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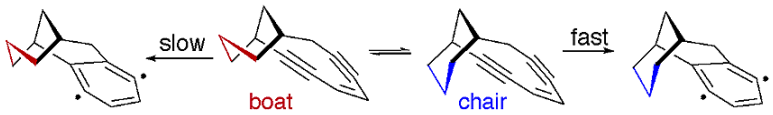

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Conformational Control in Activation of an Enediyne

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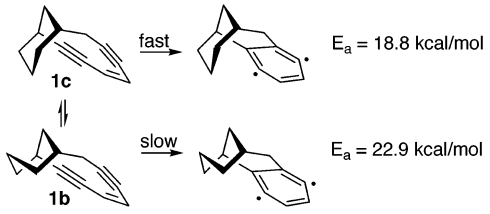
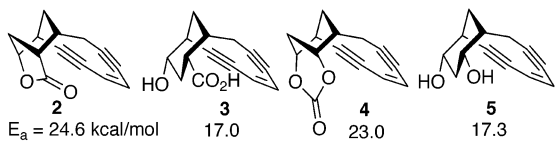
The enediyne toxins have attracted attention due to their novel structures, high toxicity, and unique mechanism of action.[1] Their activity is based on a sequence of thermal reactions: (a) a chemical triggering event which converts a stable form into a reactive form, (b) rapid cycloaromatization to an arene 1,4-diradical, and (c) DNA cleavage. There has been interest in designing novel frameworks that might allow activation under a variety of conditions and could be tailored for selective activation.[2] Efforts have been made to formulate simple structure/reactivity relationships in order to predict the reactivity of a new enediyne before and after triggering.[3−5] However, there is no general analysis that is effective in complex systems, with theoretical prediction and experimental verification. Here we explore, through computational analysis of the transition states and through synthesis, a new basis for triggering the cyclic enediynes.

It was suggested on the basis of molecular mechanics analysis in an early model study that the calicheamicin/esperamicin framework, represented by **1**, could exist in either a chair (**1c**) or boat (**1b**) conformation and that the chair form would be more reactive toward cycloaromatization.[6] We have evaluated the reactivity of **1c** compared to **1b** using DFT at the BLYP/6-31G(d) level[7] and found a relative transition state energy difference of 4.1 kcal/mol. Molecules of general structure **1** show experimental half lifetimes for cycloaromatization of ca. 10 min at 21 °C, presumably through the chair conformer.[8] If the conformation were restricted to the boat form, the framework would presumably be quite stable until the restriction is removed. The boat-to-chair conversion could then serve as a triggering event for cycloaromatization.

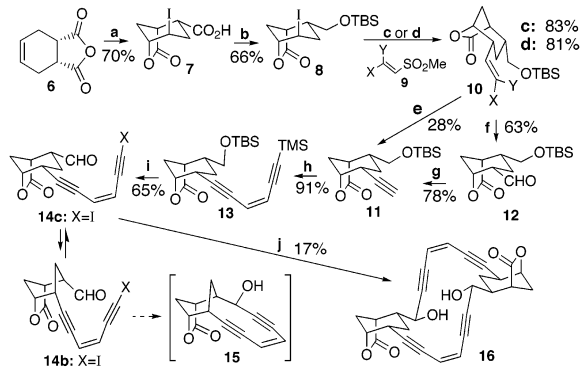


We considered the 1,3-bridged frameworks **2** and **4** and the ring-opened analogues **3** and **5**. The barrier for cycloaromatization calculated for **2** is 24.6 kcal/mol while the ring-opened version **3** has a much lower barrier, 17.0 kcal/mol. With a three-atom bridge (**4**), the framework has a barrier of 23.0 kcal/mol while the ring-opened version (**5**) is lower, at 17.3 kcal/mol. These activation energies predict long lifetimes at 25 °C for **2** and **4** but rapid rearrangement for analogues **3** and **5**.



