Dual reactivity of a photochemically-generated cyclic enyne–allene†

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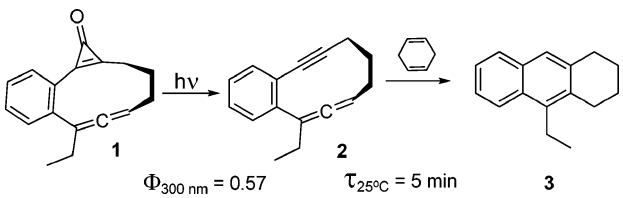
Received (in College Park, MD, USA) 17th June 2009, Accepted 27th July 2009
First published as an Advance Article on the web 14th August 2009
DOI: 10.1039/b911871c

A reactive ten-membered ring enyne–allene ($\tau_{25\ ^\circ C}$ = 5–6 min) is efficiently generated ($\Phi_{300\ nm}$ = 0.57) by UV irradiation of a thermally stable precursor in which a triple bond is masked as a cyclopropenone moiety.

Natural enediyne antibiotics are arguably the most potent antineoplastic agents ever discovered.[1] Their cytotoxicity is attributed to the ability of the (*Z*)-3-hexene-1,5-diyne (enediyne) and (*Z*)-1,2,4-heptatrien-6-yne (enyne–allene) fragments to undergo cycloaromatization, producing cytotoxic benzenoid diradicals.[2] The lack of anti-tumor selectivity of this class of natural products results in high general toxicity and hampers their clinical applications. Photo-triggering of the cycloaromatization reaction opens the possibility for the selective treatment of cancerous tissues in a fashion similar to photodynamic therapy.[1,3,4] The direct irradiation of acyclic[5] and cyclic[6] enediynes, enyne–allenes/cummulenes,[7] as well as of natural antibiotic Dynemicin A,[8] induces the formation of various diradical species albeit with rather low efficiency. The quantum yield of the photochemical Bergman cyclization can be substantially improved by adjusting the electronic properties of substituents[9] and/or using different modes of excitation energy transfer, such as MLCT.[10]

Our group has developed an alternative strategy for the photo-triggering of the cycloaromatization reaction: the *in situ* generation of reactive enediynes.[11] However, the rate of the Bergman cyclization of even highly strained nine-membered ring enediynes ($\tau_{25\ ^\circ C} \sim 2$ h)[11a] is not fast enough to allow for the temporal and spatial resolution of *p*-benzyne generation in biological systems. In order to enhance the rate of the formation of cytotoxic 1,4-diradicals, we turned our attention to compounds containing a (*Z*)-1,2,4-heptatrien-6-yne structural fragment, *i.e.*, enyne–allenes. Myers–Saito cyclization of these substrates produces α,3-didehydrotoluene analogs, which are responsible for the cytotoxicity of natural antibiotics of the neocarzinostatin family.[12] Acyclic enyne–allenes usually undergo spontaneous cyclization under ambient conditions,[13] while cyclic enyne–allenes are virtually unknown apparently due to their ability to undergo very rapid cycloaromatization.[11c,14]

Here we report the first example of the direct photochemical generation of ten-membered ring cyclic enyne–allene **2** (Scheme 1). To synthesize a thermally stable photo-precursor of enyne–allene **2** we decided to mask the triple bond as a cyclopropenone. The π-system of the cyclopropenone moiety in the enyne–allene precursor **1** is orthogonal to the plane of the ring, therefore, cyclopropenone **1** lacks the crucial in-plane overlap of π-orbitals that is required for cycloaromatization. Photochemical decarbonylation of cyclopropenones is usually an efficient process[15] and has been successfully employed for the generation of reactive enediynes.[11a,b] Thus, irradiation of cyclopropenone **1** results in the loss of carbon monoxide and regeneration of the triple bond, making the substrate susceptible to the Myers–Saito cyclization (Scheme 1).



Scheme 1 Photochemical generation of enyne–allene **2**.

The crucial cyclopropenone moiety was synthesized in a two step procedure (Scheme 2).† First, the addition of difluorocarbene, which was generated by the thermolysis of trimethylsilyl fluorosulfonyldifluoroacetate,[16] to the acetylene **4** produced 1,1-difluorocyclopropene **5**. Then, the latter was hydrolyzed on wet silica gel to give cyclopropenone **6**. The presence of the cyclopropenone moiety in synthetic intermediate **6** limits the range of reagents and reaction conditions that can be employed, since cyclopropenones readily form salts with Lewis acids and give ring-opening products with various nucleophiles.[17] Conversion of **6** into 2,2-dimethyl-1,3-propanediyl acetal[18] **7** allows us to circumvent these difficulties. The second acetylenic substituent was introduced using conventional Stille coupling conditions (**8**, Scheme 2). Simultaneous saponification of the acetate and removal of the trimethylsilyl protecting group to give **9** was achieved using potassium carbonate in aqueous methanol. Iodination of terminal acetylene with an iodine–morpholine system,[19] followed by Dess–Martin oxidation[20] gave iodoaldehyde **11**. Macrocyclization to form ten-membered cycle **12** was achieved under Nozaki–Hiyama–Kishi conditions.[21] The key step in the synthesis of enyne–allene precursor **1** is the acetylene–allene rearrangement. Several enyne–allenes were prepared by isomerization of propargyl alcohol employing Mitsunobu reaction with 2-nitro-benzenesulfonyl hydrazide.[22] Acetal **12**, however, is not stable under Mitsunobu conditions and we had to adopt an alternative procedure.[23] The reaction of propargylic mesylate **13** with EtMgBr in the presence of an excess of CuCN and LiCl led to the exclusive formation of the desired allene (**14**). Acetal deprotection was achieved

