

Triggering of the Bergman Cyclization by Photochemical Ring Contraction. Facile Cycloaromatization of Benzannulated Cyclodeca-3,7-diene-1,5-dynes

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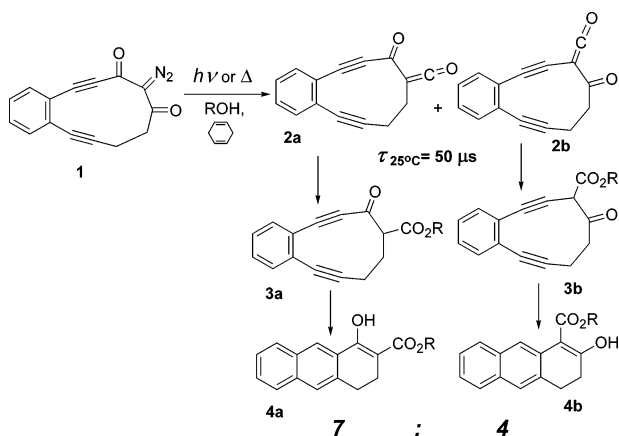
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The extreme cytotoxicity of natural enediyne antibiotics is attributed to the ability of the (*Z*)-3-ene-1,5-diyne fragment to undergo Bergman cyclization and produce a DNA-damaging *p*-benzyne diradical.^{1,2} Photochemical triggering of this reaction allows for the spatial and temporal control of enediyne reactivity. Several examples of light-induced cycloaromatization of acyclic^{3,4} and cyclic⁵ enediynes, as well as of natural antibiotic Dynemicin A,⁶ have been reported in literature. Our group explores an alternative strategy of photoactivation: the in situ generation of a reactive enediyne system, which subsequently undergoes the cycloaromatization.⁷

Here we report the first example of triggering of the thermal Bergman cyclization by the photochemical ring contraction. The latter process causes substantial increase in the strain energy of cyclic enediynes, thus triggering the cycloaromatization. It is known that 11-membered ring enediynes are stable at ambient temperatures, while 10-membered analogues undergo spontaneous cyclization.⁸ We have designed and synthesized 11-membered enediyne (**1**), which incorporates an α -diazo- β -diketone moiety. Upon irradiation or thermolysis, **1** undergoes Wolff rearrangement to produce reactive 10-membered enediynes **3a** and **3b**. The latter undergo spontaneous Bergman cyclization (Scheme 1).

Scheme 1

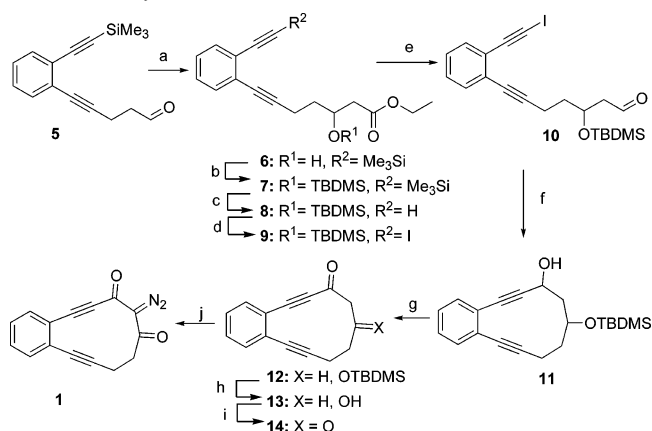


The target 2-diazo-6,7-benzocycloundeca-4,8-diyne-1,3-dione (**1**) was prepared by the diazo transfer reaction from tosyl azide onto the β -diketone **14** (Scheme 2).⁹ The latter was in turn prepared by successive Dess–Martin oxidations of 1,3-diol **11**. The crucial cyclization step has been achieved using the Nozaki–Hiyama–Kishi procedure (Scheme 2).¹⁰

The photo-Wolff reaction¹¹ of diazodiketone **1** was expected to produce two isomeric β -ketoketenes **2a** and **2b**, which should rapidly react with the hydroxylic solvents ($\tau_{\text{H}_2\text{O}} \sim 1 \mu\text{s}$)¹² to give β -ketoesters **3a** and **3b** (Scheme 1).

