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A simple synthesis and evaluation of the bicyclo[8.3.0] enediyne framework

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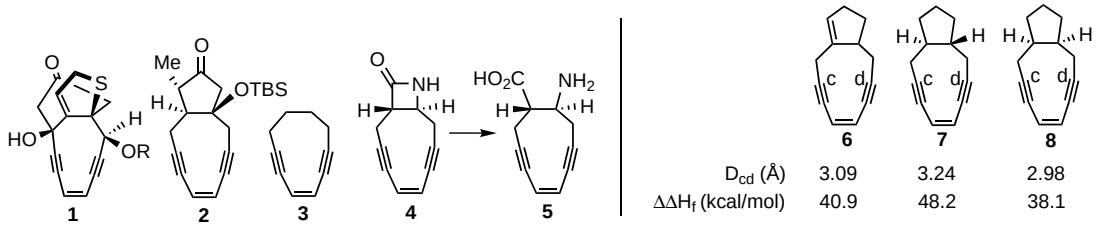
Abstract—A synthesis of a simple *trans* fused [8.3.0]bicyclic enediyne framework was developed from cyclopentanone-*trans*-3,4-dicarboxylate. The rates of rearrangement of several derivatives of the framework were measured, and correlated with structural features. Preliminary studies to adjust the configuration about the ring fusion, expected to be an activation step, are discussed.

The intriguing toxin calicheamicin and related natural compounds[1] have served as the inspiration for the design of functional models. The models should incorporate a chemical trigger that can lead, through H-atom abstraction, to a cascade of reactions effecting DNA cleavage, but they might also allow for selective triggering, selectivity not typical of the natural products. An aspect of the problem of designing functional models is defining which structural features are responsible for the high reactivity ($t_{1/2}$ 4.5 s at 37°C[2]) of activated calicheamicin (represented by **1**) toward diradical formation. We have noted the relationship between **1** and the bicyclo[8.3.0] framework, in the simplified derivative, **2**.[3] The simple monocycle **3** was the prototype that began the effort to define the relationship between structure and reactivity in this series.[4] It was found to be much less reactive than **1** (half-life of 18 h at 37°C). In a related series, the *trans*-fused β-lactam (**4**) is quite stable (100°C) toward cycloaromatization, and the ring opened version (**5**) shows reactivity ($t_{1/2}$ ca. 2 h at 50°C) comparable to **3**.[5] A general question is the effect of ring fusion on the reactivity of the 10-membered enediyne. As estimated for **4**, the *trans*-fused four-membered ring introduces substantial strain as the *cyclo*-aromatization proceeds.[5]

In our analysis, the [8.3.0] system should also show relative stability for the *trans*-fused version, **7**, but the *cis* isomer (**8**) and the dehydro version (**6**) should be more reactive.[3,6] This prediction is based on the calculated distance between the alkyne terminii (referred to as the cd distance;[4] calculated values are shown on the structure in Fig. 1, shorter distance implies higher rate). Comparison of the calculated heat of formation of the enediyne compared to the arene diyl (Fig. 1, $\Delta\Delta H_f$[7]) leads to a similar prediction.[3,6] A larger $\Delta\Delta H_f$ implies a slower rate of rearrangement.

The derivative **2** was chosen in our earlier work with the expectation of β-elimination of the angular alkoxy group to convert the *trans* ring fusion derivative (as in **2** or **7**) to the dehydro compound (as in **6**), and then



	6	7	8
D_{cd} (Å)	3.09	3.24	2.98
$\Delta\Delta H_f$ (kcal/mol)	40.9	48.2	38.1

Figure 1. Ene–diyne models.

