarsinostatin (**2**)—natural products three orders of magnitude more potent than other anti-cancer drugs.[1] In following years, other powerful enediyne toxins such as dynemicin, kedarcidin, esperamicin, maduropeptin, and C-1027 were discovered.[2] Preliminary studies focused on the total synthesis and elucidation of the biological mode of action of these natural products.

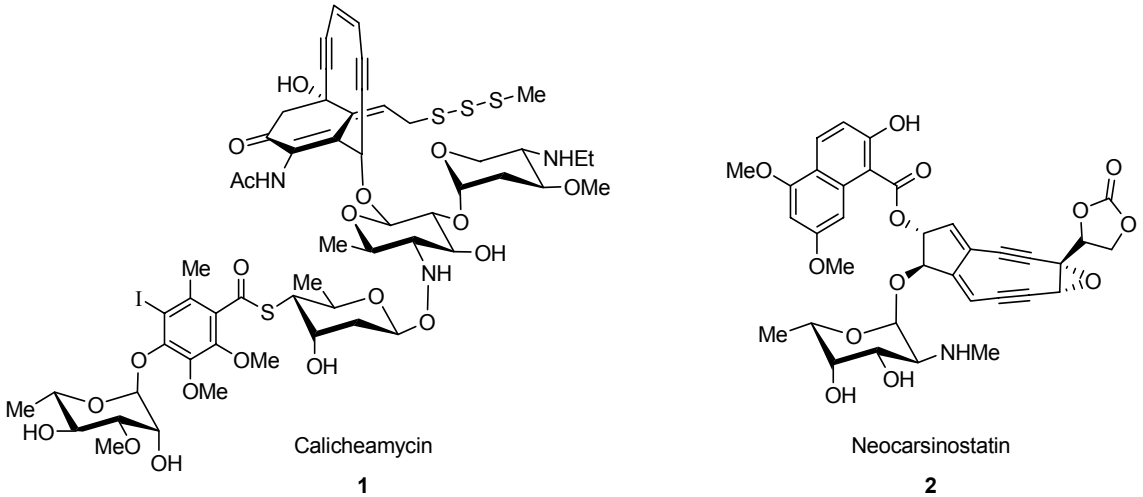
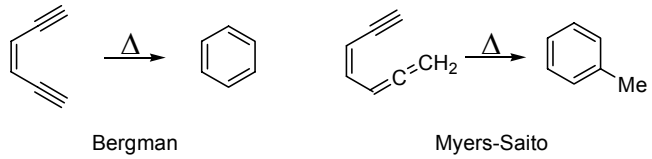



**Figure 1.** Enediyne antitumor agents calicheamycin and neocarsinostatin.

Although enediynes have stimulated considerable synthetic interest, their clinical use has been limited because of their modest selectivity for cancer cells.[3] It was determined that the biological activity of these enediyne compounds is dependent on the Bergman cyclization, or in the case of Neocarsinostatin (**2**), the Myers-Saito cyclization (Scheme 1).[2] To understand and modify the biological activity of these toxins, factors that influence the reactivity of the Bergman and Myers-Saito cyclizations have been explored. These new advances will be reported herein.

