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Conformationally Gated Fragmentations and Rearrangements Promoted by Interception of the Bergman Cyclization through Intramolecular H-Abstraction: A Possible Mechanism of Auto-Resistance to Natural Enediyne Antibiotics?

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Abstract: A variety of fragmentations and rearrangements can follow Bergman cyclization in enediynes equipped with acetal rings mimicking the carbohydrate moiety of natural enediyne antibiotics of the esperamicine and calchiamicine families. In the first step of all these processes, *intra*molecular H-atom abstraction efficiently intercepts the *p*-benzyne product of the Bergman cyclization through a six-membered TS and transforms the *p*-benzyne into a new more stable radical. Depending on the substitution pattern and reaction conditions, this radical follows four alternative paths: (a) abstraction of an external hydrogen atom, (b) O-neophyl rearrangement which transposes O- and C-atoms of the substituent, (c) fragmentation of the O−C bond in the acetal ring, or (d) fragmentation with elimination of the appended acetal moiety as a whole. Experiments with varying concentrations of external H-atom donor (1,4-cyclohexadiene) were performed to gain further insight into the competition between intermolecular H-abstraction and the fragmentations. The Thorpe−Ingold effect in *gem*-dimethyl substituted enediynes enhances the efficiency of fragmentation to the extent where it cannot be prevented even by a large excess of external H-atom donor. These processes provide insight into a possible mechanism of unusual fragmentation of esperamicin A_1 upon its Bergman cycloaromatization and lay foundation for a new approach for the conformational control of reactivity of these natural antitumor antibiotics. Such an approach, in conjunction with supramolecular constraints, may provide a plausible mechanism for resistance to enediyne antibiotics by the enediyne-producing microorganisms.

Introduction

Biological activity of natural enediyne antibiotics stems from the formation of *p*-benzyne (1,4-dehydrobenzene diradical) via Bergman cycloaromatization (BC)[1] of the enediyne functional core. The diradical can abstract hydrogen atoms from the two strands of the DNA duplex, causing double strand DNA cleavage and subsequent apoptosis, that is, self-programmed cell death.[2−5] This process is remarkably efficient and, as a result, enediynes display activity against a wide range of human tumor cell lines at very low concentrations.[6,7] For example, C1027 displays cytotoxicity against KB carcinoma cells with IC_{50} of 0.1 ng/mL in vitro.[8] It is astonishing that molecules with such levels of toxicity can be produced and utilized by microorganisms without sustaining lethal self-damage.

Many of the natural enediynes, like esperamicins and calicheamicins, have a carbohydrate moiety positioned directly next to the enediyne functionality (Figure 1). It is generally established that the carbohydrate part plays an important role of binding to DNA and orienting the enediyne warhead ap-

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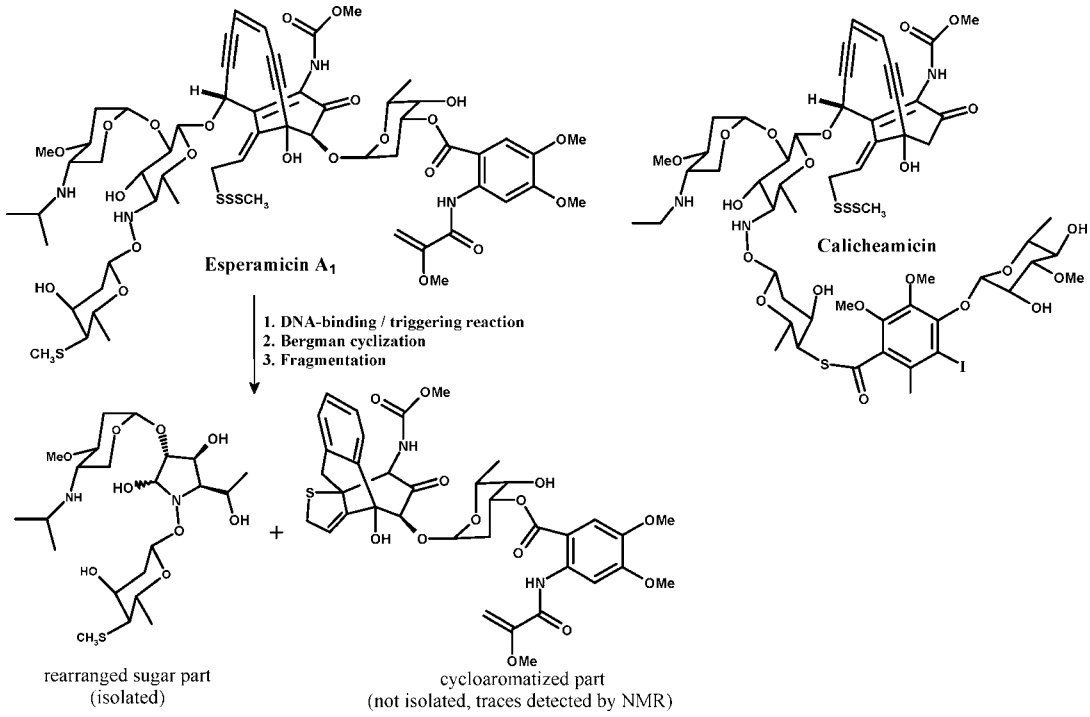

Figure 1. Structures of natural enediynes: esperamicin and calicheamicin.

propriately relative to the target.[9] However, other functions of the carbohydrate moiety are less understood. For example, Langley and co-workers found that esperamicin A_1 undergoes fragmentation upon cycloaromatization[10] and isolated a "rearranged trisaccharide" derived from the carbohydrate part fragmented from esperamicin A_1. The aromatized core has never been isolated and fully characterized—only traces of it were detected by ^{1}H NMR spectroscopy. Hence, Langley and co-workers suggested that a self-quenching mechanism exists in esperamicin A_1 that delivers one hydrogen atom *intra*molecularly to one of the *p*-benzyne radical centers with the subsequent fragmentation of the sugar part (Figure 1). The remaining aryl radical center would abstract a hydrogen atom from DNA, inducing predominantly single-strand DNA cleavage.

Our recent studies of the Bergman cyclization of 2,3-diethynyl-1-methoxybenzene, **1**, discovered that *intra*molecular abstraction of a hydrogen atom from the methoxy group by the *p*-benzyne diradical can effectively intercept the diradical (Figure 2).[11] Internal trapping of the diradical renders the retro-Bergman opening/deactivation less likely by transforming the transient *p*-benzyne species into a more stable diradical.

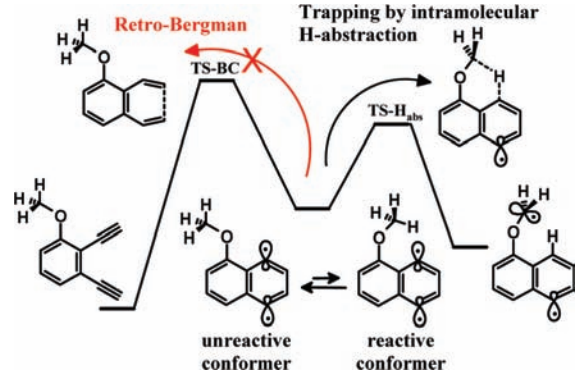

Figure 2. Hydrogen atom transfer from the *o*-methoxy group in *intra*molecular trapping of the *p*-benzyne diradical formed in the Bergman cyclization of 2,3-diethynyl-1-methoxybenzene.

The two sets of observations can be combined in an intriguing hypothesis on how the enediyne reactivity may be controlled through a conformational change of a substituent positioned next to the enediyne moiety (Figure 2). This concept is a direct development of our continuing research efforts to achieve the steric or electronic activation of enediynes by spatially close substituents related to the ortho-effect in the Bergman cyclization[12] and a broader effort of controlling cycloaromatization reactions through substituent effects.[13,14]

The carbohydrate moieties of esperamicins and calicheamicins possess a weak C−H bond at the anomeric position and may participate in H-abstraction analogous to that described in Figure 2. Providing that full understanding of the mechanism of esperamicin A_1 fragmentation is potentially useful for the future

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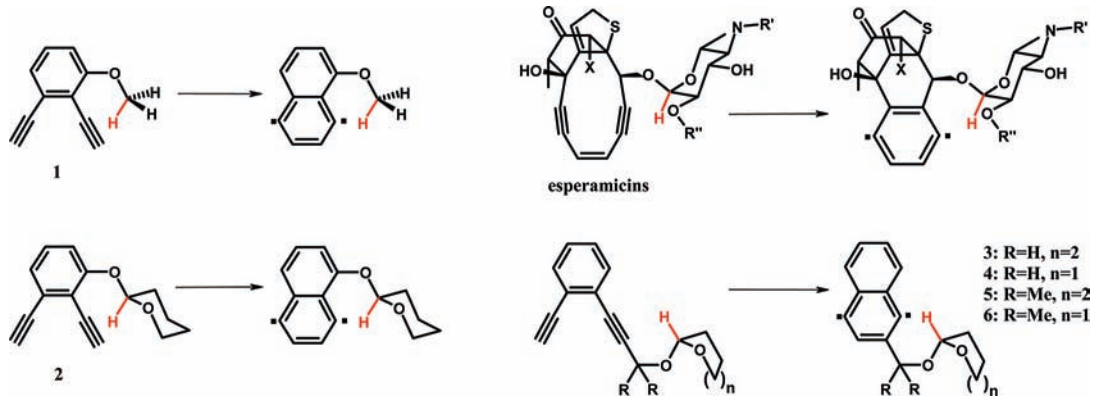
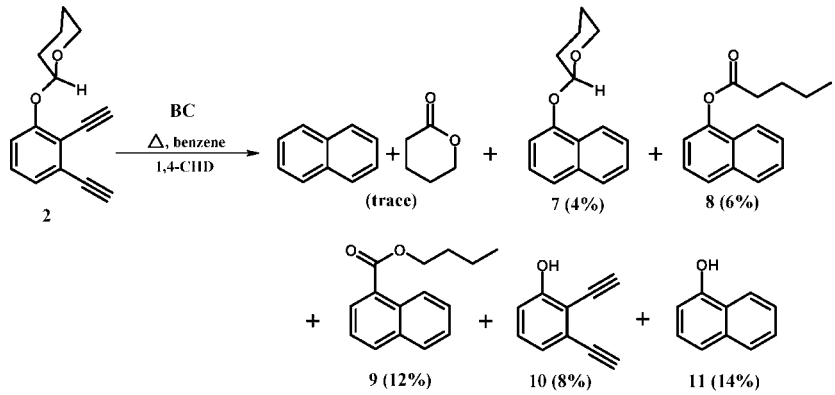
Scheme 1. *Intra*molecular H-Abstraction in *p*-Benzynes Derived from Natural Enediyne Antibiotics and Model Enediynes **1**−**6**[a]



[a] Abstracted hydrogen atoms are shown in red.

