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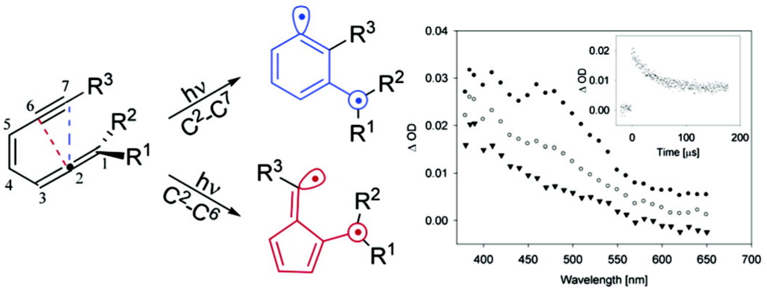

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Photochemical Myers−Saito and C^2-C^6 Cyclizations of Enyne−Allenes: Direct Detection of Intermediates in Solution

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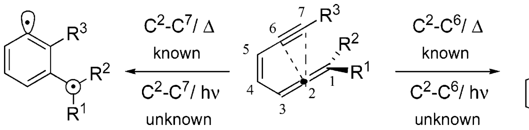
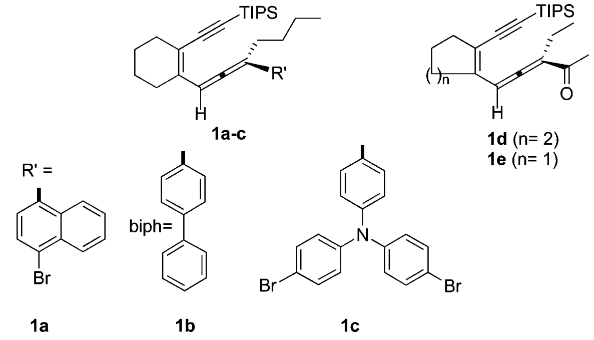
Natural enediyne antitumor antibiotics utilize two thermally triggered biradical cyclizations to ultimately damage DNA by hydrogen abstraction: the Bergman[1] and Myers−Saito[2] reaction. In recent years, photochemical analogues[3] of the Bergman cyclization[4] and alternative photochemically triggered enediyne[5] processes have attracted numerous research activities due to their potential applicability for photodynamic therapy (PDT).[6] In contrast, photochemical analogues of the Myers−Saito or the C^2-C^6 cyclization of enyne−allenes have remained a *terra incognita*.

To design photochemically ignitable enyne−allenes, we resorted to the recently described photochemical reactions of enyne−heteroallenes,[7] that is, enyne−carbodiimides and enyne−ketenimines, for some meaningful clues. These cyclizations occur very effectively along the C^2-C^6, but interestingly not along the C^2-C^7 (Myers−Saito) path. Theoretical studies by Engels[8] explained the preference for the C^2-C^6 route and suggested, as did our experimental results,[7] that the process is initiated by triplet sensitization. Moreover, for a photochemical enyne−allene cyclization to be successful, the study recommended to avoid benzannulated derivatives due to their high excitation energy.[8] Herein, we wish to illustrate that photochemical C^2-C^7 and C^2-C^6 cyclizations of enyne−allenes can be ignited when specially designed systems are used.

Scheme 1. Thermal and Photochemical Myers−Saito (C^2-C^7) and C^2-C^6 Cyclizations of Enyne−Allenes

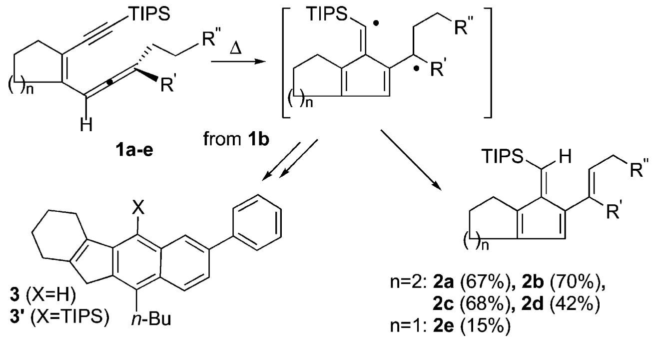


Scheme 2. Model Compounds **1a**−**e**



Enyne−allenes **1a**−**e** (Scheme 2) were composed along the input requirements: (i) avoid benzannulation, (ii) use cycloalkenes to prevent cis−trans isomerization, (iii) attach internal triplet sensitizer units as in enyne−heteroallenes[7] at position R′ (e.g., naphthalene, triphenylamine, and carbonyl groups), and (iv) use a TIPS group at the alkyne to raise the cyclization barrier and thus to avoid thermal reactions during photolysis.[9a]