In fact, the formation of a characteristic ketene band at 2212 cm^{-1} in laser flash photolysis of **1** was detected by transient IR

Scheme 2. Synthesis of Diazodiketone **1**^a



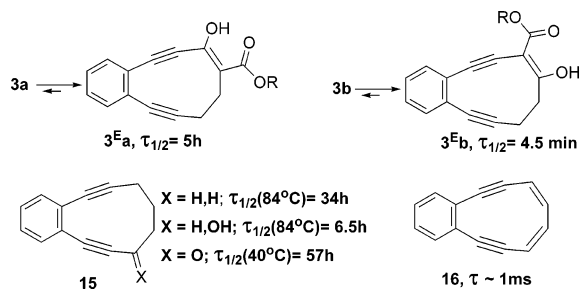
^a Reagents and conditions: (a) LDA/EtOAc, 90%; (b) TBDMS–Cl, imidazole/DMAP, 90%; (c) $\text{K}_2\text{CO}_3/\text{MeOH}$, 97%; (d) $\text{I}_2/\text{morpholine}$, benzene, 50 °C, 91%; (e) DIBAL, 91%; (f) $\text{CrCl}_2/\text{NiCl}_2$, THF, 84%; (g) Dess–Martin periodinane, 92%; (h) HF, MeCN 88%; (i) Dess–Martin periodinane, 84%; (j) DBU, TsN_3 , 84%.

(TIR) spectroscopy. Ketenes **2a** and **2b**, which are indistinguishable at the resolution of the TIR instrument,⁹ are formed within 30 ns after the laser pulse and decay with a lifetime of ca. 50 μs in the presence of 5% methanol in CCl_4 . The 350 nm irradiation of **1** results in the efficient ($\Phi_{350} = 0.36$) dediazotization of the starting material. However, dihydroanthracene derivatives **4a** (54%) and **4b** (31%), as well as small amounts of diketone **14** (<10%), were the only isolated products upon photolysis in 2-propanol ($R = i\text{-Pr}$, Scheme 1). **4a** and **4b** are the major products even at low conversion (5–10%) of **1**. Low-temperature photolysis of **1** allowed us to isolate unstable ketoester **3a**, which undergoes clean cyclization to **4a** with $\tau_{1/2} = 5 \text{ h}$ at 36 °C in 2-propanol. However, enediyne **3b** was not detected in the photolysate even at 0 °C. This observation allows us to conclude that enediyne **3b** is also formed in the photo-Wolff reaction of **1** but undergoes rapid thermal Bergman cyclization to **4b**. The lifetime of enediyne **3b** ($\tau_{1/2} = 4.5 \text{ min}$) was measured by following the growth of absorbance of **4b** at 248 nm after 2 min of irradiation.

The facile cycloaromatization of benzannulated 10-membered ring cyclic enediynes **3a,b**, which resembles that of the strained nine-membered C-1027 chromophore,¹³ is rather unusual. Other known derivatives of 3,4-benzocyclodeca-1,5-diyne (**15**, Scheme 3) are stable under ambient conditions and undergo slow Bergman cyclization only at elevated temperatures.¹⁴ NMR data⁹ indicate that ketoesters **3a**, and presumably **3b**, predominantly exist in the enol form (i.e., **3^Ea** and **3^Eb**, correspondingly, Scheme 3). An additional endocyclic double bond apparently reduces the barrier for the Bergman cyclization. In fact, attempts to prepare 3,4-8,9-dibenzocyclodeca-1,5-diyne produced only 5,12-dihydronaphthalene,¹⁵ while annulene **16** (Scheme 3), which can be generated photo-

chemically or using flash vacuum pyrolysis, is a short-lived transient at room temperature¹⁶ and is relatively stable only in cryogenic matrices.¹⁷

Scheme 3



The reactivity difference between regioisomeric enediynes **3a** and **3b** is also quite remarkable. We believe that this phenomenon is caused by the electronic influence of the substituent at the vinylic terminus of the π -conjugated system. The electron-rich hydroxyl group in **3b** donates electron density to the out-of-plane π -orbitals, thus increasing the aromatic stabilization of the Bergman cyclization transition state.¹⁸ The electron-withdrawing carbonyl group in **3a**, on the other hand, retards the cycloaromatization reaction.