The synthesis (Scheme 1) of a test case begins with the iodolactonization of **6** to give **7** which was then converted to the TBS ether **8**.[9] Several tactics were tested for replacement of iodide by a carbon unit with inversion of configuration.[10] Two versions of a radical addition/elimination process using vinyl sulfones **9** were remarkably stereoselective, giving **10** in > 9:1 ratio over the epimer.[11] Reaction of **10** (X,Y = Cl) with tBuLi[12] gave **11** directly in 28% yield, while **10** (X = H, Y = Ph) was converted to **11** by ozonolysis to aldehyde **12** followed by Gilbert's reagent (49% yield overall).[13]

Scheme 1. Preparation of Key Intermediates and Attempted Cyclization[a]



[a] (a) i. H_2O, Me_2CO, 23 °C, 24 h; ii. I_2/KI, $NaHCO_3$, H_2O, 23 °C, 2 h; (b) i. ClC(O)OEt, NEt_3, THF, −78 °C; ii. $NaBH_4$, H_2O/THF, 0 °C, 2 h; iii. TBSCl, imidazole, DMF, 23 °C, 12 h; (c) for X, Y = Cl, lauroyl peroxide, heptane/PhCl, 90 °C, 12 h; (d) for X = Ph, Y = H, $(tBuO)_2$, PhCl, 130 °C, 12 h; (e) X, Y = Cl, tBuLi, THF, −78 °C, 3 h; (f) for X = Ph, Y=H: i. O_3, CH_2Cl_2, −78 °C; ii. Me_2S, −78 °C; (g) $N_2CHP(O)(OMe)_2$, tBuOK, THF, −78 to 0 °C, 10 h. (h) ClHC=CHC≡CTMS, $Pd(PPh_3)_4$, CuI, $BuNH_2$, C_6H_6, 23 °C, 24 h; (i) i. NIS, $AgNO_3$, DMF, 23 °C, 5 h; ii. HF, MeCN/H_2O, 0 °C, 0.5 h; ii. ClC(O)C(O)Cl, DMSO, NEt_3, CH_2Cl_2, −78 to 0 °C; (j) $CrCl_2$, THF, 23 °C, 24 h.

An alternate strategy is based on the Cr(II)-promoted addition of an allylic bromide to an aldehyde,[17] with an expectation of coordination of the allyl-Cr(III) unit to the aldehyde carbonyl in a large ring (Scheme 2, structure **A**) in order to favor the desired conformer for cyclization.[18] The sequence began with alkyne addition (Scheme 2, step a) to aldehyde **17** (obtained from **11** by desilylation and Swern oxidation; 74% yield) to give a mixture of epimers at the new hydroxyl group (ratio 2:1 by ^{1}H NMR). After chromatography, the epimers were protected as **18a** and **18b** (yields: **18a** 45%; **18b** 26%) and carried forward separately; only

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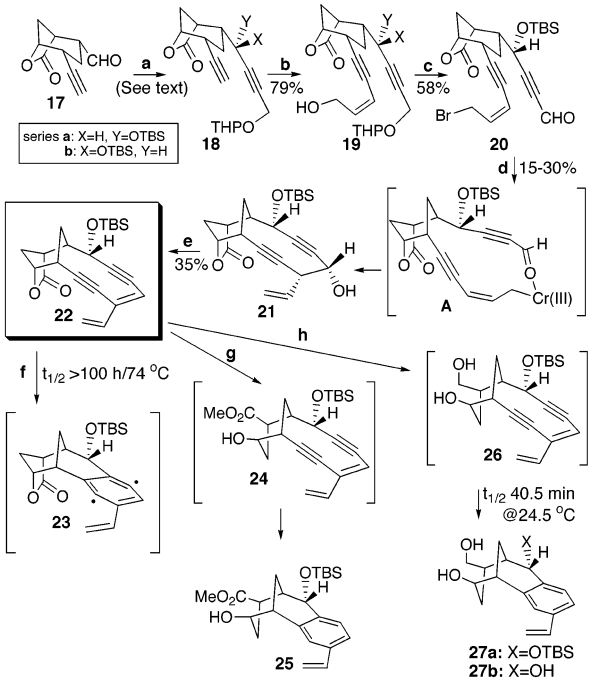
Scheme 2. Successful Synthesis and Rearrangement Kinetics[a]