As programmed, enyne−allenes **1** underwent thermal cyclization only at elevated temperatures (DSC[9b] results: **1a**, $T_{\mathrm{onset}} = 152$ °C; **1b**, $T_{\mathrm{onset}} = 135$ °C; **1c**, $T_{\mathrm{onset}} = 143$ °C; **1d**, $T_{\mathrm{onset}} = 151$ °C; **1e**, $T_{\mathrm{onset}} \approx 190$ °C [affected by polymerization]). In line with other enyne−allenes[10a−c] carrying bulky groups[10d] at the alkyne terminus, the thermal cyclization of **1a**−**e** furnished only C^2-C^6 products (i.e., **2a**−**e**) by a stepwise ene process. Formal Diels−Alder products[10c] were not formed except for trace amounts of **3** from **1b**. Loss of the TIPS group in **3** may be due to desilylation of the highly strained **3′** in the chromatographic process.[11]



All efforts to photocyclize **1a** in hexane or toluene were met with failure, most likely due to the low triplet energy (E_T) of bromonaphthalene ($E_T = 59$ kcal mol^{-1}),[12] suggesting to go to stronger internal triplet sensitizers. Indeed, irradiation of **1b** (R′ = biphenyl; $E_T = 65.0$ kcal mol^{-1})[12] in toluene at 300 nm in the presence of 1,4-cyclohexadiene led to photocyclization (Table 1) revealing both the C^2-C^6 product **3** (12%) and the Myers−Saito product **4** (24%). Their structures were confirmed using NMR techniques and also by spectral comparison of **4** with independently synthesized **6**. **4** and **6** showed a characteristic triplet for the benzhydrylic hydrogen at ∼3.8 ppm ($^3J \sim 7.5$ Hz). Notably, calculations[8] predicted parallel formation of both Myers−Saito and C^2-C^6 products via triplet excitation of simple enyne−allenes, although with a preference for C^2-C^6 products.

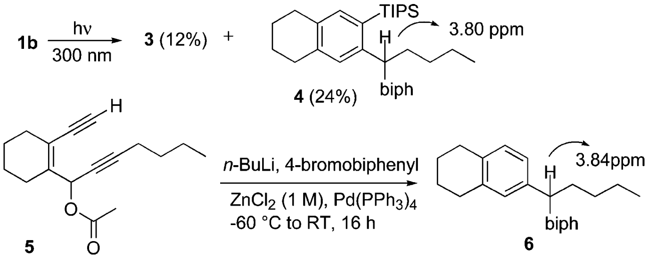


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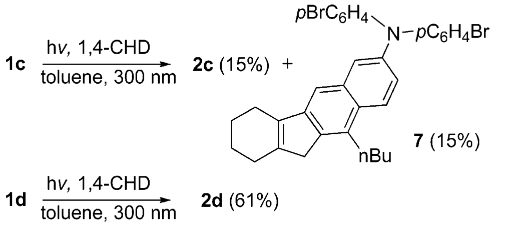
Table 1. Yields of Photochemical Myers−Saito (C^2-C^7)and C^2-C^6 Cyclization Products (1,4-CHD: 1,4-cyclohexadiene) at 17 ± 2 °C

compound (conc)	solvent (irradiation time)	λ_{max}/nm (in hexane)	C^2-C^6 products (yield)	C^2-C^7 products (yield)
1a (1.78 mM)	toluene + 1,4-CHD[a] (6 h)	283, 300		
1b (1.96 mM)	toluene + 1,4-CHD[a] (7 h)	290, 300 (sh)	**3** (12%)[b]	**4** (24%)[b]
1c (1.36 mM)	toluene + 1,4-CHD[a] (6 h)	320	**2c** (15%) + **7** (15%)[c]	
1d (5.28 mM)	2:1 hexane/1,4-CHD (14 h)	277, 290 (sh)	**2d** (32%)[d]	
1d (5.28 mM)	2:1 hexane/1,4-CHD (4 h)	277, 290 (sh)	**2d** (61%)[e]	
1e (7.29 mM)	toluene + 290 equiv of 1, 4-CHD (22 h)	282, 296	**2e** (7%)[c]	

[a] 100-fold amount of 1,4-CHD compared to **1**. [b] Isolated yield based on **1b**. [c] Isolated yield. [d] Isolated yield based on **1d**: 75:25 mixture of **2d** and a geometrical isomer. [e] Yield based on **1d** after 4 h (18% conversion).