Scheme 2. Rearrangements and Fragmentations Triggered by the Bergman Cyclization of Enediynes **2**



design of antitumor drugs, we decided to gain a deeper insight into this process through the model studies described below. In this paper, we report synthesis and reactivity of enediynes **2**−**6** equipped with tetrahydropyran (THP) and tetrahydrofuran (THF) rings introduced to mimic the carbohydrate moiety of natural enediynes (Scheme 1). Different placement of the THP and THF rings relative to the enediyne moiety was used to probe the interplay between different fragmentation modes. We also investigated the competition between hydrogen abstraction and fragmentations through variations in the concentrations of H-atom donor. The experimental studies were complemented by DFT analysis of transition states and intermediates for the proposed reaction pathways. At the end of this paper, we will provide a new model for the control of enediyne reactivity and suggest how this model may be related to a mechanism of resistance to natural enediyne antibiotics by the microorganisms producing these toxins.

Computational Details and Methods

Calculations were performed using Gaussian 03 software.[15] All structures were fully optimized at the UB3LYP/6-31G** level with the employment of broken spin-symmetry wave function.[16] This level of theory has been shown to provide reaction barriers which accurately agree with the experimental values for a number of radical reactions and was used to model enediyne chemistry on many occasions.[17] Stability of the wave function was tested for each diradical species. Frequency calculations were carried out for all structures to confirm that every Transition State (TS) has only one imaginary frequency. The structures for all reactants and fragmented products have no imaginary numbers. Constrained geometries utilized for the analysis of the Thorpe-Ingold effect on the efficiency of intramolecular H-abstraction in enediynes **3**−**6** had energies ∼1−3 kcal/mol higher than the unconstrained optimized structures (vide infra). Frequency calculations for all the optimized constrained structures showed one imaginary frequency.

Results and Discussion

Synthesis of the model enediynes is given in the Supporting Information (SI). The products resulted from the processes initiated by the Bergman cyclizations of enediyne **2** are given in Scheme 2. Only traces of the expected fragmentation products (δ-valerolactone and naphthalene) derived from the Bergman

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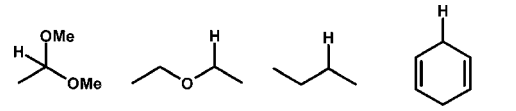

Figure 3. Effects of double anomeric and allylic stabilization on the C−H bond dissociation energy.

cyclization reaction/*intra*molecular H-abstraction/fragmentation cascade were observed by GC analysis of the reaction mixture when enediyne **2** reacted in the presence of 1,4-CHD (132 mM). Instead, NMR and GC analysis showed complete conversion of **2** with the formation of a mixture of five products which included only 4% of the Bergman product **7**. Interestingly, two other isolated products were 1-naphthyl pentanoate **8** (6%) and butyl-1-naphthoate **9** (12%, Scheme 2). The rest were enediyne **10** (8%),[18] 1-naphthol **11** (14%), and other minor unidentified products. The structures of rearranged products **8** and **9** were confirmed through comparison with the literature spectral data and through independent synthesis from 1-naphthol and 1-naphthoyl chloride, respectively (see SI).

Analysis of Radical Cascades Initiated by the Bergman Cyclization of Enediyne 2. In principle, product **7** can be formed via *inter*molecular abstraction of hydrogen atoms by the *p*-benzyne diradical. However, in an earlier study we found that *intra*molecular H-abstraction in **1** is much faster than the hydrogen atom abstraction from 1,4-CHD.[11] *Intra*molecular H-abstraction is likely to proceed even faster in the *p*-benzynes derived from enediynes **2**−**6** with the THP group in comparison with that in the OMe-substituted enediyne **1**. This expectation is based on the lower C−H bond dissociation energy in this system due to increased stabilization of the radical center through two n(O) → n(C) anomeric interactions with the lone pairs of the two α-oxygen atoms. For example, C−H bond dissociation energy (BDE) in 1,1-dimethoxyethane is ∼7 kcal/mol lower than in diethyl ether and 11 kcal/mol lower than a typical secondary C−H bond (Figure 3).[19] The much greater thermodynamic force for the H-transfer is likely to compensate for the statistical disadvantage (the OTHP group in enediynes **2**−**6** has only one hydrogen compared to the three hydrogens of OMe group in **1**), although the unfavorable statistics for this process may contribute to the low yields of compounds **7**−**9** (*vide infra*). On the other hand, the even lower BDE for the C−H bond of 1,4-CHD[20] is consistent with the notion that the major pathway forming **7** should be H-transfer to the anomeric radical **a** (Scheme 3) from 1,4-CHD. Interestingly, the Bergman cyclization of enediyne **2** is faster than that of enediyne **10** suggesting that the O-THP group plays a role in the cycloaromatization process.

The formation of ester **8** can be easily explained by a ring-opening of the intermediate **a** followed by hydrogen abstraction from 1,4-CHD (Scheme 3). Similar fragmentation patterns are described in the literature.[21,22] For example, in a detailed computational study, Roberts and co-workers found that the ring-opening of 2-phenyl-1,2-dioxan-2-yl radicals[23] stabilized simultaneously by resonance and anomeric interactions, proceeds with the β-scission rate constants in the order of 10^3 s^{-1} at 130 °C. Since our radical **a** is *only* stabilized by the anomeric interactions, we expect it to fragment even faster. The relatively high expected efficiency of such processes is also consistent with the fact that Crich et al. were able to take advantage of a similar fragmentation in the synthesis of β-(1→3)-D-Rhamnotetraose.[24]

The fragmentation of the anomeric radical derived from enediyne **2** is selective and affects only one of the three σ-bonds stereoelectronically aligned for the fragmentation (bond "y", Scheme 3). Although cleavage of two bonds ("x" and "y") may lead to the thermodynamically favorable formation of carbonyl moiety, cleavage of a weaker C(sp^3)—O bond "y" is preferred over the cleavage of the stronger C(sp^2)—O bond "x".

Formation of ester **9** is especially interesting because it suggests an intriguing possibility for the design of a synthetically useful direct transformation of protected phenols into benzoic acid derivatives through a C−O translocation step. *A priori*, two mechanisms for the formation of this product could be considered as shown in Scheme 4.

Mechanism A is the O-neophyl rearrangement pathway[25] where a strained three-membered ring dearomatized intermediate is reversibly formed by the ipso attack of the THP radical **a** at the aromatic ring. Subsequent C−O bond scission leads to the formation of a reactive oxygen radical **b** that yields product **9** after fragmentation and hydrogen abstraction from 1,4-CHD. The selectivity of the fragmentation step in Scheme 3 correlates with the relative strength of the broken bond. We observe only the pathway y′ which corresponds to the $C_{(sp3)}$−$C_{(sp3)}$ bond cleavage.

In the alternative pathway B, radical **a** undergoes cyclization to form the five-membered dearomatized intermediate **c** (Scheme 4). A 1,3-hydrogen shift followed by C−O bond scission would result in the formation of an oxygen radical similar to the radical **b** formed in pathway A. Fragmentation of this radical followed by hydrogen abstractions from 1,4-CHD would produce ester **9**. Although the first step in pathway B should produce a more stable intermediate than the one formed in the *ipso*-attack of

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(18) Thermal loss of the THP group at similar temperatures has been reported by Pinhey et al. for many THP-protected phenol derivatives. Pinhey, J. T.; Xuan, P. T. *Aust. J. Chem.* **1988**, *41*, 69. Control experiments suggest that the Bergman cyclization of unprotected enediyne **10** is slower than that of **2** and that the thermal O-THP deprotection occurs mostly (∼60%) after the Bergman cyclization of enediyne **2**. Based on these experiments (described in the SI), one can evaluate that 40% of 1-naphthol **11** is formed from the Bergman cyclization of the deprotected phenol **10** whereas 60% of the naphthol is formed from the O-THF naphthol **7**.