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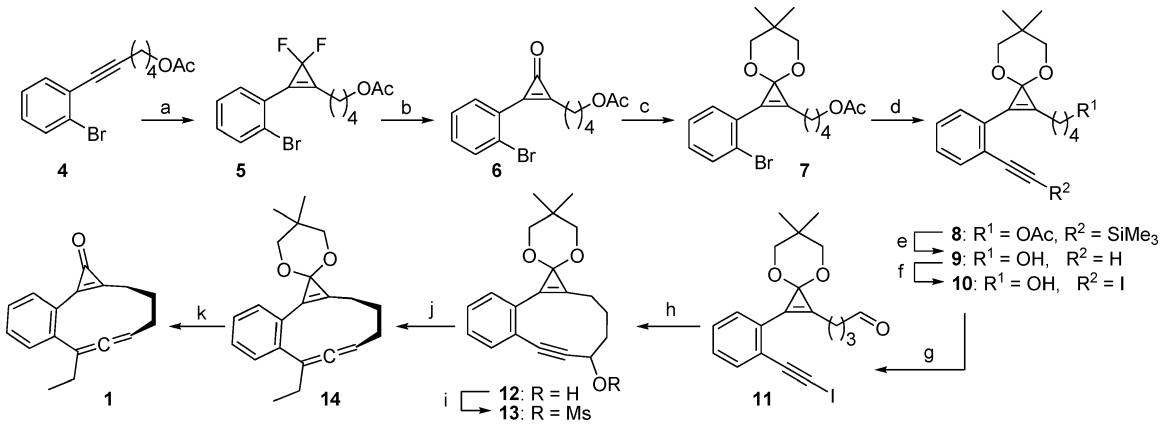
† Electronic supplementary information (ESI) available: Preparation of cyclopropenone **1**, detailed experimental procedures, ^{1}H and ^{13}C spectra of newly synthesized compounds. See DOI: 10.1039/b911871c



Scheme 2 *Reagents and conditions*: (a) NaF, TFDA, 120 °C; (b) wet SiO_2, 85% over two steps; (c) Et_3OBF_4, neopentylglycol, Et_3N, 80%; (d) $Pd(PPh_3)_4$, $Bu_3SnC{\equiv}CSiMe_3$, 90 °C, 72%; (e) K_2CO_3, MeOH (aq.), 84%; (f) I_2–morpholine, 72%; (g) DMP, 73%; (h) $CrCl_2$, $NiCl_2$, 95%; (i) MsCl, 90%; (j) CuCN, LiCl, EtMgBr, 83%; (k) Amberlyst® 15, acetone, 75%.

using Amberlyst® 15 in aqueous acetone to produce target 7-ethyl-6-dehydro-2,3,4-trihydro-1*H*-benzo[*a*]cyclo-propa[*c*]-cyclode-cen-1-one (**1**, Scheme 2).

The UV spectrum of cyclopropenone **1** shows three close lying absorbance bands at 237 nm (log ε = 4.3), 267 nm (log ε = 3.8), and 317 nm (log ε = 3.4). Irradiation of cyclopropenone **1** with 300 or 350 nm light results in the efficient decarbonylation ($\Phi_{300\ nm} = 0.57 \pm 0.03$) and formation of the target ten-membered ring enyne–allene (**2**, Scheme 1). The latter is quite reactive and undergoes facile spontaneous Myers–Saito cyclization. The accurate rate measurements of cycloaromatization of the enyne–allene **2** were conducted by UV spectroscopy following the growth of the characteristic 232 nm band of tetrahydroanthracenes **3** or **17** (Scheme 3). As shown in Fig. 1, the reaction shows first order kinetics. The rate of the cycloaromatization at 25 ± 0.1 °C was $k = (2.735 \pm 0.046) \times 10^{-3}\ s^{-1}$ in 2-propanol and $k = (3.41 \pm 1.01) \times 10^{-3}\ s^{-1}$ in THF containing 0.05 M 1,4-cyclohexadiene (Fig. 1).