**Scheme 1**




### Biological Mode of Action

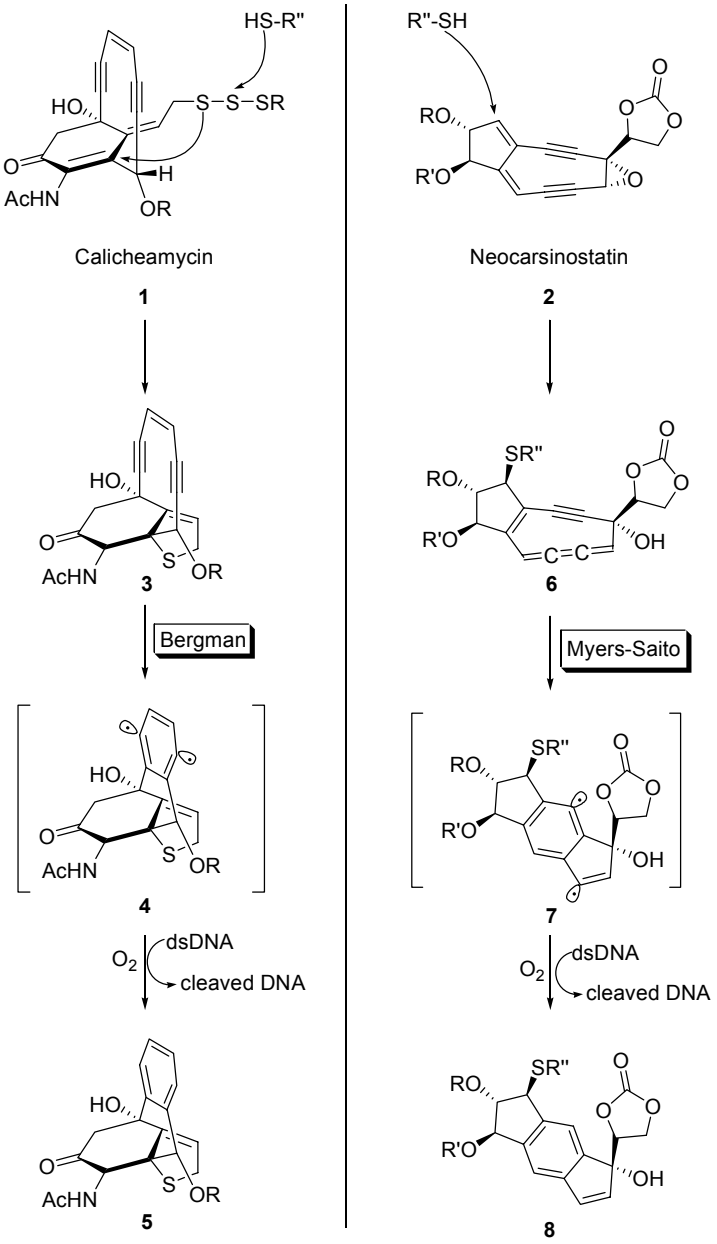
The antitumor activity of enediyne natural products stems from their ability to cleave double-stranded DNA (dsDNA), which induces cell apoptosis.[4] The biological mode of action occurs along one of two general pathways, depending on the type of enediyne structure (Scheme 2). The majority of enediyne natural products, including Calicheamicin (**1**), undergo Bergman cyclization. The sequence of

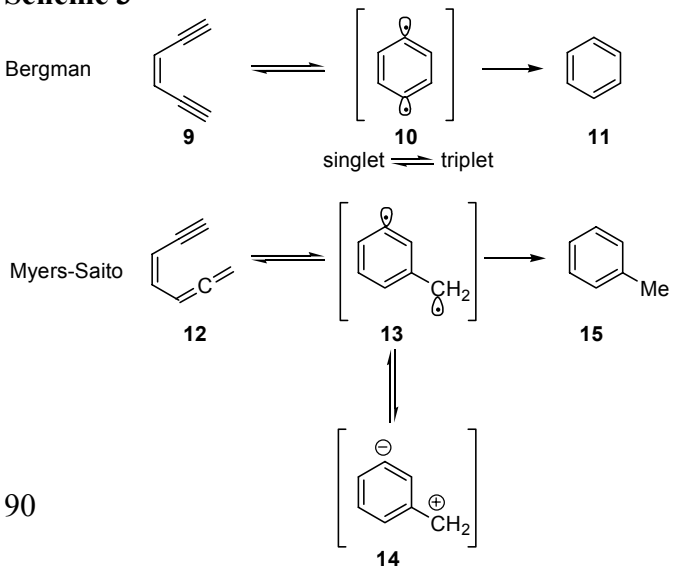
reactions that leads to this cyclization begins when a cellular thiol, such as glutathione, attacks the trisulfide bond, liberating a thiolate which then reacts with the unsaturated enone via 1,4 addition. The resulting rehybridization of the bridgehead carbon ($sp^2$ to $sp^3$) induces a conformational change that decreases the distance between diyne termini in **3**. The Bergman cyclization now proceeds readily to afford the *p*-benzyne diradical **4** that abstracts two hydrogen atoms, one each from the opposite strands of a complementary base pair producing the arene **5**.[4] The chemical consequences of these hydrogen atom abstractions lead to double-stranded DNA cleavage, which induces apoptosis.[4]