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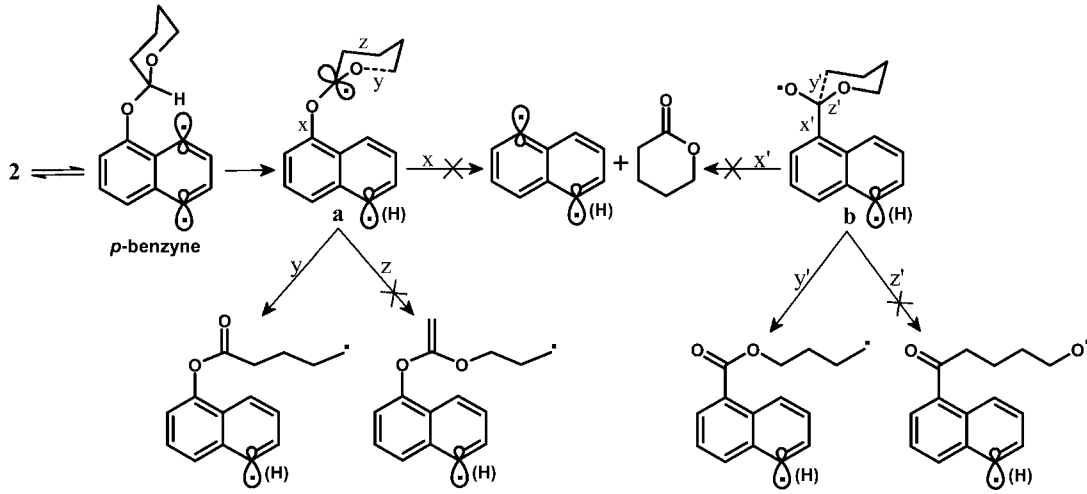
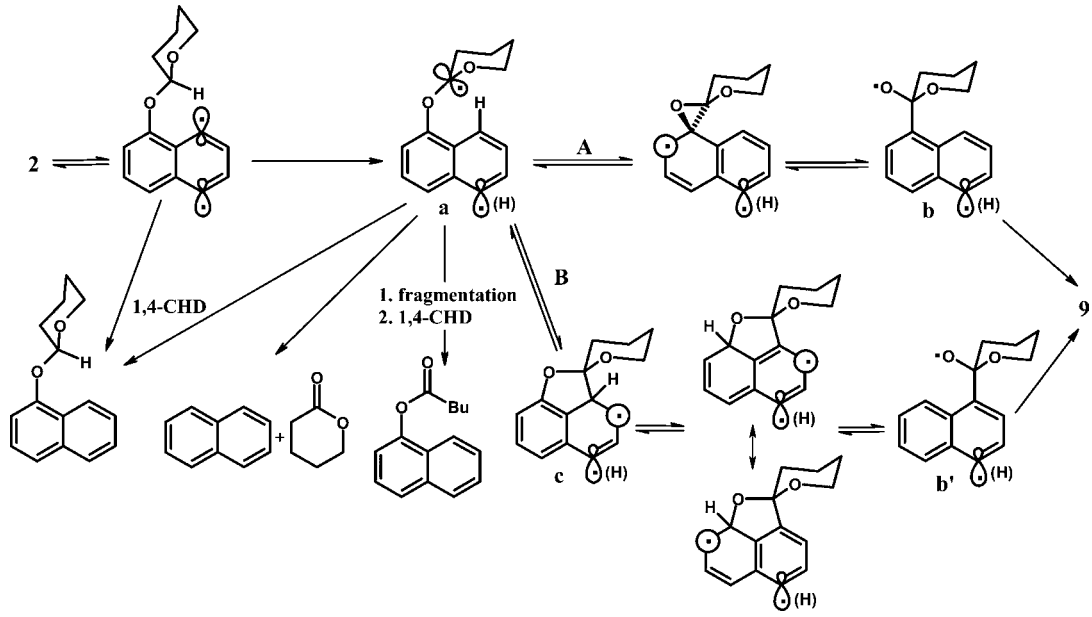
Scheme 3. Comparison of Possible Fragmentation Pathways for the Anomeric Radical Derived from Enediyne **2**[a]



[a] Dotted lines correspond to the bonds which are broken in the experimentally observed pathway.

Scheme 4. Possible Mechanisms for the Rearrangement of Enediyne **2**



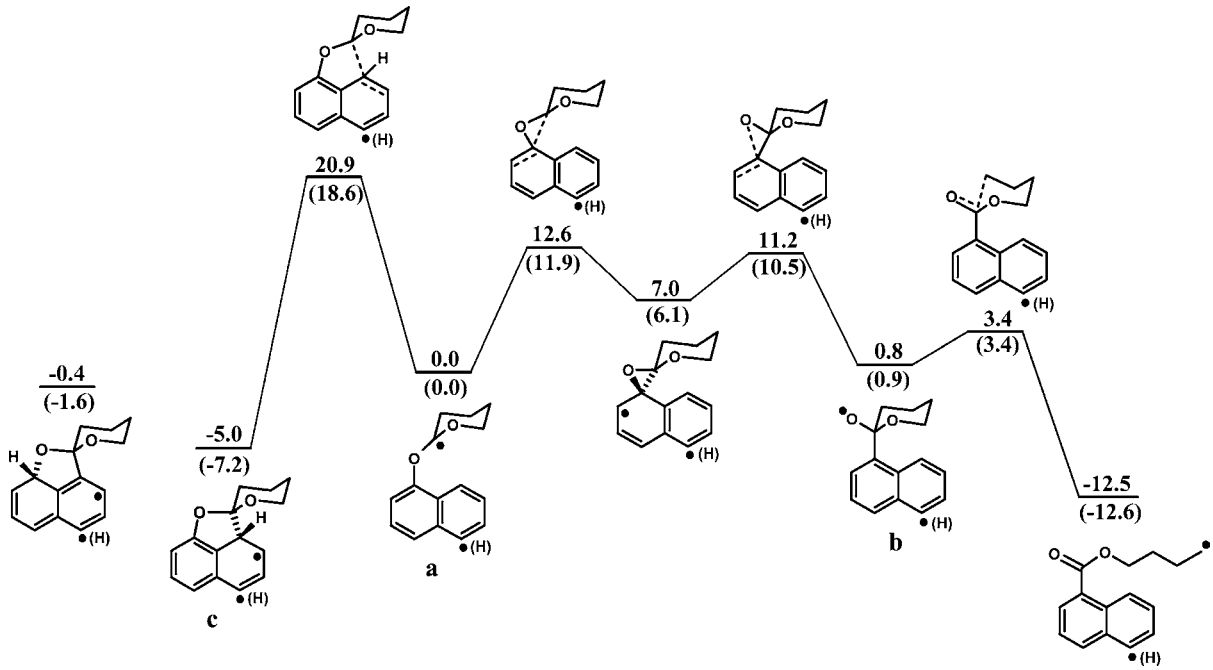
pathway A, the following two steps in the pathway B appear to be less plausible.

Computational analysis (Scheme 5) supports the O-neophyl rearrangement (pathway A) as the kinetically favorable path. The ~12 kcal/mol calculated activated barrier for the *ipso*-attack is ~7−8 kcal/mol lower than that for *peri*-attack in path B. On the other hand, the formation of **b** is more endothermic than that of **c** by ~6−8 kcal/mol, and thus, path B will be favored thermodynamically unless further steps such as the fragmentation (ring-opening) of **b** would direct the reaction through pathway A (see next section for a detailed analysis of the fragmentation step). Although pathway B does end up with an intermediate similar to **b** (**b′**), it should proceed through an unlikely thermal 1,3-hydrogen shift. We were not able to locate the TS for the 1,3-shift computationally. In order to distinguish between the two pathways, we analyzed the cyclization of D-labeled 2-(2,3-diethynyl-d_2-phenoxy)tetrahydro-2H-pyran **12** under the conditions analogous to those for enediyne **2** (Scheme 6).

The Bergman cyclization of **12** resulted in the formation of three analogous products with the distribution analogous to that found for enediyne **2** (Scheme 2). According to the ^{1}H NMR analysis for the rearranged product **13** shown in Figure 4, signals for H(b) and H(c) completely disappear whereas signals for H(a) and H(d) transform from doublets into singlets due to the absence of coupling between H(a) and H(d) with their neighboring protons, H(b) and H(c). These observations indicate that the two deuterium atoms are located at positions 6 and 7, D(b) and D(c), of the naphthalene moiety. This result confirms that the carbonyl carbon is attached to the same position as phenolic oxygen in the reactant and excludes pathway B for the formation of compound **9**.

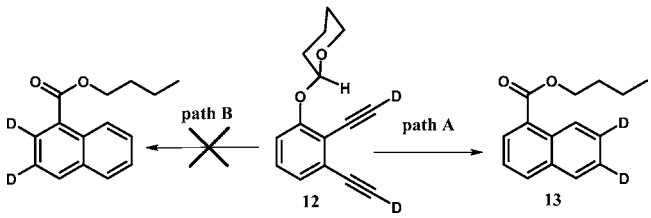
Role of Fragmentations in the Reversal of *O*-Neophyl Rearrangement. This experiment clearly shows that product **9** was formed through the O-neophyl rearrangement of a carbon-centered radical to an oxygen-centered radical. The opposite is found in most of the O-neophyl rearrangement examples in the

Scheme 5. Summary of Computational Study at the UB3LYP/6-31G** Level of Theory that Favors Pathway A (*O*-Neophyl Rearrangement) Over B[a]



[a] All energies are given in kcal/mol relative to **a**. Data in parentheses correspond to the respective monoradicals.