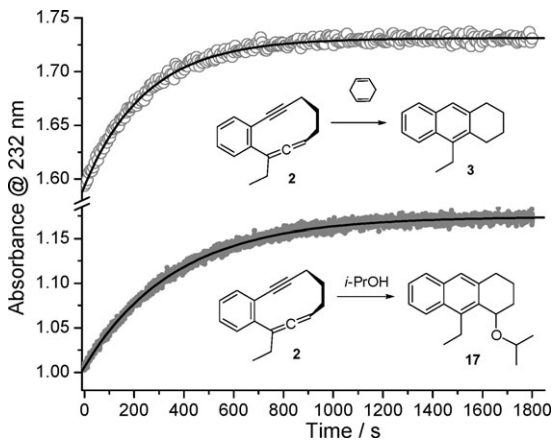
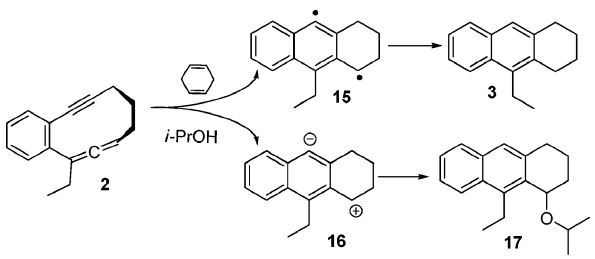


Fig. 1 Cycloaromatization of the photo-generated enyne–allene **2** in THF–1,4-cyclohexadiene (open circles) and in 2-propanol (filled circles) at 25 °C. Solid lines represent fitting of the experimental data to a single exponential equation.

It is interesting to note that the life-time of enyne–allene **2** shows little sensitivity to the reaction media ($\tau_{25\ °C} \sim$ 5–6 min).

The outcome of the cyclization reaction, on the other hand, strongly depends on the solvent. In THF, in the presence of 1,4-cyclohexadiene, 9-ethyl-1,2,3,4-tetrahydroanthracene (**3**) is formed as a major product (Scheme 3). This compound is the expected product of the Myers–Saito cyclization and is apparently formed *via* double hydrogen abstraction by the diradical **15** (Scheme 3). In 2-propanol, however, insertion of the solvent into the O–H bond, which produces 9-ethyl-1-isopropoxy-1,2,3,4-tetra-hydroanthracene (**17**), is a predominant process (Scheme 3). Minor amounts of 10-ethyl-1,2-dihydro-anthracene were also isolated in both solvents.



Scheme 3

The formation of ether **17** is inconsistent with the conventional diradical mechanism of the Myers–Saito cyclization. In 2-propanol, the σ,π-diradical **15** is expected to abstract hydrogen from the secondary carbon of the alcohol, since this C–H bond is much weaker than the O–H bond. The O–H insertion observed in 2-propanol suggests a polar, rather than a radical, pathway of the cycloaromatization in that medium (**16**, Scheme 3). Similar "dual reactivity" has been reported for acyclic enyne–allenes and was initially explained by the "polar" nature of the α,3-didehydrotoluene, which can be described as a resonance between a zwitterion and a diradical.[24] This hypothesis was later rejected on the basis of quantum mechanical calculations since frontier orbitals in these two electronic forms of α,3-didehydrotoluene are strictly orthogonal and can not be mixed.[25] Carpenter *et al.* proposed the formation of O–H insertion product *via* a non-adiabatic pathway.[25b] The analysis of the reactivity of acyclic enyne–allenes is complicated by the presence of conformational

equilibrium. The position of the equilibrium, which should depend on the solvent polarity, controls the rate, and potentially the mechanism, of the cycloaromatization reaction. Enyne–allene **2**, on the other hand, is locked in the most reactive conformation and allows us to focus the investigation of enyne–allene reactivity on electronic factors.

An initial evaluation of the nuclease activity of the photogenerated enyne–allene **2** 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 agarose gel electrophoresis.† To produce reactive enyne–allene **2** in the presence of DNA, a solution of cyclopropenone **1** in water–DMSO (4 : 1) mixtures was added to a solution of φX174 supercoiled circular DNA in TE buffer and irradiated for 10 min using 350 nm lamps (6 × 4W). The concentration of DNA was kept at 10 ng μL^{-1} in all experiments, while the initial concentration of cyclopropenone **1** varied from 0 to 5 mM. The duration of irradiation was sufficient to achieve at least 95% conversion of **1**, as was determined by HPLC. The irradiated and control solutions were incubated for 16 h at 25 °C in the dark and analyzed by gel electrophoresis. At concentrations above 0.1 mM, photo-generated enyne–allene **2** was found to induce *ca.* 15% single-strand cleavage of φX174 DNA (RF II), but no observable double-strand cleavage (RF III). A further increase in the concentration of precursor **1** results in the reduced photonuclease efficiency due to aggregation of the substrate. Incubation of the DNA with cyclopropenone precursor **1** in the dark does not induce any detectable DNA cleavage. The relatively low nuclease efficiency of **2** can be explained either by predominant polar cycloaromatization pathway or by the low affinity of **1** to a dDNA molecule. In order to address the latter problem, we are currently working on the design and synthesis of cyclopropenone **1** analogs containing a dDNA minor-groove binding moiety.

In summary, we have demonstrated that reactive cyclic enyne–allenes can be photochemically generated from thermally stable precursors with good quantum and chemical yields. The reactivity of benzannulated ten-membered ring enyne–allene **2** depends on the media. In solvents of low polarity products of the cycloaromatization reaction are consistent with the intermediate formation of a diradical species. In 2-propanol, on the other hand, the reactions apparently proceed *via* a polar mechanism.

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