Neocarsinostatin (**2**) represents the class of enediyne natural products that operates via a Myers-Saito pathway (Scheme 2). In **2**, 1,8-addition of a thiol to the unsaturated epoxide produces the highly reactive cumulene intermediate **6**. Compound **6** undergoes a Myers-Saito cyclization to the biradical species **7**, which in turn abstracts two hydrogen atoms from DNA, again resulting in double-strand cleavage.[4]

**Scheme 2**




**Scheme 3**




**Bergman and Myers-Saito Cyclizations: General Mechanistic Considerations**

Comparison of the Bergman and Myers-Saito mechanisms accounts for the source of differing reactivity (Scheme 3). For instance, the Bergman cyclization proceeds from an enediyne structure (**9**), so its reactivity depends on conformation and electronic effects inherent in the molecule. In contrast, Myers-Saito cyclization

requires formation of the highly reactive allene **12**; simply accessing this intermediate is paramount to controlling its reactivity.

A key difference between the two mechanisms is the nature of the biradical species formed. The Bergman cyclization forms the *p*-benzyne σ,σ biradical intermediate **10**. The putative singlet biradical **10** is thought to be in equibilbrium with a triplet state biradical.[5] This exchange is translated via field effects and through-bond effects. Because singlet biradicals are less reactive than triplet species, the expectation of intersystem crossing is that the rate of hydrogen atom abstraction increases.[6] However, attempts to induce the triplet state through application of a magnetic field have failed.[7]

In contrast to the Bergman reaction, the Myers-Saito reaction proceeds through a 1,4-toluene σ,π biradical intermediate **13**.[8] Theoretical and experimental evidence supports the existence of an equilibrium between **13** and the zwitterion **14**.[8,9] The increase in ionic character is believed to decrease the efficiency of DNA cleavage through the established biradical mechanism.[8,9]

## THE BERGMAN CYCLIZATION

### Influence of Ring Strain

The most widely studied, and arguably most influential way to alter the reactivity of the Bergman cyclization is through generation of a strained conformation. In early investigations, Nicolaou proposed that the overriding determinant of enediyne reactivity is the interatomic distance between diyne termini.[10] Despite a large body of theoretical and crystallographic evidence to support this theory, some investigators have proposed that the key factor in reactivity is the difference in strain energy between the ground state and transition state.[11]

Experimental evidence exists that supports the latter argument. An early study by the Magnus group illustrated that [7.3.1] bridgehead ketone **16**, in the presence of hydrogen atom donor 1,4-cyclohexadiene, reacted quickly at 70 °C.[12] However, the [7.2.1] bridgehead ketone **17**, with decreased distance between diyne termini, reacted 657 times slower than **16**. The [7.2.1] bicycle **18**, with a bridgehead alcohol, reacted 217 times faster than **17**, but still only one-third the rate of **16**. It was presumed that reduction of the ketone **17** to alcohol **18** diminished acetylene distance. The explanation was offered that in **16**, the six-membered

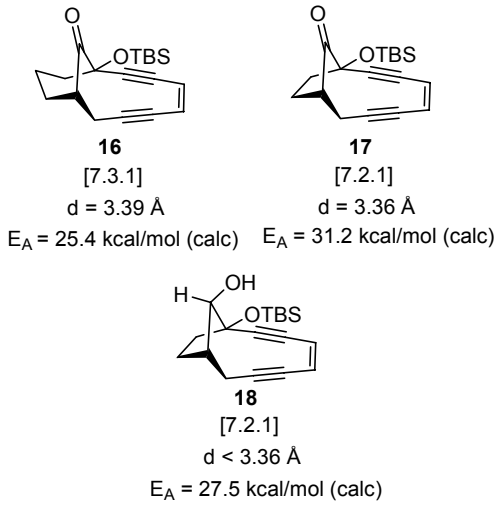



**Figure 2.** Enediynes with $sp^2$ and $sp^3$ bridgehead carbons

ring converts from a boat ground state to a chair transition state, thus alleviating 6 kcal/mol in strain energy and reducing the activation energy. This strain relief pathway is not available to the [7.2.1] systems.