Scheme 6. Bergman Cyclization of Enediyne **2-d$_2$** (**12**)



literature.[26,27] Scheme 7 shows two typical examples of alkoxy radicals that rearrange to more stable benzylic radicals. Recent computational[28] and experimental[29] studies have shown that this process is not concerted and a three-membered ring intermediate is involved in the mechanism. To the best of our knowledge, there is only one literature example where the rearrangement occurs in the direction observed by us in the reaction of enediyne **2**—from a carbon-centered radical to an oxygen-centered radical.[30] In this example, Ohno et al. reported formation of methylphenylketone in about 50% yield from the thermal decomposition of azobis(2-phenoxy)-2-propane (Scheme 8). Interestingly, in analogy with the THP ring-opening of intermediate **b** shown in Scheme 3 and Scheme 4, the O-neophyl rearrangement of 2-phenoxyprop-2-yl radical into 2-phenyl-

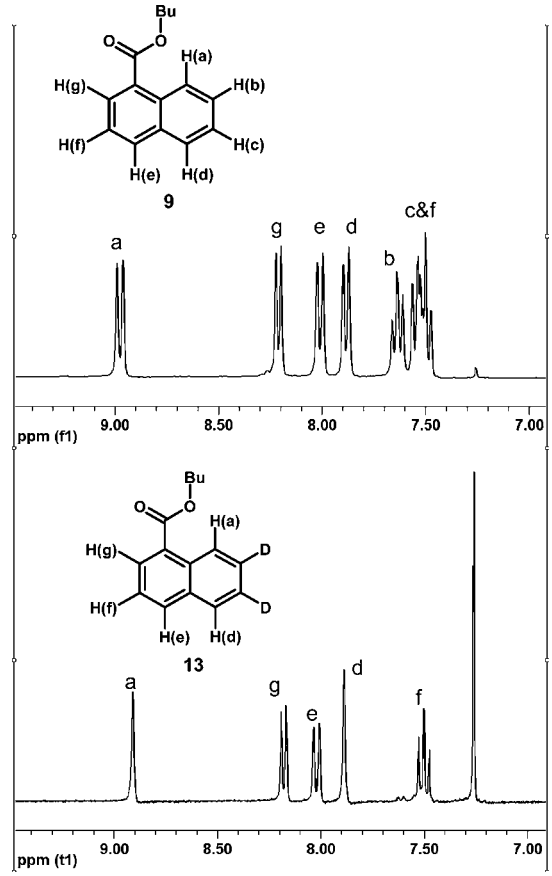


Figure 4. Comparison between NMR spectra of compounds **9** and **13**.

isopropoxy radical reported by these authors also terminated by a homolytic C−C bond cleavage. In our case, the bond cleavage leads to the ring-opening (Scheme 3) whereas, for the

(26) (a) Banks, J. T.; Scaiano, J. C. *J. Phys. Chem.* **1995**, *99*, 3527. (b) Donkers, R. L.; Tse, J.; Workentin, M. S. *Chem. Commun.* **1999**, 135. (c) Wietzerbin, K.; Bernadou, J.; Meunier, B. *Eur. J. Inorg. Chem.* **1999**, 1467.
(27) (a) Kamata, M.; Komatsu, K. *Tetrahedron Lett.* **2001**, *42*, 9027. (b) Donkers, R. L.; Workentin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1688. (c) Antunes, C. S. A.; Bietti, M.; Ercolani, G.; Lanzalunga, O.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 3884. (d) Bietti, M.; Salamone, M. *J. Org. Chem.* **2005**, *70*, 10603. (e) Ingold, K. U.; Smeu, M.; DiLabio, G. A. *J. Org. Chem.* **2006**, *71*, 9906.
(28) Bietti, M.; Ercolani, G.; Salamone, M. *J. Org. Chem.* **2007**, *72*, 4515. (b) Smeu, M.; DiLabio, G. A. *J. Org. Chem.* **2007**, *72*, 4520.
(29) Salamone, M.; Bietti, M.; Calcagni, A.; Gente, G. *Org. Lett.* **2009**, *11*, 2453.
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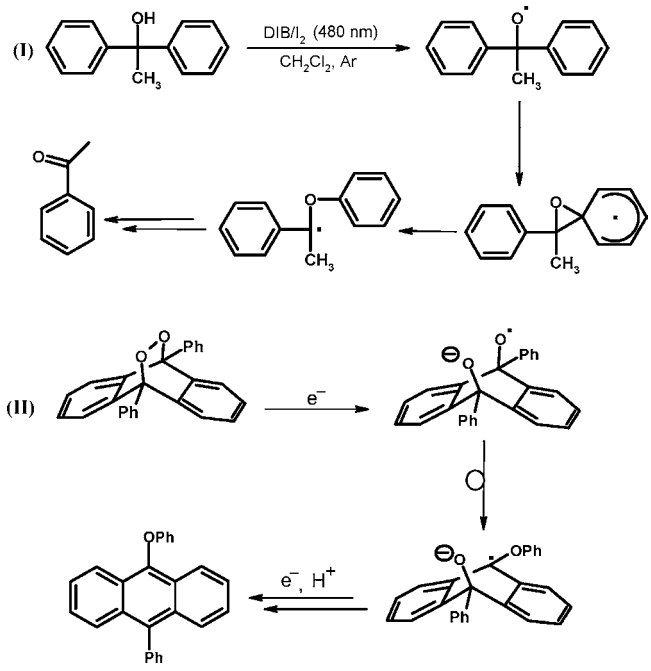
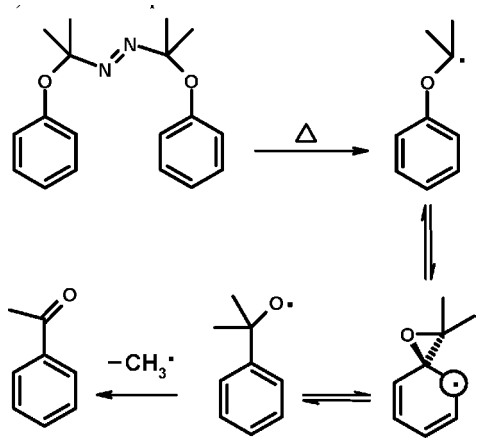
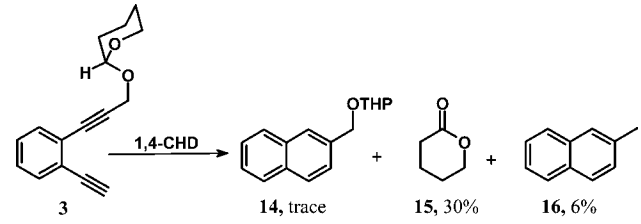
Scheme 7. Literature Examples of *O*-Neophyl Rearrangements that Form Benzylic Radicals[26,27]



Scheme 8. Reverse O-Neophyl Rearrangement in Thermal Decomposition of Azobis(2-phenoxy)-2-propane[30]



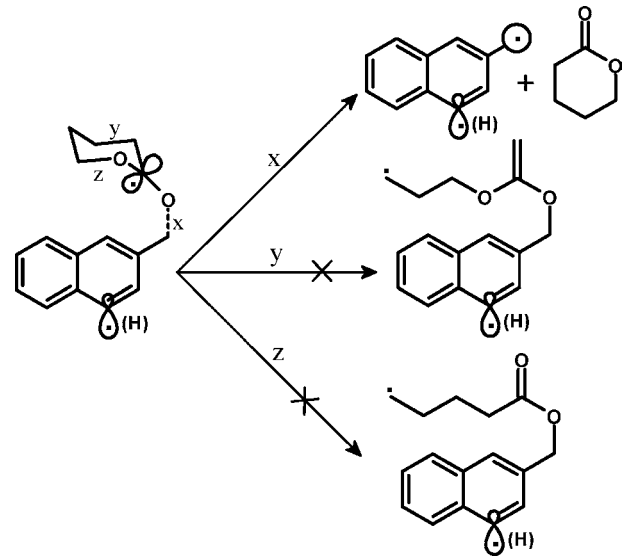
Scheme 9. Bergman Cyclization of Enediyne **3** (84 mM enediyne, 420 mM 1,4-CHD)



formation of ketone shown in Scheme 8,[30] the final cleavage leads to the loss of a methyl radical.

Analysis of Radical Cascades Initiated by the Bergman Cyclization of Enediyne 3. In contrast to the results discussed above for enediyne **2**, the Bergman cyclization of enediyne **3** leads to the formation of predicted fragmentation products, δ-valerolactone and methylnaphthalene. The difference in reactivity between enediynes **2** and **3** is likely to stem from the different stability of the proposed radical products in the key

Scheme 10. Comparison of Possible Fragmentation Pathways for the Anomeric Radical Derived from Enediyne **3**[a]



[a] Dotted line corresponds to the bond which is broken in the observed pathway.