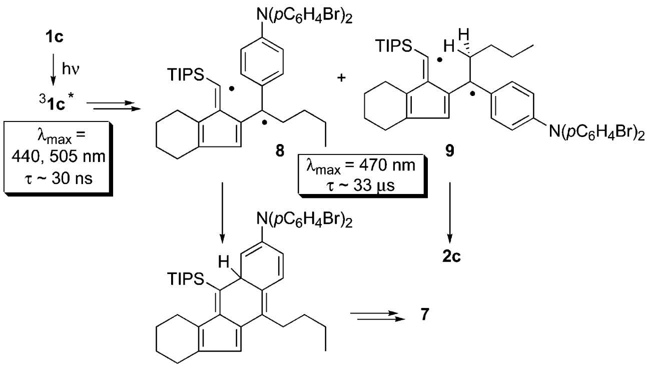
In contrast to that of **1b**, the photochemical reaction of **1c**−**d** provided only C^2-C^6 products. Irradiation of **1c** at 300 nm furnished a 1:1 mixture of **2c** and **7**. The latter is again a formal Diels−Alder product that lost a TIPS group.[11] Irradiation of **1d** under analogous conditions afforded **2d** in 32% yield after isolation as a mixture of cis−trans isomers. Due to the photolability of **2d**, the reaction was studied at low conversion (18%). Now, **2d** was the sole isolable product in 61% yield. Due to ring strain effects,[13] we had originally expected that photolysis of cyclopentenyne−allene **1e** could be directed toward the Myers−Saito pathway, but again a C^2-C^6 product (i.e., **2e**) was furnished (Table 1).



A laser flash photolysis (LFP) study of **1c** (excitation at 355 nm) revealed the existence of two transients. The first one (λ_{max} = 440 and 505 nm) with a decay rate constant $k = (3 \pm 1) \times 10^7\ s^{-1}$ ($\tau \sim 30$ ns) was quenched by $^3O_2$ at a diffusion-controlled rate. Its absorption maximum at 505 nm is actually typical for a triplet state of triphenylamine derivatives.[14] Hence, we assigned this transient to ^{3}**1c***. The second transient (λ_{max} = 470 nm) exhibited a lifetime $\tau = 33 \pm 5\ \mu s$ with $k = (3.0 \pm 0.4) \times 10^4\ s^{-1}$. Stern−Volmer quenching of the long-lived transient by $^3O_2$ indicated that ^{3}**1c*** is a precursor. Since the long-lived transient itself did not react with $^3O_2$, nBu$_3$SnH, and by 1,4-cyclohexadiene, we assigned it to the singlet biradical. Due to a high barrier (ca. 16 kcal mol^{-1}),[15] it should exist as two noninterconverting rotamers (**8** and **9**), whose ratio is reflected in the product ratio **7**/**2c**. After the decay of the long-lived transient, a residual broad absorption band remained that coincided largely with that of **2c**.

It is interesting to see that the products of the photocyclization of cyclohexenyne−allenes **1a**−**d** are related to the triplet energies of the substituents R′. Hence, with a triplet energy of about 59 kcal mol^{-1}, as in **1a**, no photocyclization occurred, whereas cyclization was seen with **1b** containing a biphenyl (E_T = 65.0 kcal mol^{-1}),[12] remarkably, mostly toward the Myers−Saito pathway. With even higher triplet energies (E_T: triphenylamine, 70 kcal mol^{-1}; ketone, 80 kcal mol^{-1})[12] of groups R′, the photocyclization exclusively furnished C^2-C^6 products.

To summarize, we have realized the first photochemical Myers−Saito and C^2-C^6 cyclizations of enyne−allenes. The presence of a triplet sensitizing unit at the allene terminus and the LFP results suggest that the cyclization proceeds along the triplet manifold as predicted by DFT calculations.[8] An intermediate with $\tau = 33 \pm 5$ μs was tentatively assigned to a singlet biradical. Further studies to elucidate the details of the photochemical initiation for enyne−allenes and other Cope-type[16] cyclizations are underway.



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Supporting Information Available: Experimental procedures, ^{1}H, ^{13}C spectra for all compounds, and LFP results. This material is available free of charge via the Internet at http://pubs.acs.org.

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