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A New Framework For The Cycloaromatization Of Enediynes Under Mild Conditions.

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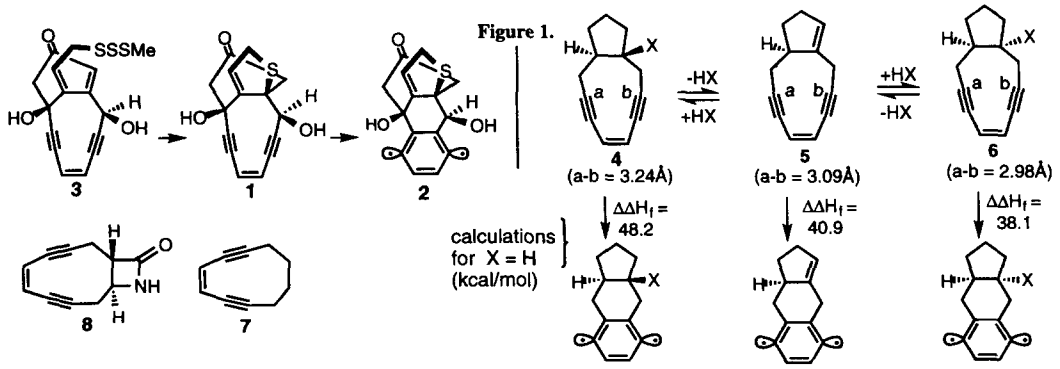
Abstract: An enediyne unit in a bicyclo[8.3.0] framework with a *trans* ring fusion has been designed, synthesized, and evaluated as a new functional model for the enediyne toxins. The cycloaromatization reaction proceeds with a half-life time of 13-14 hr at 25 °C.

The members of the family of enediyne toxins demonstrate various mechanisms of activation (triggers) leading to cycloaromatization (Bergman rearrangement) and then DNA cleavage.[1] The activated form of a prototype case (e.g., calicheamicin) is represented by structure **1** in figure 1. An important message from the natural systems is that a set of thermal reactions can convert a stable cyclic enediyne (e.g., **3**) into an activated version (**1**). The intermediate **1** in the calicheamicin series shows a rapid rate ($t_{1/2}$ = 4.5 sec) of formation of the arene diradical, **2**.[2]

It is an interesting challenge to devise alternate frameworks and triggering mechanisms, with the goal of producing a stable enediyne which can be activated under controlled conditions, especially in a way which directs the cytotoxicity toward a specific pathogen or tissue. Such studies would benefit from a better picture of the structure/reactivity parameters of the cycloaromatization reaction than is now available.[1,3] From a consideration of the essential features of **1**, we propose that a set of related structures (**4-6**) would have differential reactivity toward cycloaromatization and can be interconverted via elimination and re-addition of the unit X.

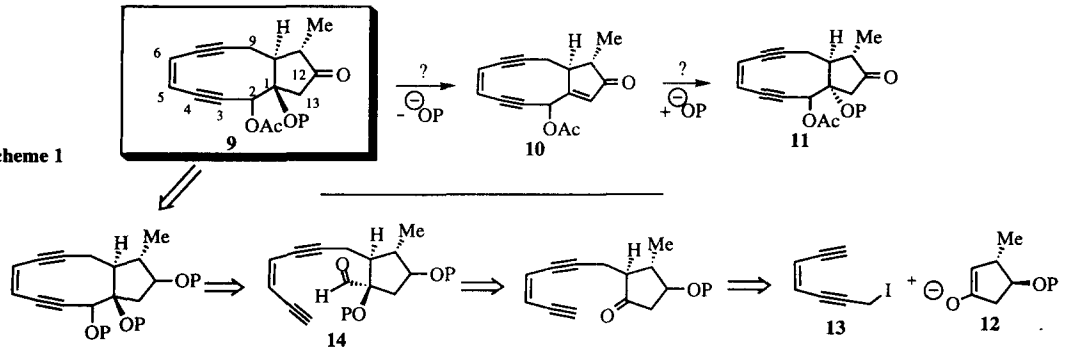


There are several ways to predict the propensity toward cycloaromatization.[3] The simplest is a comparison of the distance between the alkyne termini a-b in structures **4-6**; for simple monocyclic enediynes, the rate of cycloaromatization correlates well with the a-b distance.[4] More generally useful is a comparison of relative heats of formation of the enediyne and the product aryl 1,4-diradical.[5] We have calculated these parameters for **4-6** (X=H) and they are displayed in Figure 1.[6] Both parameters suggest the same relative reactivity toward cycloaromatization: **6** > **5** > **4**. In addition, the data for **4** suggest lower reactivity compared to the simplest 10-membered ring

enediyne, **7** ($\Delta\Delta H_f$ = 45.2), which cycloaromatizes very slowly at 25 °C.[4] During the course of this work, additional evidence for the stability of *trans* fused bicyclo[8.n.0] enediynes appeared when **8** was prepared and evaluated (no reaction at 100 °C).[7] A *cis* fused [8.3.0] structure (close analog of **6**) shows a half-life time of 108 min/25 °C.[8] *Trans* and *cis* vic-dihydroxyl analogs of the simple cyclic 10-membered enediyne show higher reactivity for the cis derivatives.[9]