Table 1. Effect of 1,4-CHD Concentration and Reaction Temperature at Cyclization of Enediyne **3**

concentration of **3**, mM	concentration of 1,4-CHD, mM	temperature, °C	time	**14** % yield	**15** % yield	**16** % yield
84	420	135	5 d	Trace	30	6
84	420	120	13 d	Trace	27	9
21	21	135	5 d	0	34	Trace
21	105	135	5 d	Trace	28	Trace
42	42	135	5 d	0	34	Trace
21	105	160	36 h	0	25−32	Trace

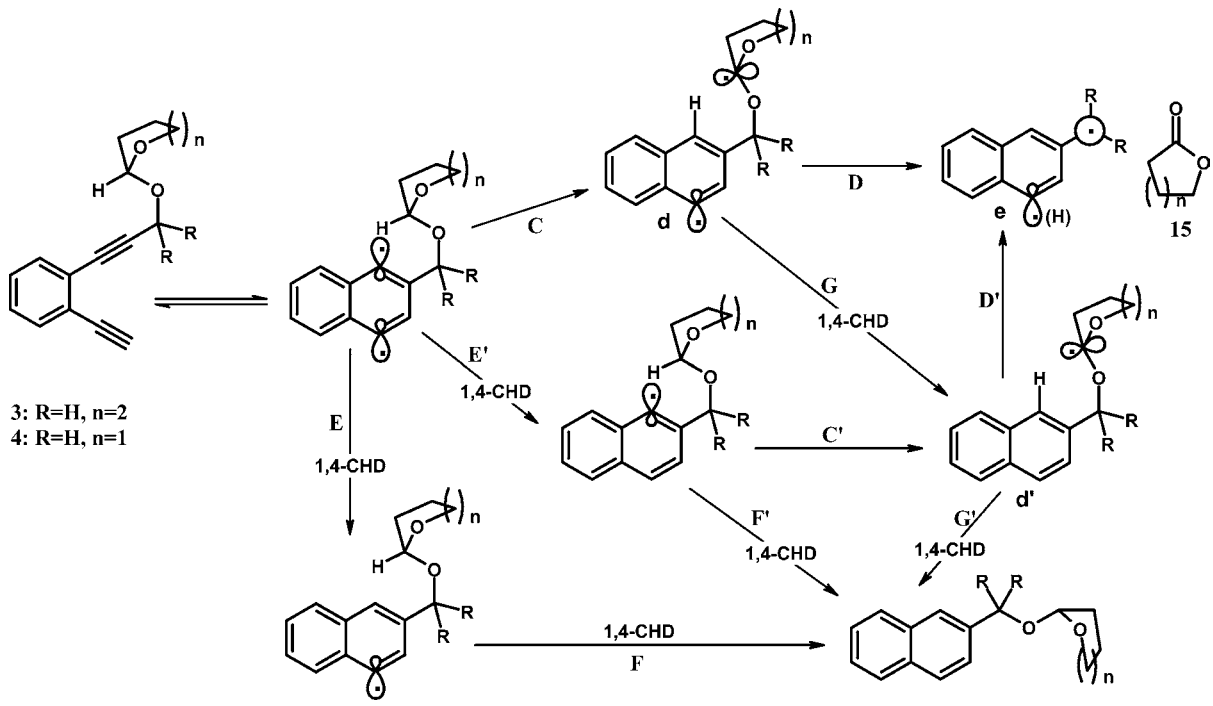
fragmentation step (*vide infra*). Whereas the fragmentation of enediyne **3** should produce a resonance stabilized "benzylic" radical, the analogous fragmentation of enediyne **2** should lead to the formation of the less stable σ-naphthyl radical. Thus, a single fragmentation path is observed in reactions of enediyne **3**. This selectivity is consistent with the increased stability of the delocalized radical formed upon cleavage of bond "x" (Scheme 10).

Although the yields of δ-valerolactone and methylnaphthalene obtained upon the cyclization of enediyne **3** were relatively low (30 and 6%, respectively), the NMR and GC analyses of the reaction mixtures do not show the presence of significant amounts of any other single product.[31] To increase the efficiency of this process and to gauge the competition between fragmentation and H-abstraction from 1,4-CHD, we performed the Bergman cyclization with different concentrations of the reagents and at different temperatures (Table 1). The yield of lactone **15** is relatively insensitive to the variations in the reaction conditions, whereas the yield of the aromatic component **16** is affected quite strongly. Formation of appreciable amounts of the naphthalene product **16** is only observed at the lower temperatures, higher concentrations of the two reagents and excess of the H-atom donor.

The available literature data suggest that δ-valerolactone has a higher tendency to polymerize than the more thermally stable

(31) A large number of minor unidentified products in <1−2% yields are detected by the GC analysis (see the SI section).

Scheme 11. Proposed Pathways for Bergman Cyclization/Fragmentation Cascades of Enediynes **3** and **4**



γ-butyrolactone.[32] The reasons for the unusual difference in stability between the two lactones were recently analyzed in a detailed computational study by Houk et al.[33] who determined that δ-valerolactone, despite having a larger ring, suffers from higher strain with respect to γ-butyrolactone. Considering that low thermal stability of δ-valerolactone could account for the low yields for this compound, we synthesized 2-[[3-(2-ethynylphenyl)-2-propyn-1-yl]oxy]tetrahydro-2H-furan **4** (the THF enediyne version of **3**) which would give γ-butyrolactone as the potentially more stable product.

Synthesis of enediyne **4** is described in the SI. Reactivity of this compound was studied under the same conditions as for the THP-enediyne **3**. However, the yield of γ-butyrolactone obtained from **4** was similar to that of δ-valerolactone obtained from **3** ($\sim$30%), indicating that, contrary to the literature data, either polymerization of δ-valerolactone was not a problem at these concentrations or that both lactones underwent this process to the same extent. In comparison with enediynes **1** and **2**, the *intra*molecular H-transfer in **3**, **4** may suffer from the statistical factor (only one weak C−H bond vs three C−H bonds of a OCH_3 moiety) and conformational flexibility of the CH_2OTHP group which could explain why *p*-benzyne interception is not quantitative.

The proposed mechanism for the formation of lactone **15** after the Bergman cyclizations of **3** and **4** is shown in Scheme 11. The reversibly formed *p*-benzyne is trapped by *intra*molecular hydrogen transfer, analogous to the one described previously for enediynes **1** and **2** (Figure 4 and Scheme 4). The newly formed diradical intermediate **d** and monoradical **d′** undergo fragmentation to the corresponding benzyl radical **e** and lactone **15**.

Relation to the Esperamicin A_1 Fragmentation. These fragmentations may shed light on the possible pathway for the esperamicin A_1 fragmentation observed after its Bergman cyclization in the presence of calf thymus DNA.[10] Whereas in the study of Langley and co-workers, the aromatized fragment of esperamicin A_1 could not be isolated, our mechanism is supported by the detection and isolation of the corresponding aromatized core, methylnaphthalene. The low yield of this product even in the presence of a very efficient H-donor suggests that detection of the aromatic core would be extremely difficult in the esperamicin case under conditions when DNA is the H-atom donor. H-abstraction by benzyl radicals from DNA is less energetically favorable than the abstraction from 1,4-CHD (BDE $C-H_{anomeric}$ = 95 kcal/mol, BDE $C-H_{double\ anomeric}$ = 88 kcal/mol, BDE $C-H_{benzyl}$ = 89 kcal/mol vs BDE (1,4-CHD) = 76−78 kcal/mol)[19,20] and thus, in the biological environment, this radical may be deactivated through a different pathway (e.g., base alkylation).[34]

Interestingly, based on the structure of the rearranged product and absence of aromatic products, Langley and co-workers suggested an alternative mechanism for the fragmentation. In their mechanism, a 1,3-H-atom transfer is suggested instead of 1,5-H-atom transfer observed in our systems. In order to accommodate the apparently unfavorable geometry for the 1,3-

(32) (a) Carothers, W. H. *Chem. Rev.* **1931**, *8*, 353. (b) Hall, H. K., Jr.; Schneider, A. K. J. *Am. Chem Soc.* **1958**, *80*, 6409. (c) Biela, T.; Kowalski, A.; Libiszowski, J.; Duda, A.; Penczek, S. *Macromol. Symp.* **2006**, *240*, 47. (d) Duda, A.; Kowalski, A.; Libiszowski, J.; Penczek, S. *Macromol. Symp.* **2005**, *224*, 71. (e) Duda, A.; Libiszowski, J.; Mosnacek, J.; Penczek, S. *Macromol. Symp.* **2005**, *226*, 18. (f) Coulembier, O.; Degu, P.; Hendrick, J. L.; Dubois, P. *Prog. Polym. Sci.* **2006**, *31*, 723. (g) Albertssohn, A. C.; Varma, I. K. *Biomacromolecules* **2003**, *4*, 1466.

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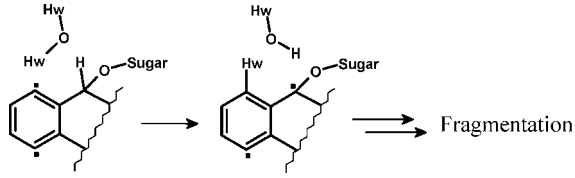
Scheme 12. Water-Assisted 1,3-H-Atom Transfer Suggested by Langley and Coworkers[10]



H-atom abstraction, authors suggested that a structurally well-defined water molecule positioned next to the enediyne in its complex with DNA assists hydrogen transfer between the *p*-benzyne and the benzylic hydrogen atoms (Scheme 12).

Reactivity of Gem-Dimethyl Substituted Enediynes. In this context, it was interesting to investigate reactivity of 2-[[3-(2-ethynylphenyl)-1,1-dimethyl-2-propyn-1-yl]oxy]tetrahydro-2H-pyran **5** and 2-[[3-(2-ethynylphenyl)-1,1-dimethyl-2-propyn-1-yl]oxy]tetrahydro-2H-furan **6**, both of which possess *gem*-dimethyl substituents instead of hydrogens at the benzylic position.

Synthesis of enediynes and experimental conditions for their cycloaromatization is described in the SI. Reactions of enediynes **5** and **6** were accompanied by the identical fragmentation indicating that, under our conditions, the absence of benzylic hydrogen atoms does not stop the fragmentation.[35] In fact, the yield of the lactone significantly increased (from ca. 30% to ca. 45%, Table 2).