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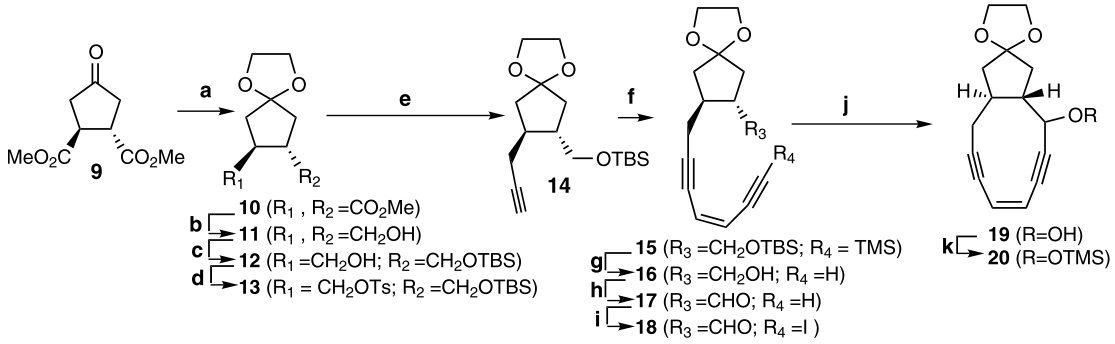
re-addition would give the *cis* isomer. However, **2** itself was surprisingly reactive toward cycloaromatization ($t_{1/2}=13$ h at 23°C) relative to simple monocyclic enediynes (e.g. **3**; $t_{1/2}$ 18 h at 37°C).[3] Computational analysis supports the possibility that the angular alkoxy group substantially increases the propensity of **2** toward cycloaromatization. These results prompted an effort to develop a short synthesis of a simple version of **7** for evaluation of its reactivity toward cycloaromatization and elaboration to isomers (**6**, **8**) of higher reactivity.

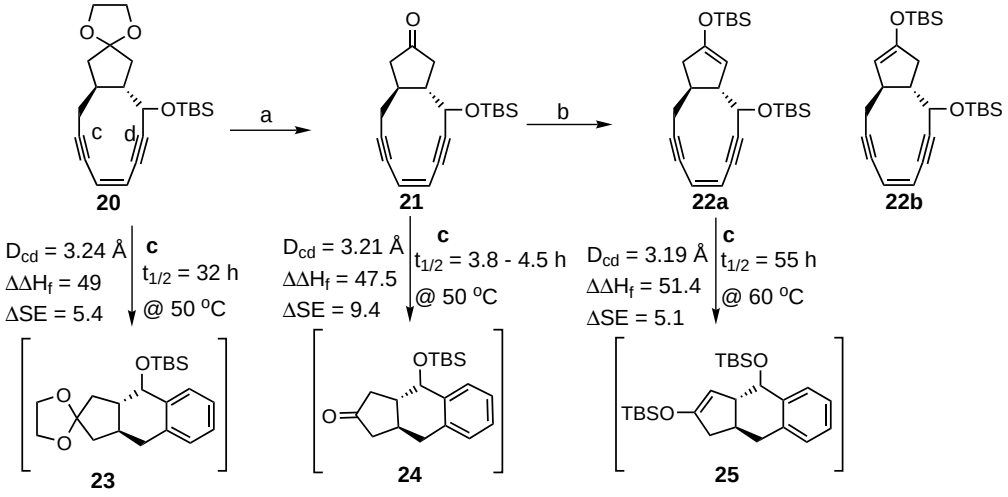
Cyclopentanone **9**[8] was modified by protection of the carbonyl group with bis(trimethylsiloxy)ethane and catalytic TBS triflate[9] (**9**→**10**). Reduction of the ester units with $LiAlH_4$ (**11**) and then selective monosilylation afforded **12**. Tosylation (90%; **13**) and then displacement by lithium acetylide[10] produced **14** in 66% yield. Side reactions including elimination as well as silyl transfer to the alkyne anion account for the modest yield. Sonogashira coupling[11] with Pd(0) and 1-chloro-4-trimethylsilylbut-1-ene-3-yne gave the enediyne **15** in 93% yield. Double desilylation (**16**; 90% yield) followed by oxidation created the aldehyde unit (**17**) poised for ring closure. Conventional methods of ring closure via generation of the alkyne anion failed to give useful yields of the cyclized product, which we attribute to enolization of the aldehyde group. Instead, the alkyne was iodinated using $AgNO_3$ and *N*-iodosuccinimide[12] (giving **18**) which allowed ring closure to **19** in 47% yield using $CrCl_2/NiCl_2$.[13] For further manipulation, the propargylic alcohol was protected as the TBS ether (**20**) (Scheme 1).