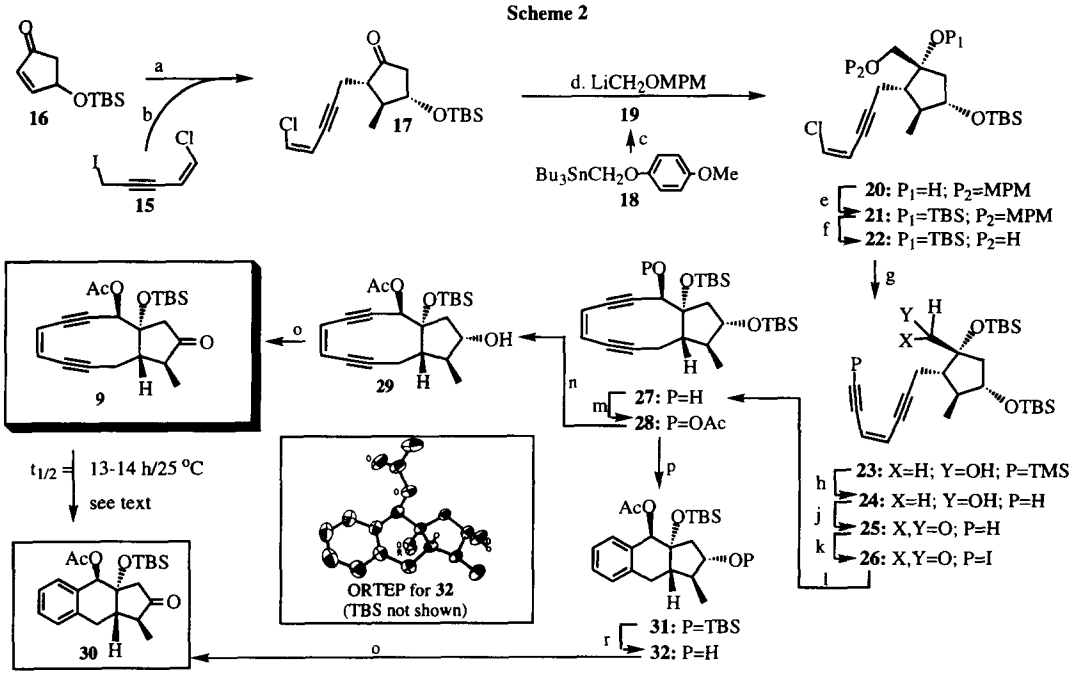
We chose as our target the ketone **9**, with the expectation that β-elimination and re-addition of the alkoxy group (to **10** and **11**) would serve as an activation step (Scheme 1). The key steps in a synthesis plan include the regiospecific generation of enolate **12** via conjugate addition to 4-hydroxycyclopentenone, and alkylation with **13** or an equivalent, introduction of a formyl group (as in **14**) with stereocontrol, and ring closure by acetylide anion addition to the formyl group.[10] The key keto unit (C-12) proceeds through the process as a protected alcohol, and oxidation would produce the target ketone, **9**. The methyl substituent at C-11 is present for synthesis convenience, taking advantage of a standard protocol for regiospecific enolate generation (in **12**, see below). AM1 calculated heat-of-formation comparisons suggest no significant effect of the Me group on the cycloaromatization barrier.

Scheme 1



The synthesis begins with the known coupling of propargyl alcohol with cis-1,2-dichloroethylene[11] and then conversion[12] to the iodide, **15** (65% yield). Protected 4-hydroxycyclopent-2-enone **16** underwent conjugate addition of a methyl group using Me_3ZnLi.[13] The intermediate enolate anion was alkylated with the propargylic iodide **15** to give the trisubstituted cyclopentenone **17** (62% yield), assumed to have the *trans* relationship of the substituents.[14] Several methods were evaluated for the introduction of a formyl group equivalent at C-1 in **17** with stereocontrol. The best process is an application of the alkoxymethyl lithium reagent.[15] Alkylation of p-methoxybenzyl alkoxide with $(nBu)_3SnCH_2I$ gives the MPM version of Still's precursor[15] (**18**, 87%). Tin-lithium exchange[16] gives *in situ* the reactive organolithium reagent, **19**. Addition to ketone **17** proceeded at -78 °C to give **20** in 87% yield; no other isomer was detected in the crude product nor during chromatographic purification. Protection of the tertiary hydroxyl group with t-butyldimethylsilyl trifluoromethanesulfonate gave the TBS ether, **21** (91% yield). Initial plans to remove the MPM group after completing the construction of the enediyne unit were complicated by side reactions during MPM deprotection in the presence of the enediyne functionality. Therefore, the MPM group was removed at this stage with DDQ,[16] giving **22** (90% yield). The primary hydroxyl group did not interfere with the conventional Pd(0) coupling with TMS-acetylene,[17] and **23** was obtained in 85% yield. Selective de-silylation of the alkynyl Me_3Si group to give **24** (76% yield)[18] was followed by oxidation of the primary hydroxyl group with Ru(II)/NMO to give the aldehyde **25** in 75% yield,[19] and set the stage for ring closure by alkynyl addition to the aldehyde. A variety of bases and conditions was employed to generate the acetylide anion from **25**, but the desired ring closed product **27** could not be detected. Modified conditions, beginning with conversion of the alkyne to the alkynyl iodide (**26**) allowed ring closure promoted by Cr(II)[20] and produced the cyclic enediyne **27** in 53% yield as a low mp colorless solid.[21] Acetylation gave **28**, which was relatively stable and easy to purify. Selective mono-desilylation (**29**) followed by oxidation gave the target, **9**, in about 60% yield overall for deprotection and oxidation.