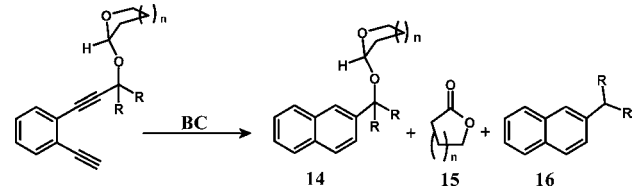
A priori, this enhancement can either result from two effects: (a) favorable Thorpe-Ingold effect assisting in the intramolecular H-abstraction by *p*-benzyne, or (b) increased efficiency of the fragmentation step due to the additional stabilization of the radical center in the product by the two methyl groups (*vide infra*).

H-Donor Concentration Effects on the Competition between Bergman H-Abstraction and Fragmentation. To test if the above differences are important from an experimental perspective and to gain further mechanistic insight into the competition between different reaction pathways, we carried out a more detailed analysis of external H-atom donor concentration effects on the product distribution. Table 2 summarizes the results for the four enediynes **3**−**6** under conditions where the concentration of 1,4-CHD was varied from 0 to 1.52 M.

In each case, lactone **15** is the only observable product in the absence of an external hydrogen donor. This is expected because no external hydrogen atoms are needed to furnish this compound. On the other hand, naphthalene **14** cannot be formed unless either 1,4-CHD or an analogous H-atom donor is present in concentrations sufficient for the interception of the *p*-benzyne and/or radical **d** before *intra*molecular H-abstraction (pathways C and C′, Scheme 11) and/or fragmentation (pathways D and D′). In a similar way, naphthalene **16** can only be formed by H-abstraction from 1,4-CHD *after* fragmentation (pathways D and D′). Formation of naphthalene **16** is complicated by the fact that H-atom transfer to these highly stabilized benzylic-type radicals from 1,4-CHD (or from DNA) is expected to be relatively slow. The inefficiency of the capture can explain the presence of the numerous unidentified products which may result from recombination/disproportionation of such radicals or their addition to 1,4-CHD and compounds derived from 1,4-CHD.

(35) Because no water was present in our reaction mixtures, our experiments do not exclude the mechanism illustrated for the Esperamicin/DNA system, in Scheme 12. Instead, our results suggest that alternative fragmentation pathways are viable. Our findings also indicate that such fragmentations may not be limited to esperamicins but may occur in other natural enediynes, equipped with similar carbohydrate moieties.

Table 2. Influence of 1,4-CHD Concentration on the Competition between H-Abstraction/Fragmentation of the Radical Species from the Four Enediynes **3**−**6**



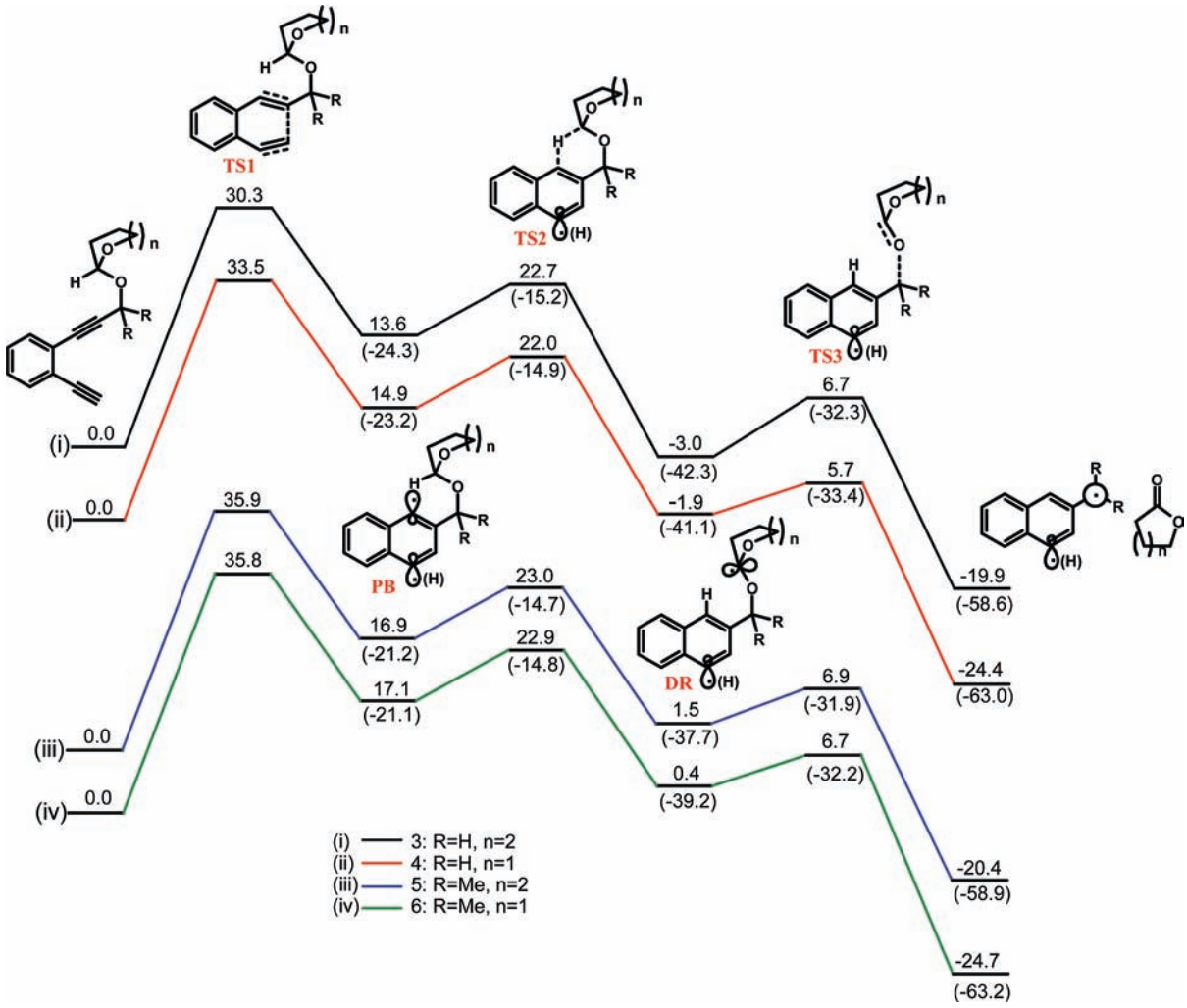
entry (enediyne)	R	*n*	concentration of 1,4-CHD, mM	**14**[a], % yield	**15**[a], % yield	**16**[a], % yield
1 (**3**)	H	2	0	0	30	0
2 (**3**)			95	Trace	33	10
3 (**3**)			380	Trace	23	18
4 (**3**)			1520	26	18	15
5 (**4**)	H	1	0	0	29	0
6 (**4**)			95	11	31	10
7 (**4**)			380	43	29	15
8 (**4**)			1520	73	6	6
9 (**5**)	Me	2	0	0	40	0
10 (**5**)			95	<1[b]	44	8[b]
11 (**5**)			380	1[b]	44	16[b]
12 (**5**)			1520	2[b]	41	31[b]
13 (**6**)	Me	1	0	0	44	0
14 (**6**)			95	<1[b]	42	7[b]
15 (**6**)			380	1[b]	41	15[b]
16 (**6**)			1520	2[b]	30	9[b]

[a] All enediynes were heated at 135 °C at a concentration of 19 mM. Reaction time was 2 days for enediynes **3** and **4**, and 3 days for **5** and **6**. All yields were determined by NMR unless stated otherwise. [b] Yields were determined by GC.

The variation of yields with the increase of 1,4-CHD concentration illustrates that, at the 19 mM concentration of the enediynes, the amount of lactone remained constant as long as 1,4-CHD was present at the concentrations of ≤95 mM and 380 mM, for enediynes **3** and **4** respectively. On the other hand, the yield of methylnaphthalene increased with 1,4-CHD concentration, steadily approaching the yield of lactone. At 1.52 M of 1,4-CHD and 19 mM of enediyne, yields of the two fragmentation products are almost the same (18% vs 15% for **3**, and 6% vs 6% for **4**), suggesting that most of the radical precursor of **16** (**e**) is successfully trapped through H-abstraction to furnish the product. The lower yields of the fragmented aromatic core at low 1,4-CHD concentrations indicates the inefficiency of H-atom abstraction in intercepting the benzylic radical formed from the fragmentation of **d** and/or **d′**. Such inefficiency would increase the role of other side-reactions of the radical and explain the lack of isolable products. For enediyne **3** at 19 mM concentration, the usual Bergman product, naphthalene **14**, was not formed in considerable amounts until 1,4-CHD was present in 95−380 mM concentrations.

