Photoswitchable enediynes: use of cyclopropenone as photocleavable masking group for the enediyne triple bond†

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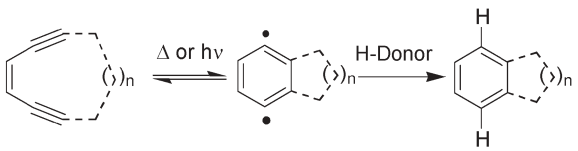
Cyclopropenone 1, 2,3-benzobicyclo[8.1.0]undec-1(10)-en-4-yn-11-one, is a thermally stable compound showing no signs of decomposition after heating at 84 °C for 7 d, UV irradiation of which results in an efficient (Φ_{300} = 0.45) and quantitative formation of benzannelated enediyne 2, which undergoes Bergman cyclization at the above temperature.

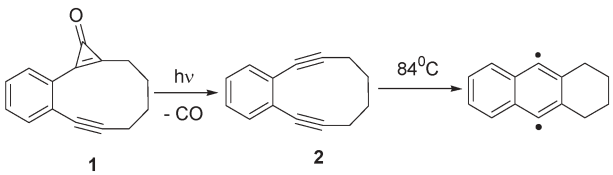
The thermal rearrangement of (*Z*)-3-ene-1,5-diynes to *p*-benzyne diradicals was first reported by Robert Bergman in 1972[1] and has become known as the Bergman cyclization (Scheme 1). This reaction was recently found to be responsible for the cytotoxicity of naturally occurring enediyne antibiotics.[2] The enediyne natural products are highly potent antineoplastic agents, but their clinical use is hampered by inadequate anti-tumor selectivity.[2] The cycloaromatization of enediynes is also employed in the development of selective nucleases[3] and high performance linear aromatic polymers for microelectronic fabrication.[4]



Scheme 1

The photochemical triggering of enediyne cycloaromatization is a very attractive idea as it allows for the spatial and temporal control of the Bergman cyclization. The direct irradiation of acyclic[5] and cyclic[6] enediynes, as well as the natural enediyne antibiotic Dynemicin A,[7] demonstrated that the Bergman cyclization can be triggered photochemically. The efficiency of the photochemical Bergman cyclization can be substantially improved by adjusting the electronic properties of substituents[8] and/or using different modes of excitation energy transfer, for example MLCT.[9] In addition, several caged enediynes have been prepared, which undergo conventional chemical activation after the photochemical uncaging step.[10]

Our group explores a strategy, which is alternative to the photo-Bergman cyclization: the *in situ* generation of reactive enediynes. We develop precursors, which are stable in the dark but efficiently produce enediynes upon irradiation. We decided to test the photochemical decarbonylation of the cyclopropenones[11] as the method for the generation of one of the enediyne triple bonds. Here we report the synthesis and photochemistry of cyclopropenone-containing enediyne precursor, 2,3-benzobicyclo[8.1.0]undec-1(10)-en-4-yn-11-one (**1**, Scheme 2).



Scheme 2

The π-system of the cyclopropenone moiety in the enediyne precursor compound **1** is orthogonal to the plane of the ring and, therefore, **1** cannot undergo cycloaromatization. Irradiation of cyclopropenone **1** is expected to result in decarbonylation and the formation of a triple bond, completing the enediyne system. The benzannelated enediyne **2** is relatively stable at room temperature, thus allowing us to separate photochemical enediyne generation and thermal Bergman cyclization steps of the process shown on Scheme 2. Substrate **2**, however, undergoes efficient cycloaromatization to give a *p*-benzene diradical at elevated temperature.[12]

Several synthetic methods are available for the preparation of the cyclopropenone group, which is the key moiety of the photoactivatable enediyne precursor **1**.[11,13] The modified Favorskii reaction of α,α′-dibromoketones gives dialkylcyclopropenones in moderate yields.[13a] A number of cyclopropenones were synthesized by alkylation or arylation of the parent cyclopropenone acetal,[13b] or by the reaction of trichlorocyclopropenium cation with arenes[13c–f] and alkenes,[13g] followed by controlled hydrolysis of the resulting dichlorocyclopropene. Dichlorocyclopropenes can also be prepared by the addition of dichlorocarbenes to corresponding alkynes, providing a short and efficient method for the introduction of the cyclopropenone functionality. The best yields of cyclopropenones are achieved using trichloromethyl lithium in THF at −78 °C followed by acidic hydrolysis at a low temperature.[14,15] In case of diynes, this procedure allows to avoid the formation of bis-adducts even in the presence of excess of the reagent.[16] Other methods for the *in situ* generation of dichlorocabenes often produce substantial amounts of by-products and low yields of a target compound.[17]

Masked enediyne **1** was prepared by the low temperature selective mono-addition of the dichlorocarbene to the 3,4-benzocyclodeca-1,5-diyne (**2**). The preparation of **2** started with the coupling of *o*-diiodobenzene with two equivalents of trimethylsilyl acetylene under Sonogashira conditions. The deprotection

† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of compounds **1–4**; ^{1}H, ^{13}C, and IR spectra for cyclopropenone **1**. See http://www.rsc.org/suppdata/cc/b4/b414951c/

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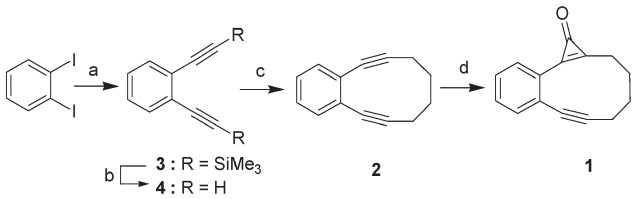

Scheme 3 Reagents and conditions: (a) $HCCSiMe_3$, $Pd(PPh_3)_2Cl_2$, CuI, PPh_3, Et_3N, THF, 40 °C; (b) K_2CO_3, MeOH, rt, 84% over two steps; (c) *n*-BuLi, $I(CH_2)_4I$, THF, rt, 40%; (d) $CHCl_3$, *n*-BuLi, THF, −78 °C, 67%.

of the resulting 1,2-bis(2′-trimethylsilyl ethynyl) benzene (**3**) was accomplished by treating the substrate with potassium carbonate in methanol to give 1,2-diethynyl benzene (**4**). The reaction of the dianion of **4** with of 1,4-diiodobutane in THF at −78 °C produced 3,4-benzocyclodeca-1,5-diyne (**2**) in a 67% yield (Scheme 3).

The reaction of benzannelated enediyne **2** with dichlorocarbene, followed by the hydrolysis in concentrated hydrochloric acid produced a target cyclopropenone-containing macrocycle, 2,3-benzobicyclo[8.1.0]undec-1(10)-ene-4yn-11-one (**1c**), in a 67% yield. It is interesting to note that benzannelated enediyne analog of **2**, which contains TBDMS-protected hydroxy group in propargylic position, is inert under these cyclopropanation conditions. We believe that this phenomenon can be explained by the high acidity of the propargylic proton The same very low reactivity towards dichlorocarbene was demonstrated by 6-methoxy-1-[2-[(trimethylsilyl)ethynyl]phenyl]hexyne and several other *ortho*-dialkynylbenzenes. We attribute the low reactivity of these substrates to steric effect of the *o*- substituent, since *m*-(1-pentynyl)anisole produces a good yield of corresponding cyclopropenone.

The enediyne precursor **1** is a surprisingly stable compound. No apparent changes were observed in the UV spectra of the cyclopropenone **1** even after heating for 7 d at 84 °C and the substrate was quantitatively recovered. The corresponding benzannulated enediyne **2**, on the other hand, undergoes Bergman cyclization with a half life time of 6 h at this temperature.[12]

The UV photolysis of 2,3-benzobicyclo[8.1.0]undec-1(10)-ene-4-yn-11-one (**1**) results in a rapid decarbonylation of the substrate quantitatively producing enediyne analog **2** (Fig. 1). Thus, irradiation of 2 mg of the cyclopropenone **1** for 20 min at 300 nm resulted in a complete conversion and the formation of

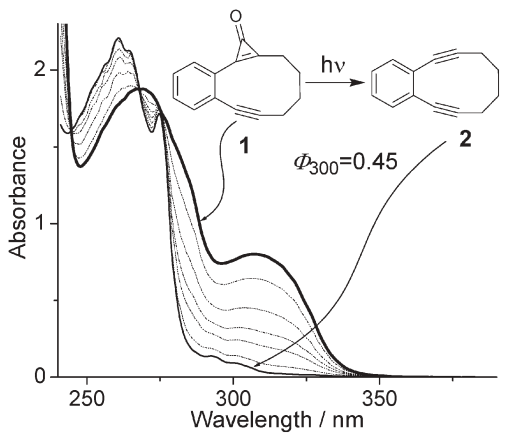

Fig. 1 UV spectra of 300 nm photolysis of *ca.* 5×10^{-4} M methanol solutions of cyclopropenone **1**. Spectra were recorded *ca.* every 1 min.

NMR-pure 3,4-benzocyclodeca-1,5-diyne (**2**). This photochemical reaction was also found to be quite efficient with a quantum yield at 300 nm of $\Phi_{300} = 0.45$ (in methanol).

In summary, we have shown the feasibility of the *in situ* activation of enediynes by the photochemical generation of one of the triple bonds. The cyclopropenone-containing enediyne precursor **1** does not undergo cycloaromatization even at elevated temperatures and survives prolonged heating without decomposition. UV irradiation of the substrate **1**, on the other hand, results in an efficient and clean decarbonylation reaction producing benzannulated enediyne **2**. The latter is known to undergo Bergman cyclization at 84 °C.

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