In a recent study employing density functional theory, Schreiner confirmed that differential ring strain between the ground state and transition state is the determining factor and some enediynes with relatively small acetylenic distances were predicted to react slowly.[6]

**Stereoelectronic Effects**

An emerging field in enediyne chemistry concerns stereoelectronic effects on the Bergman cyclization. In one study, chlorine substitution at the vinyl position was investigated. The nine-membered enediyne **19** has never been isolated, whereas the chlorosubstituted analogue **20** has a half-life of 6 minutes at 40 $^{o}$C.[13] The ten-membered enediyne **21** has been typically isolated in poor yields and reacts readily at 25 $^{o}$C. By contrast, the chloroanalogue **22** shows a marked stability towards Bergman cyclization. These results show that chlorine substitution at the vinyl position retards the rate of Bergman cyclization.

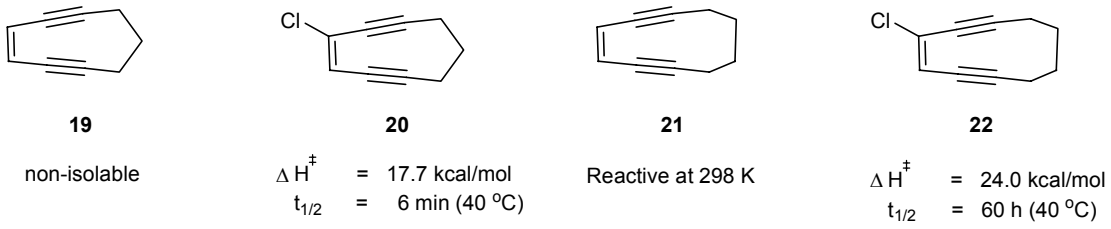
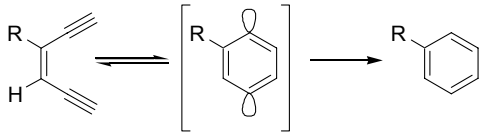



**Figure 3.** Effects of chlorine substitution on 9 and 10 membered rings.

In a later theoretical study, vinylic substitution on hex-3-ene-1,5-diyne **23** was explored (Table 1).[14] Monosubstitution with a halogen, such as chlorine or fluorine, was predicted to increase the barrier to cylization (entries 1-3) and it was argued that σ-electron withdrawing groups serve to destabilize the electron deficient biradical intermediate **24.** The *p*-FPh substituent was predicted to have a minor influence, thus ruling out the influence of π electrons. In addition, a field effect between the halogen lone pair and the developing radical was postulated to further destabilize the transition state. This trend holds for $NO_2$ substitution (entry 5).

This study also reported cases where predicted cyclization barriers were attenuated. For instance $BH_2$ (co-planar with the enediyne) was expected to have the lowest cyclization barrier

**Table 1. Effect of vinyl substitution.**



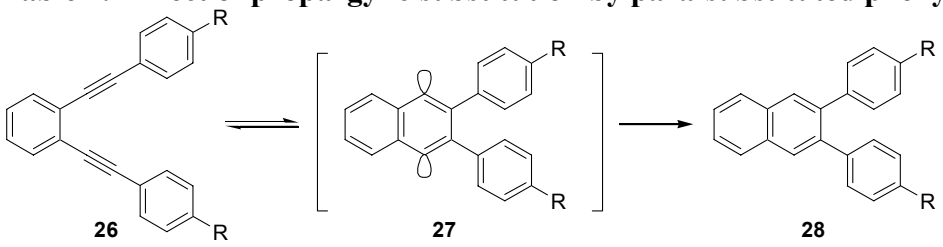

**23** **24** **25**

| Entry | R | Theoretical $\Delta H^{\ddagger}$ ( kcal/mol) |
|---|---|---|
| 1 | H | 27.4 |
| 2 | Cl | 28.9 |
| 3 | F | 29.1 |
| 4 | *p*-FPh | 26.8 |
| 5 | $NO_2$ | 28.6 |
| 6 | $BH_2$ | 25.3 |

(entry 6), likely due to destabilization of the ground state via withdrawal of π electrons from the electron deficient enediyne. Although these stereoelectronic effects are subtle, overall the activation enthalphies listed in Table 1 represent a two thousand-fold change of reactivity.

Substitution on the alkyne termini has also been investigated (Table 2). In one study, para-substituted phenyl rings were attached to the alkyne termini. The authors argue, based on an early theoretical treatment,[15] that *p*-Nitro phenyl substitution decreases the Bergman activation energy through alleviation of electronic repulsions between p-orbitals in the transition state (entry 3).[16] Alternatively, later arguments have suggested that π-electron acceptors destabilize the ground state relative to the transition state[17]. The π-donating methoxy substitutent raises the activation energy.