Interestingly, in the case of enediyne **4**, a much greater increase in the yield of naphthalene **14** was observed with the increase of 1,4-CHD concentration. However, the yield of lactone remained constant (∼30%) even when the THF-substituted naphthalene **14** was formed in 43% in the presence of 20 equivalents of 1,4-CHD. This result suggests that **14** only forms by the hydrogen abstraction of *p*-benzyne from 1,4-CHD (pathways E, E′, F and F′) before the *intra*molecular H-abstraction (pathways C and C′) occurs. In other words, abstraction of H-atom by anomeric radicals **d** or **d′** (pathways G and G′) does not contribute significantly to the formation of **14**. Consequently, the rate of fragmentation of **d** and **d′** should

Scheme 13. Summary of the Computational Results for the Cycloaromatization/H-Abstraction Reaction for Enediynes **3**−**6** at the UB3LYP/6-31G** Level of Theory[a]



[a] All energies are given in kcal/mol relative to the enediyne starting materials. Data in parentheses correspond to the respective monoradicals and include energies of 1,4-CHD and respective cyclohexadienyl radical.

be much greater than that of the hydrogen abstraction by the anomerically stabilized radical from 1,4-CHD (pathway G'), even when the concentration of the hydrogen donor is significantly large to intercept *p*-benzyne en route to lactone! This implies that the decrease in the lactone formation (entry 8, Table 2) is a result of an increase in the rate of *inter*molecular H-abstraction by the *p*-benzyne, relative to the *intra*molecular H-abstraction rate, observed with the increase of the hydrogen donor concentration.

Interestingly, entries 9−12 of Table 2 show that for enediyne **5**, the formation of naphthalene **14** was negligible and the yield of lactone **15** was completely insensitive to the increase of the hydrogen donor concentration. In contrast, a small decrease in the lactone formation from enediyne **6** was observed at the very high excess of 1,4-CHD, the only exception being entry 16. This difference may be due to the relative inefficiency of the Thorpe-Ingold effect upon the conformation equilibrium in enediyne **6**. However, notwithstanding this subtle difference, results summarized in Table 2 clearly show the significant increase in the efficiency of *intra*molecular H-abstraction/fragmentation cascade for the *gem*-dimethyl substituted enediynes **5** and **6**. This increase could be a consequence of either an increase in the rate of *intra*molecular H-abstraction or/and an increase in the rate of the fragmentation step. To understand the relative importance of individual steps in the overall cascade, we carried out a detailed computational analysis of the full reaction potential energy surface discussed in the following section.

Computational Analysis of the Full Reaction Cascade. Computational studies on the full Bergman Cyclization/H-abstraction/fragmentation cascade of enediynes **3**−**6** are summarized in Scheme 13.

a. Relative Efficiency of the Bergman Cyclization. Due to the steric repulsion exerted by the propargylic methyl groups in enediynes **5** and **6**, it is expected for the cycloaromatization step to be slower. This expectation is consistent with the ∼3−6 kcal/mol higher activation barriers found by B3LYP/6-31G** calculations (Scheme 13) with respect to those for enediynes **3** and **4**. In agreement with these values, experimental observations confirm that reactions of the more hindered enediynes require longer times.

b. Relative Efficiency of Intramolecular H-Abstraction. The Thorpe-Ingold effect caused by the methyl substituents at the benzylic position of the *p*-benzyne can manifest itself in two different ways: (a) shift in the equilibrium between the "open" and "closed" conformations (Scheme 14) toward the "closed"

Scheme 14. Relative Inefficiency of the Thorpe−Ingold Effect on the Conformational Equilibrium in Substituted *p*-Benzynes According to B3LYP/6-31G** Calculations

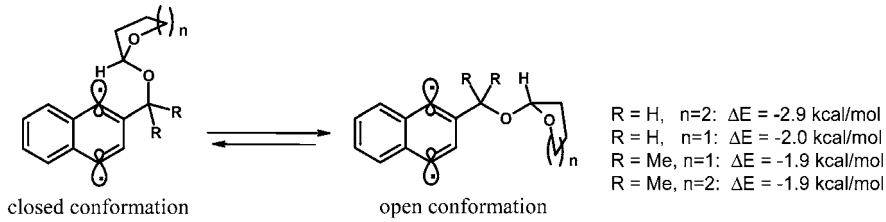
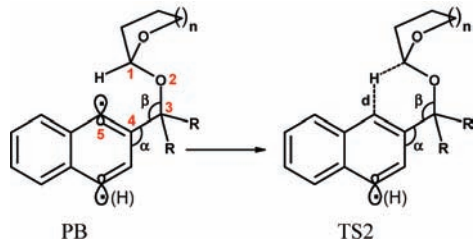


Table 3. Estimation of the Degree of Molecular Distortion in *Intra*molecular H-Abstraction by Comparing Geometrical Differences[a]



entry (enediyne)	R	*n*	α_{PB}	α_{TS}	β_{PB}	β_{TS}	d_{PB} Å	d_{TS2} Å	E_a,[b] kcal/mol	ΔE,[c] kcal/mol
1 (**3**)	H	2	116.99 (117.96)	120.61 (121.37)	116.47 (117.34)	112.07 (112.32)	2.260 (2.200)	1.449 (1.450)	6.3 (5.7)	–16.6 (–18.0)
2 (**4**)	H	1	117.03 (118.32)	120.43 (121.14)	116.51 (116.79)	112.19 (112.51)	2.280 (2.270)	1.464 (1.468)	5.6 (6.5)	–16.8 (–17.9)
3 (**5**)	Me	2	119.53 (120.69)	120.18 (120.90)	111.76 (112.08)	111.01 (111.44)	2.240 (2.240)	1.449 (1.450)	4.3 (4.6)	–15.4 (–16.5)
4 (**6**)	Me	1	119.52 (120.68)	119.97 (120.64)	111.88 (112.22)	111.09 (111.55)	2.210 (2.210)	1.473 (1.470)	4.0 (4.2)	–16.7 (–18.1)

[a] Data in parentheses correspond to the respective monoradicals. [b] Activation barriers are given relative to the constrained reactants (See Scheme 13 for the barrier values relative to unconstrained reactants). [c] Reaction energies are given relative to the local minimum corresponding to "near-attack" conformer of the reactants.

conformation which would render the formation of intermediates **d** and **d′** more efficient and/or (b) compression of the valence angle at the benzylic carbon which would bring the reacting groups closer.[36] According to B3LYP/6-31G** computations, the open conformation is always lower in energy, which could be the reason for the relatively low yields of lactones from the four enediynes. Interestingly, the presence of the two methyl groups at the benzylic position decreases the energy difference between the "closed" and "open" conformations of *p*-benzynes from ~3 kcal/mol in case of enediyne **3** to ~2 kcal/mol for enediyne **5**. On the other hand, the difference between the two conformations was the same (~2 kcal/mol) for both THF-substituted enediynes **4** and **6.** Together, these results suggest that the *gem*-dimethyl effect in these systems is unlikely to be limited to the simple increase in the population of the reactive conformer.

Computational results in Table 3 provide a deeper insight into the origin of the Thorpe-Ingold effect in this system. The calculated activation barriers for the *intra*molecular H-abstraction of both *gem*-dimethyl substituted *p*-benzynes of **5** and **6** are ~2 kcal/mol lower than the respective barriers in enediynes **3** and **4**, which lack the additional benzylic substituents. These results are in excellent agreement with the experimental data obtained for **5** and **6** (Table 2).

To determine whether the angle compression often attributed to the Thorpe-Ingold effect is responsible for the observed decrease in the activation energy, we analyzed the geometric differences between the transition states for the *intra*molecular H-abstraction and the corresponding *p*-benzyne. In order to eliminate other stereoelectronic effects, we constrained *p*-benzynes in the "pre-attack" conformation by choosing the two dihedral angles 1234 (COCC) and 2345 (OCCC), assigned in Table 3, so that the anomeric hydrogen is in a position where a six membered transition state for the *intra*molecular H-abstraction can be formed. All four *p*-benzynes were constrained in the same way with the identical key dihedral angles for each diradical and monoradical (see the SI).

Comparison of geometries of the four constrained *p*-benzynes (PB) and their respective *intra*molecular H-abstraction TSs is very instructive. Clearly, the differences in angle values between PB and TS structures are significantly larger for the species unsubstituted at the benzylic position (entries 1 and 2) than those for the *gem*-dimethyl substituted species (entries 3 and 4). In fact, the key valence angles α and β are essentially identical for the PB and TS geometries in entries 3 and 4. Therefore, the greater angular distortion, which the corresponding *p*-benzyne has to undergo in order to reach the *intra*molecular H-abstraction TS, is responsible for the higher activation barriers for enediynes **3** and **4**.

As expected, H-abstraction by diradicals is less exothermic than the analogous H-abstraction by the respective monoradicals (data in parentheses, Table 3). This is a well-understood consequence of Through-Bond (TB) interaction between the two radical centers in *p*-benzynes.[37−39] It is also interesting that earlier transition states with the longer incipient C−H distances were found for both THF-substituted *p*-benzynes.

c. Relative Efficiency of Fragmentations. All fragmentation were calculated to proceed through the relatively low barriers (<10 kcal/mol) and lead to the formation of more thermodynamically stable products. Fragmentation steps of the two THF-substituted substrates **4** and **6** are more exothermic than fragmentations of the respective THP-substituted species **3** and

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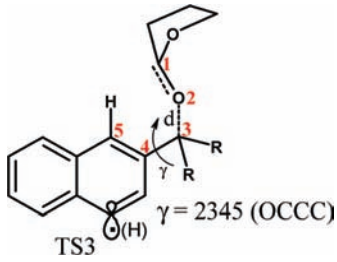
Table 4. Summary of the Geometrical Differences in TS3 of the Four Enediynes and the Activation Barriers for the Fragmentation Step. Data in Parentheses Correspond to the Respective Monoradicals



entry (enediyne)	dihedral angle γ	d_{TS3} Å	E_a, kcal/mol	ΔE, kcal/mol
1 (**3**)	94.14 (94.75)	1.750 (1.760)	9.7 (10.0)	−16.9 (−16.3)
2 (**4**)	93.82 (94.89)	1.718 (1.720)	7.6 (7.7)	−22.5 (−21.9)
3 (**5**)	61.15 (69.77)	1.750 (1.750)	5.4 (5.8)	−18.9 (−21.2)
4 (**6**)	50.34 (55.41)	1.710 (1.710)	6.9 (7.0)	−24.7 (−24.0)

5. In addition, the activation barriers for the fragmentation of **5** and **6** are lower with respect to those of **3** and **4**. All activation barriers for the fragmentation step, C−O incipient bond distances and the dihedral angles between the breaking C−O bond and the plane of the naphthalene moiety are summarized in Table 4.