Scheme 2



(a) *i.* $ZnCl_2$, MeLi (3 mol-eq), THF, 0 °C, 5 min; *ii.* add **16** (1 mol-eq in THF) at -78 °C, 1 h; (b) add **15** (5 mol-eq) in HMPA, -78 °C, 24 h; (c) nBuLi (1.3 mol-eq), THF, -78 °C, 5 min; (d) add **19** to **17** (1.3 mol-eq) in THF, -78 °C; stir 10 min; (e) $tBuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 25 °C, 12 h; (f) DDQ (2 mol-eq), CH_2Cl_2, H_2O, 25 °C, 2.5 h; (g) $Me_3SiC{\equiv}CH$ (7 mol-eq), $BuNH_2$ (11 mol-eq), $(Ph_3P)_4Pd$ (0.05 mol-eq), CuI (0.5 mol-eq), 25 °C, 4.5 h; (h) $AgNO_3$ (5 mol-eq), EtOH:H_2O:THF (1:1:1), 25 °C, 10 min; then KCN (7 mol-eq), 25 °C, 10 min; (j) *i.* $(Ph_3P)_3RuCl_2$ (0.2 mol-eq), 4-Me-morpholine-N-oxide (16 mol-eq), mol sieves, acetone, 25 °C, 3 h; *ii.* repeat $(Ph_3P)_3RuCl_2$ (0.2 mol-eq), 4-Me-morpholine-N-oxide (16 mol-eq), 25 °C, 3 h; (k) DMAP (10 mol-eq), I_2 (4 mol-eq), benzene, 49 °C, 1 h; (l) $NiCl_2$ (0.5 mol-eq), $CrCl_2$ (10 mol-eq), THF, 25 °C, 16 h; (m) DMAP (0.25 mol-eq), Ac_2O (35 mol-eq), py, 25 °C, 1.75 h; (n) aq HF (48%, ca 40 mol-eq), MeCN, 25 °C, 0.5 h; (o) $(Ph_3P)_3RuCl_2$ (0.18 mol-eq), 4-Me-morpholine-N-oxide (16 mol-eq), mol sieves, acetone, 25 °C, 3 h.; (p) 1,4-cyclohexadiene, toluene, 90 °C, 0.5 h

Our expectation was that **9** would be relatively stable toward cycloaromatization, but elimination and readdition of alkoxy would produce **10** or **11**, either of which could be highly reactive. However, **9** was surprisingly reactive and cyclized to **30** in the presence of 1,4-cyclohexadiene (65-85% yield) with a half-life time of 13-14 h/23 °C under a variety of conditions. Efforts to produce the more activated structures (i.e., **10** or **11**) by inducing elimination of alkoxy from **9** (Et_3N, TFA, etc) did not significantly affect the rate nor the product of cycloaromatization. Structure **30** was established by chemical correlation. Heating of **28** (90 °C/0.5 h) gave **31** (80% yield); then selective desilylation (to **32**) and oxidation gave a ketone (**30**) which was identical (^1H, ^{13}C NMR) with the product from cycloaromatization of **9**. The structure of alcohol **32** was verified by X-ray crystallography.[22] Elimination and readdition of alkoxy from **9** at any stage is unlikely, as reaction of **9** in the presence of excess MeOH saw no incorporation of MeOH into recovered **9** nor into a cycloaromatized product (analog of **30**).

The target molecule **9** represents a new framework for cycloaromatization, with the interesting feature that oxidation of an alcohol unit (in **29**) to a ketone (**9**) provides the activation step. This contrasts with three other systems, in which reduction of a ketone to an alcohol unit is a strong activation.[23,24,25] The hydroxyl→ketone change is being pursued as a potential trigger for enediyne activation. This system also reminds us that the structure/reactivity correlations for cycloaromatization of enediynes are not yet very refined.[26]

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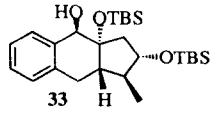
21. It is interesting to note that while **27** is relatively stable toward thermally-induced cycloaromatization, the product (**33**) from such a process was isolated in 74% yield when the ring closure was carried out with a large excess (16 mol-eq) of Cr(II) at 25 °C. Presumably, the cyclized product **27** forms and is then induced by the Cr(II) to cycloaromatize, by an unknown mechanism.



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