**Table 2. Effect of propargylic substitution by para-substituted phenyl rings.**

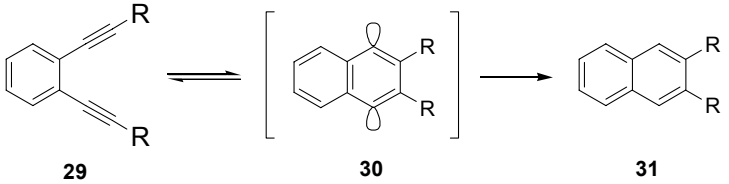



| Entry | R | T for $t_{1/2}$ = 71 min |
|---|---|---|
| 1 | H | 280.2 °C |
| 2 | OMe | 285.9 °C |
| 3 | $NO_2$ | 249.6 °C |

Theoretical support exists for the electronic effects thus far presented. A recent study by Schreiner and coworkers, employing both Hartree-Fock and density functional theory valence bond methods, led the authors to propose that the Bergman transition state is eighty percent product-like geometrically, but only thirty percent product-like electronically. It was proposed that π electrons would have minimal effect on the transition state, whereas the influence of sigma electrons, in a 6σ electron aromatic array, was predicted to be kinetically significant.[18]

In an experimental inquiry it was found that ketone and ester substituents increase the activation energy of cyclization (Table 3).[19] The authors suggest that π-electron acceptors manifest unfavourable interactions, which outweigh favourable σ-acceptor interactions. Notably, these *arguments* contradict the aforementioned theoretical frameworks.

**Table 3. Effect of carbonyl functionality at propargylic position.**




| Entry | R | $t_{1/2}$ (162° C) |
|---|---|---|
| 1 | H | 29 min |
| 2 | C(O)Me | 481 min |
| 3 | $CO_2Me$ | 660 min |

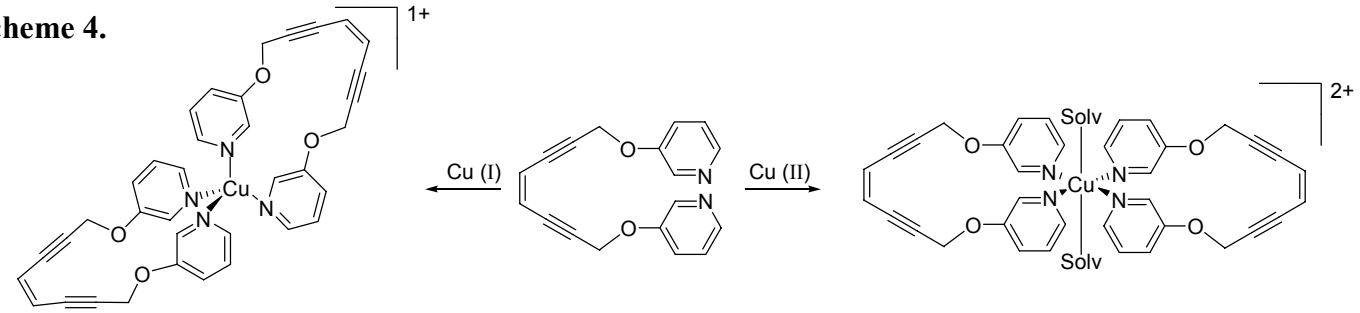
**Transition Metal Triggers**

Methods for triggering the Bergman reaction, outside of strain

induction by nucleophilic attack (i.e. calicheamicin), are uncommon. Recently, efforts toward metal promoted Bergman cyclization have been reported.

Zaleski and coworkers report on ligand field control over the Bergman reaction using copper (I) and copper (II) compounds.[20] The addition of Cu (I) to a solution of the enediyne ligand **32** formed the chelated tetrahedral copper complex **33**. Similarly, addition of Cu (II) to the free enediyne ligand formed the chelated octahedral copper complex **34**. The cyclization temperatures were determined by differential scanning calorimetry in the solid-state. The tetrahedral coordinated species was found to undergo Bergman cyclization at 203 $^{o}$C, while the square planar compound cyclized at 121 $^{o}$C. The Cu (II) octahedral geometry was verified by electron spin resonance and electron absorption spectroscopy.