The higher stability of γ-butyrolactone relative to δ-valerolactone could be the reason behind the higher exothermicity of the BC/Fragmentation of enediynes **4** and **6**. On the basis of the correlation between reaction energy and activation barriers,[40] this would contribute to the lowering of the activation barriers of the fragmentation step.

Since both enediynes **5** and **6** have the *gem*-dimethyl substituents at the benzylic position in TS2, one would expect a higher stabilization for the incipient radical in the transition state. Such stabilization could be the reason behind lower activation barriers and higher exothermicities for the fragmentation step of the two *gem*-dimethyl substituted enediynes. However, the activation barrier for enediyne **5** is ∼1 kcal/mol lower than that of **6**, which is not consistent with the result obtained for enediynes **3** and **4.** In order to understand the reasons for this discrepancy, we examined the alignment of the breaking C−O bond with the naphthalene π-system (the OCCC dihedral angle, γ in Table 4). A value of $\gamma = 90°$ would correspond to a maximum interaction (orbital overlap) between the C−O bond and the π-system which would provide maximum stabilization to the incipient radical center. Table 4 illustrates that this geometry is achieved in the TS3 of enediynes **3** and **4**. On the other hand, the γ values are lower in the case of enediynes **5** and **6** (50−70°). This deviation in the γ values is probably a result of the steric interaction exerted by the *gem*-dimethyl substitution in **5** and **6.** Although the calculated dihedral angles in **5** and **6** still allow substantial C−O and π-system overlap, benzylic stabilization in these systems does not assist to the C−O bond cleavage to its full extent. While hyperconjugative assistance from the methyl groups in **5** and **6** compensates for the partial loss of benzylic stabilization, the overall activation barriers seem to result from the tug-of-war of the electronic and steric effects. For example, the lower γ value observed for enediyne **6** could explain the slight increase in the activation barrier (∼1 kcal/mol) obtained for the fragmentation step of this molecule.

Summary of Computational Analysis. The first, highly endothermic, step of the cascade transformation in Scheme 13 (the Bergman cyclization) is thermodynamically unfavorable and, unless a suitable trapping step is available, rapidly reversible. However, each subsequent transition state is lower in absolute energy than the previous one, and overall sequence of reactions culminates in the final products which are 20−25 kcal/mol lower than the starting materials, thus providing a strong driving force for the overall transformation. Overall, this potential energy surface can be classified as an example of a "slippery slope" reaction energy profile.[41]

Conformational Control of Bergman Cyclization and Resistance to Natural Antibiotics by the Producing Organisms. Together with the available literature data, our results fit well into the following logical progression of facts and observations: (a) Esperamicins are produced by microorganisms and exported outside of the cell in a full, unfragmented form; (b) Esperamicins fragment into the aromatized and carbohydrate parts upon their activation and subsequent Bergman cyclization; (c) compounds **3**−**6**, designed to mimic esperamicins, also undergo fragmentation after their Bergman cyclization; (d) chemical similarity between our molecules and esperamicins suggests that these fragmentations proceed via a similar mechanism; and (e) this "conformationally gated" mechanism depends on the orientation of the carbohydrate moiety because its proximity to the *p*-benzyne radical is required to enable the intramolecular H-abstraction step. When all of the above points are considered together from a more general perspective, they can be combined in an intriguing hypothesis outlined in this section.

The microorganisms which produce natural antibiotics must protect themselves from the lethal effects of their own toxins as these molecules are produced, transported, and exported.[7b] Medicinal chemists who develop thermally activated prodrugs face the same problem when designing drugs which are nontoxic and shelf-stable until they reach their clinical target.

Results outlined in this paper illustrated how conformational effects can be used in conjunction with *intra*molecular reactions for control of enediyne reactivity through shifting the enediyne/*p*-benzyne equilibrium toward the radical species. Because Bergman cyclizations are often endothermic, equilibrium con-

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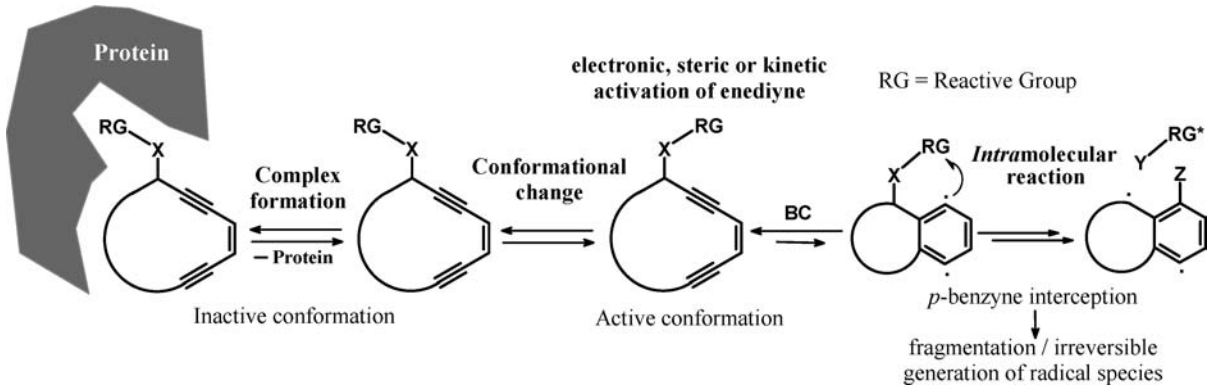

Figure 5. Conformational control of enediyne reactivity through a switch between an unreactive and reactive conformations followed by *intra*molecular trapping of *p*-benzyne.

centrations of *p*-benzynes are exceedingly low even for many highly reactive enediynes (e.g., K_{eq} was estimated as $\sim 2 \times 10^{-9}$ even for highly reactive nine-membered cyclic enediynes).[42] As the result, in the absence of suitable H-atom donor, the diradical product quickly undergoes deactivation through the retro-Bergman opening which reforms the starting material. However, if this diradical is trapped through a conformationally gated intramolecular reaction which is faster than retro-Bergman opening, the overall process becomes effectively irreversible.

A hypothetical scenario which illustrates how a similar conformational effect might operate in some of natural enediynes is outlined in Figure 5. In this scenario, enediyne forms a supramolecular complex (perhaps similar to apoprotein/C-1027 or apoprotein /NCS enediyne complexes)[43] in which a reactive group is trapped in a conformation where its intramolecular reaction with the transiently formed *p*-benzyne is impossible. Even if the Bergman diradical is formed, it is quickly converted back to the enediyne starting material through the retro-Bergman step. On the other hand, dissociation of the complex would allow a conformational change which places this group in the vicinity of enediyne moiety and allows it to intercept *p*-benzyne through one of the fragmentation pathways described in this paper. This cascade renders formation of the radical species from enediynes effectively irreversible. Such effects would be more efficient for endothermic and, hence reversible, Bergman cyclizations.[44]

Conclusion

In summary, a variety of fragmentations and rearrangements can follow Bergman cyclization of enediynes equipped with acetal rings mimicking the carbohydrate moiety of natural enediynes of esperamicine and calchiamicine families. In the first step, *intra*molecular H-atom abstraction through a six-membered TS efficiently transforms the *p*-benzyne product of the Bergman cyclization into a new more stable radical. Depending on the substitution pattern and reaction conditions, this radical undergoes several reactions, such as O-neophyl rearrangement or fragmentation with elimination of the appended acetal moiety as a whole. The later reaction may provide insight into the mechanism of unusual fragmentation of esperamicin A_1 upon its Bergman cycloaromatization and serves as an alternative to the water-assisted H-transfer mechanism for the fragmentation of esperamicin A_1 proposed earlier by Langley and co-workers. Thorpe-Ingold effect in *gem*-dimethyl substituted enediynes can enhance the fragmentation process efficiency to the extent where it cannot be prevented even by a large excess of external H-atom donor.

In addition, this work lays foundation for a new approach for the control of reactivity of this highly reactive class of molecules through a conformational change followed by an irreversible interception of *p*-benzyne diradical. Combination of such an approach with supramolecular constraints may also offer a plausible mechanism for the resistance to natural enediyne antibiotics by the enediyne-producing organisms.

Finally, the isolation of the rearranged benzoic ester **9** through the O-neophyl rearrangement/fragmentation sequence of enediyne **2** has opened the door for the design of radical processes that would allow a useful transformation of phenols into benzoic acid derivatives. We are currently investigating the scope of this transformation and working on making this process more efficient.

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Supporting Information Available: General experimental procedures for Bergman cyclization reaction and synthesis of compounds. ^{1}H and ^{13}C NMR spectroscopic data for new compounds. Complete ref 15. GC and NMR analysis for the BC of enediynes **2** and **3**, and GC analysis for the BC of enediyne **10** and the reaction of compound **7**. Total energy and Cartesian coordinates for each optimized structure. This material is available free of charge via the Internet at http://pubs.acs.org.

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