Gentle deketalization of **20** with Cu(II)[14] gave the ketone **21**. To probe for the effect of introducing a second sp^2 center, and to prepare for elimination procedures towards an enone (see below), the silyl enol ether enediyne **22** was prepared by trapping the enolate of keto-enediyne **21** with TBS–triflate at low temperature. A mixture of regioisomers (**22a**/**22b**) was obtained in a ratio of 6:1 (determined by ^1H NMR[15]). The structure of the major isomer, assigned as **22a**, was confirmed indirectly by X-ray analysis (see below).

The ketal enediyne **20** was found to be quite stable, undergoing Bergman rearrangement in the presence of 1,4-cyclohexadiene (1,4-CHD) with $t_{1/2}=32$ h at 50°C (Scheme 2). Introducing one sp^2 center (ketone **21**)



Scheme 1. Synthesis of the [8,3,0] framework. *Reagents and conditions*: (a) $TMSO(CH_2)_2OTMS$, TBS–triflate, 92%; (b) $LiAlH_4$, 88%; (c) NaH, TBSCl, 97%; (d) *n*-BuLi, TsCl, 90%; (e) lithium acetylide–ethylenediamine complex, DMSO, 66%; (f) $Pd(PPh_3)_4$, CuI, (*Z*)-ClCHCHTMS, 93%; (g) K_2CO_3, TBAF, 90%; (h) PCC, 89%; (i) $AgNO_3$, NIS, 98%; (j) $CrCl_2$, $NiCl_2$, 47%; (k) 2,6-lutidine, TBS–triflate, 99%.

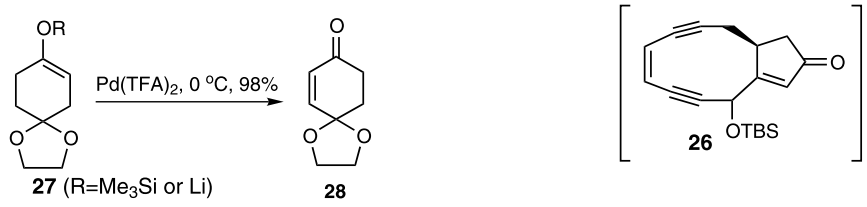


Scheme 2. Thermal rearrangement of the enediynes. *Reagents and conditions*: (a) $CuCl_2{\cdot}2H_2O$, CH_3CN, 70%; (b) LiHMDS, TBS triflate, 98%; (c) 1,4-CHD.

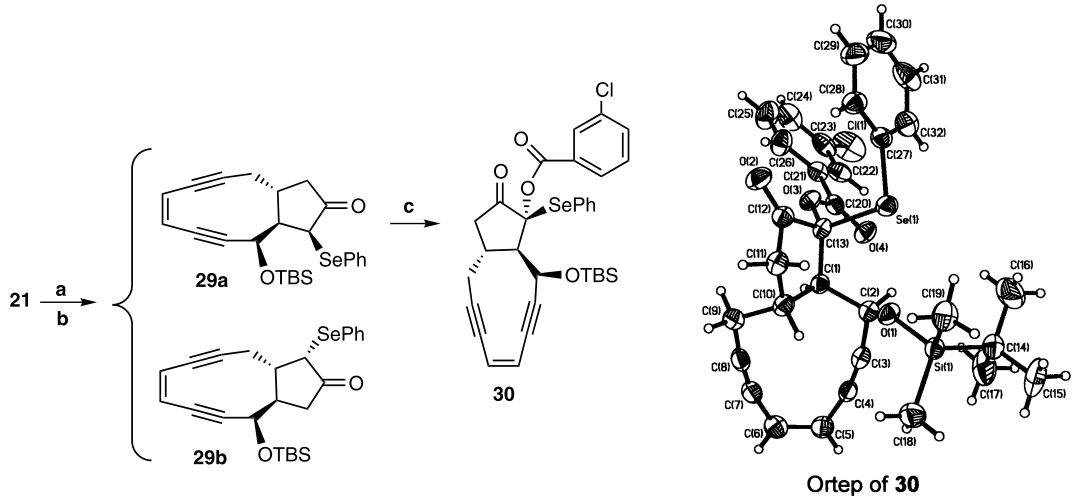
increased the reactivity ($t_{1/2}$ ca. 4 h at 50°C). A study of the rearrangement of the mixture of regioisomers **22a** and **22b** by ^{1}H NMR showed them to be of comparable reactivity and quite stable toward cycloaromatization, with $t_{1/2}$ ca. 55 h at 60°C (6 h at 90°C). The rates of cycloaromatization for **20**, **21**, and **22** are approximately consistent with predictions based on a comparison of $\Delta\Delta H_f$, but do not correlate well with ΔSE[16] nor D_{cd} numbers.