**Scheme 4.**

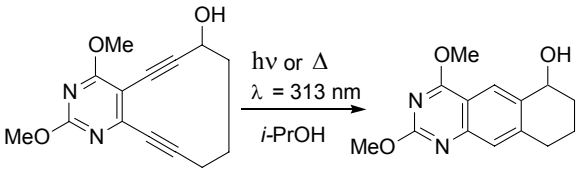



**33** 203 $^{o}$C **32** 245 $^{o}$C **34** 121 $^{o}$C

**Photochemical Triggers.**

The photochemical Bergman cyclization has received considerable attention due to the medicinal potential for inducing localized drug action by selective illumination of tumors. In a recent example reported by Russell and coworkers, the photochemical pathway provides a significant rate increase in an otherwise thermally stable enediyne structure **35** (Table 4).[21] Upon irradiation with ultraviolet light, the Bergman reaction occurs with 82% yield at 40 $^{o}$C using 2-propanol as the source of hydrogen atoms. It is of note that studies have shown annulated enediynes to be more photochemically reactive than non-annulated enediynes.[22]

**Table 4. Photochemical Bergman Cyclization.**




**35** **36**

| Entry | Conc. | Conditions | Yield |
|---|---|---|---|
| 1 | 0.020 | 80 $^{o}$C, 10 h | 93% |
| 2 | 0.001 | 40 $^{o}$C, 36 h | trace |
| 3 | 0.001 | 40 $^{o}$C, hν, 24 h | 82% |

## THE MYERS-SAITO CYCLIZATION

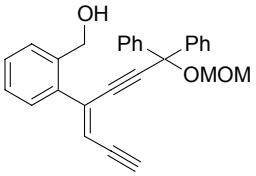
### pH Dependent Myers-Saito Cylization.

Research into the Myers-Saito mechanism has focused on accessing the highly reactive enyne-allene intermediate. In many systems its formation is sufficient to drive cyclization, as it releases

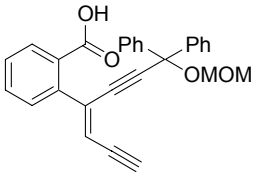
approximately 15 kcal/mol upon conversion to the σ,π biradical.[19] As a consequence of its great reactivity, methods to mask and unveil the allene have been developed.

One promising result was observed upon incubating enediyne systems **37** and **38** at 37 °C for 24h with supercoiled DNA (Table 5).[23] In this reaction, the hydroxyl group is believed to induce allene formation via acid-mediated elimination of the methoxymethyl (MOM) ether. No rationale for the differing reactivities between **37** and **38** was provided. Particularly interesting is that **38** shows selective reactivity in the pH range of 5-6. Since cancer cells (pH 5.5) are more acidic than normal cells (physiological pH 7.4), this compound may prove to be of practical importance.[24]