In addition, the photochemistry of α -diazo- β -diketone **1** provides us with the first direct experimental comparison of migratory aptitudes of sp^3 - and sp -hybridized carbon atoms in the Wolff rearrangement. β -Ketoesters **4a** and **4b**, which are formed by the migration of alkyl and acetylenic substituents, correspondingly, are obtained in the ratio of 7:4. This observation indicates the preferential migration of the alkyl versus alkynyl substituents in the Wolff rearrangement. Thermolysis of **1** at 100°C in ethanol in the presence of 1,4-cyclohexadiene produces **4a** and **4b** (R = Et) in a similar ratio.

An initial evaluation of the DNA cleavage ability of photogenerated 10-membered ring enediynes **3a** and **3b** was carried out using supercoiled plasmid DNA cleavage assays. Three forms of this DNA [native (RF I), circular relaxed (RF II, produced by single-strand cleavage), and linear (RF III, formed by scission of both strand in close proximity)] are readily separated by the agarose gel electrophoresis.

Solutions containing various concentrations of **1** and ϕX174 supercoiled circular DNA ($30\text{ ng}/\mu\text{L}$) were irradiated at 351.1 nm using an argon ion laser at ca. -5°C . Diazodiketone **1** induces substantial single-strand cleavage (RF II) of ϕX174 DNA upon irradiation, while the linearized form (RF III) was observed only at higher concentrations of the cleaving agent ($>500\ \mu\text{M}$) and prolonged irradiation (Figure 1). The relatively high concentrations of **1**, which are required to achieve double-strand DNA photocleavage, indicate that **1** has low affinity to a dDNA molecule. In order to improve the photonuclease activity of enediyne **1**, it is being conjugated with a dDNA minor-groove binding moiety. It is also interesting to note that irradiation of **1** in the presence of ϕX174 produces a new modification of DNA with lowest electrophoretic mobility (Figure 1). The nature of this band, which was preliminarily attributed to the covalently cross-linked dimer, is under investigation.

In conclusion, the photoswitchable enediyne compound, which is stable in the dark but converted into a very reactive form by light-induced ring contraction, has been designed and synthesized. Benzannulated 10-membered ring enediynes containing an additional endocyclic double bond undergo facile cycloaromatization even at 0°C . The electronic properties of substituents at the alkene

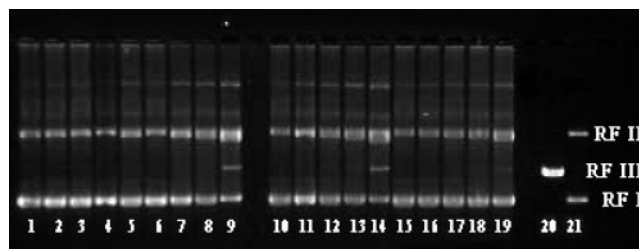


Figure 1. Light-induced cleavage of ϕX174 DNA in the presence of **1**. Lanes 1–5: DNA irradiated for 0, 15, 45, 180, and 480 s. Lanes 6–9: DNA + **1** ($1787\ \mu\text{M}$), irradiated for 0, 15, 45, and 180 s. Lanes 10–14: DNA + **1** ($488\ \mu\text{M}$), irradiated for 0, 15, 45, 180, and 480 s. Lanes 15–19: DNA + **1** ($82\ \mu\text{M}$), irradiated for 0, 15, 45, 180, and 480 s. Lane 20: DNA incubated with Pst-I restriction enzyme for 1 h at 37°C . Lane 21: DNA alone.

termini of the extended π -system have pronounced effect on the reactivity of the dienediene system.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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