Several methods were studied in an attempt to introduce an α,β-alkene unit into the ketone framework, as in **26**. The general reaction of Pd(II) reagents with enol silyl ethers[17] and enolate anions[18] was considered for this system, with the advantage that it begins with a regio-defined enol derivative. $Pd(OAc)_2$ is the usual reagent, reacting at room temperature or above. In an effort to carry out the process at low temperature, the more electrophilic reagent $Pd(TFA)_2$ was evaluated with the model substrate **27**. Reaction was complete after 2 h at 0°C, from either the enol silyl ether or enolate, to give the cyclohexenone in 98% yield. Starting from the enol silyl ethers (mainly **22a**), reaction with $Pd(TFA)_2$ led to a rapid reaction at 0°C and complete conversion, but no identifiable product.[19] In a related process, direct oxidation of **22** with Ce(IV)[20] again failed to give an isolable product. Compound **26** was expected to be quite reactive toward cycloaromatization and the oxidation procedures were carried out both in the presence and absence of the H-atom donor, 1,4-CHD, in order to trap efficiently any arene-1,4-diyl forming spontaneously. No cycloaromatized product was observed (Scheme 3).

A different approach, based on the elimination of α-selenoxyketones,[21] began with ketone **21**. Generation of the kinetic enolate followed by treatment with PhSeCl gave a rapid reaction at 23°C leading to a mixture of regio-isomeric α-selenoketones, **29a**/**b**. The regio-isomers were separable by chromatography; the major isomer was assigned as **29a**[22] and subjected to the usual conditions for oxidation/elimination. Oxidation with *m*CPBA[23] (1.1 mol equiv.) proceeded at 0°C in 1,4-CHD as solvent over 2 h. However, instead of the expected enone-enediyne **26** or its corresponding cycloaromatized product, we isolated the Pummerer rearrangement product **30** in 32% yield; the structure was confirmed by X-ray crystallography (Scheme 4). In an effort to slow the Pummerer reaction, we turned to hydrogen peroxide[24] as a more neutral oxidizing agent. With 30% H_2O_2 at 0°C in 1:1 CH_2Cl_2:1,4-CHD over 2 h, phenyl selenyl enediyne **29a** was converted to a complex mixture of products. An analysis of the crude product indicates a disappearance of the vinylic hydrogens (loss of the enediyne) by ^{1}H NMR and the appearance of new aromatic protons, consistent with cycloaromatization. However, we have as yet been unable to characterize a product to confirm cycloaromatization.



Scheme 3. Elimination with $Pd(TFA)_2$ at 0°C.



Scheme 4. Attempted selenoxide elimination. *Reagents and conditions*: (a) LiHMDS, −78°C; (b) PhSeCl, −78→0°C; (c) *m*CPBA, 0°C.

This communication outlines an efficient route to the preparation of an [8.3.0] bicyclic enediyne in quantity and should allow a full exploration of the structure–reactivity parameters in cycloaromatization for this system. Our preliminary analysis indicates that subtle changes in hybridization within the [8.3.0] framework lead to changes in reactivity which correlate well with $\Delta\Delta H_f$ values obtained from semiempirical calculations.

Acknowledgements

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