**Table 5. pH Dependent Myers-Saito Cylization.**



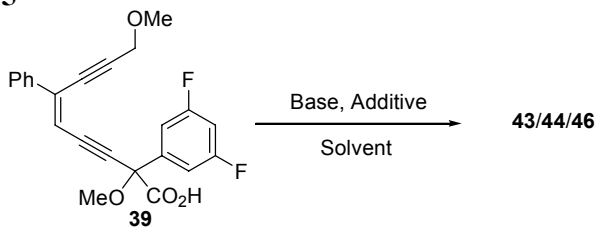
**37**



**38**

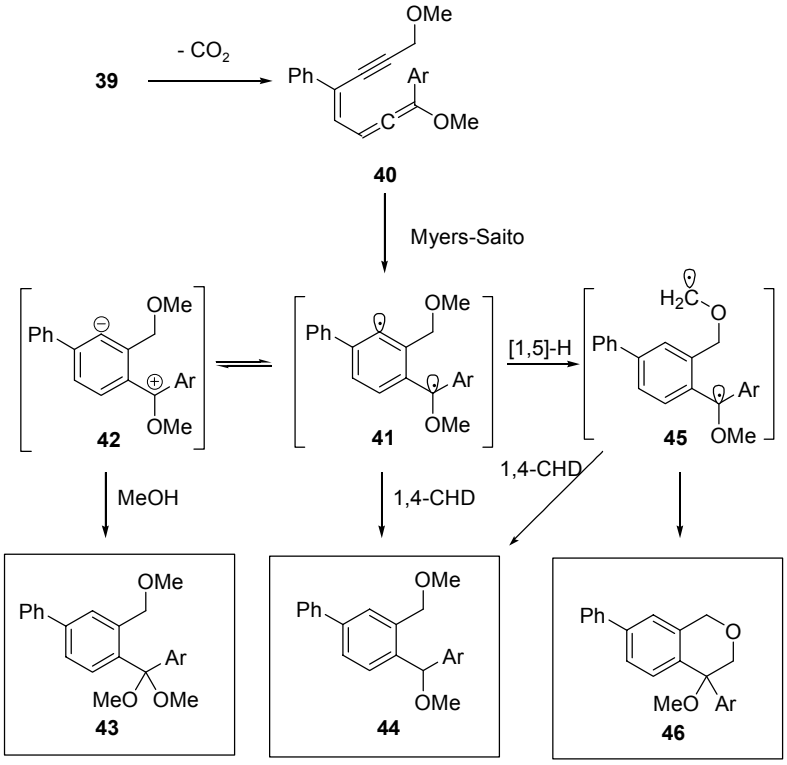
| | Percent DNA Cleaved | |
|---|---|---|
| pH | **40** | **41** |
| 5 | 29 | 19 |
| 6 | 37 | 5 |
| 7 | 35 | 3 |
| 8 | 20 | 3 |
| 9 | 18 | 1 |
| 10 | 11 | 0 |

**Scheme 5**



**39**

| Entry | Solvent | Base | Additive | Reaction Time (min) | Product Yield **43** | **44** | **46** |
|---|---|---|---|---|---|---|---|
| 1 | MeOH | $NEt_3$ | $CHD/O_2$ | 390 | 77 | - | - |
| 2 | Benzene | $NEt_3$ | CHD | 70 | - | 23 | 10 |
| 3 | DMF | - | - | <1 | - | - | 31 |
| 4 | DMF/MeOH (9/1) | - | - | <1 | 58 | - | - |



**40** **41** **42** **43** **44** **45** **46**

**Decarboxylation Trigger**

Another recent report details decarboxylation as a trigger for Myers-Saito cycloaromatization. Scheme 5 highlights the influence of solvent on the reaction.[24] Decarboxylation of **39** under basic conditions triggers formation of the allene **40**. In protic solvent such as methanol, an ionic pathway prevails (entry 1). The reaction path digresses from radical chemistry likely because of the ability of a protic solvent to stabilize ionic species like **42**; methanol then traps the zwitterion to yield **43**. In benzene, the radical pathway dominates

the reaction as evidenced by the formation of **44** and **46**, with no evidence of **43** (entry 2). Under these conditions, decarboxylation to afford **40** followed by Myers-Saito cylization gives **41** and 1,4-cyclohexadiene traps the biradical, providing **44** directly. Use of an ortho methoxy methyl substituent adds an element of complexity to the reaction pathway, because the biradical **41** may undergo intramolecular 1,5 hydrogen abstraction to form the oxygen stabilized radical **45** leading to **46**. Interestingly, when DMF is employed as solvent, the radical pathway proceeds even without 1,4-cyclohexadiene; however, even 10% methanol directs the reaction along the ionic pathway. The authors suggest that the ionic pathway renders the abstraction of hydrogen atoms from DNA less likely, thus highlighting the importance of reaction environment on the Myers-Saito cyclization.

## CONCLUSION

Control over the reactivity of the Bergman cyclization through ring strain, electronic, and steric effects allows for fine-tuning of reactivity. The development of metal and photochemical triggers provides alternative means of activation. Although less is known concerning factors that govern the reactivity of the Myers-Saito cyclizations, the influence of solvents is pronounced. A pH dependent reaction offers a lead into novel triggering mechanisms of this reaction.

What is the significance of investigations into controlling enediyne chemistry? The newfound understanding of reactivity may allow for controlled rates of biological activity. More importantly, new triggering mechanisms offer potential to exploit differential properties of tumor cells, such as increased permeability, increased oxygen content, and increased acidity, leading to more selective antitumor agents. A well-designed enediyne and trigger may offer a significant advance in anti-cancer therapy.

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