[a] (a) i. LiC≡CCH$_2$OTHP, CeCl$_3$, THF, −78 °C, 5 h; ii. TBSCl, imidazole, DMF, 23 °C; (b) *cis*-ICH═CHCH$_2$OH, Pd(PPh$_3$)$_4$, CuI, NEt$_3$, THF, 23 °C, 12 h; (c) i. MsCl, NEt$_3$, CH$_2$Cl$_2$, −50 °C, 1 h; ii. NaBr, CH$_2$Cl$_2$, 23 °C, 3 h; iii. PPTS, IPA, 48 h, 23 °C; iv. ClC(O)C(O)Cl, DMSO, NEt$_3$, CH$_2$Cl$_2$, −78 to 0 °C; (d) CrCl$_2$, THF, 23 °C, 12 h; (e) i. MsCl, NEt$_2$, CH$_2$Cl$_2$, −20 °C, 2 h; ii. DBU, CH$_2$Cl$_2$, 23 °C, 4 h; (f) 74 °C, C$_6$D$_6$; (g) 1 M NaOMe, MeOH, 1,4−CHD, 23 °C, 4 h; (h) (iBu)$_2$AlH, 1,4-CHD, THF, 23 °C.

the major epimer was successful in the key cyclization step. The yields reported in Scheme 2 are for series a.

Both epimers were converted through Sonogashira coupling with 3-hydroxy-1-iodo-(*Z*)-prop-1-ene into alcohols **19**.[19] The hydroxyl group was activated as the mesylate and converted to the bromide. Then cleavage of the THP ether allowed oxidation to the aldehydes, **20**. The critical cyclization step was carried out on **20a** with Cr(II) activation and gave a fairly complex mixture from which the cyclic diyne **21** was isolated in 15−30% yield. An X-ray determination established the structure of **21** and then elimination of water was provoked under mild conditions to give the cyclic enediyne **22**. Attempted cyclization of **20b** under the same conditions gave a complex mixture from which only dimeric products could be isolated.

Consistent with the calculations, **22** is indefinitely stable at 23 °C and decomposes with a half lifetime of 110 h at 74 °C (but gives none of the typical cycloaromatization products from the expected intermediate diradical, **23**).

To evaluate the conformational effect on cycloaromatization reactivity, **22** was stirred at 23 °C in 1.0 M NaOMe/MeOH solution containing a ca. 20-fold excess of 1,4-cyclohexadiene (1,4-CHD). Attempts to isolate the ring-opened ester **24** through rapid workup failed, and the only discrete product characterized was **25** from cycloaromatization, in ca. 20% yield. From this experiment, the half lifetime of **24** is less than about 2 h at 23 °C. In an effort to open the ring rapidly at low temperature and follow the cycloaromatization process by spectroscopy, the reaction of **22** with diisobutylaluminum hydride was studied. Reproducible data were obtained by following the disappearance of the UV absorption for the enediyne unit (λ_{max} 296 nm) upon reaction with DIBALH in THF.[20] The half lifetime for the intermediate **26** was 43.5 min at 24.5 °C (average of three runs). From a multi-milligram run in THF containing excess CHD, the cycloaromatized product **27b** (spontaneous loss of the silyl protecting group) was isolated in 20% yield.

The observed half lifetimes for **22** and intermediate **26** correspond to free energies of activation for the cyclizations of approximately 29 and 22 kcal/mol, respectively. Thus the BLYP/6-31G(d) calculations underestimate the barriers but correctly predict the difference in the activation energies for the framework and ring-opened compounds. These results open the way for the design of selective triggers for cycloaromatization on the basis of conformational control.

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Supporting Information Available: Full characterization data on all new compounds including selected NMR spectra; a crystallographic information file (CIF) containing the full X-ray structural data for **10** (X,Y = Cl), **16** and **21**; an ASCII text file containing the atomic coordinates of **1b**, **1c**, **2**−**5**, and the corresponding transition states; and general conditions for rate studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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