Pergamon

Tetrahedron Letters 39 (1998) 6923-6926

TETRAHEDRON
LETTERS

Multiple Cycloaromatization of Novel Aromatic Enediynes Bearing a Triggering Device on the Terminal Acetylene Carbon

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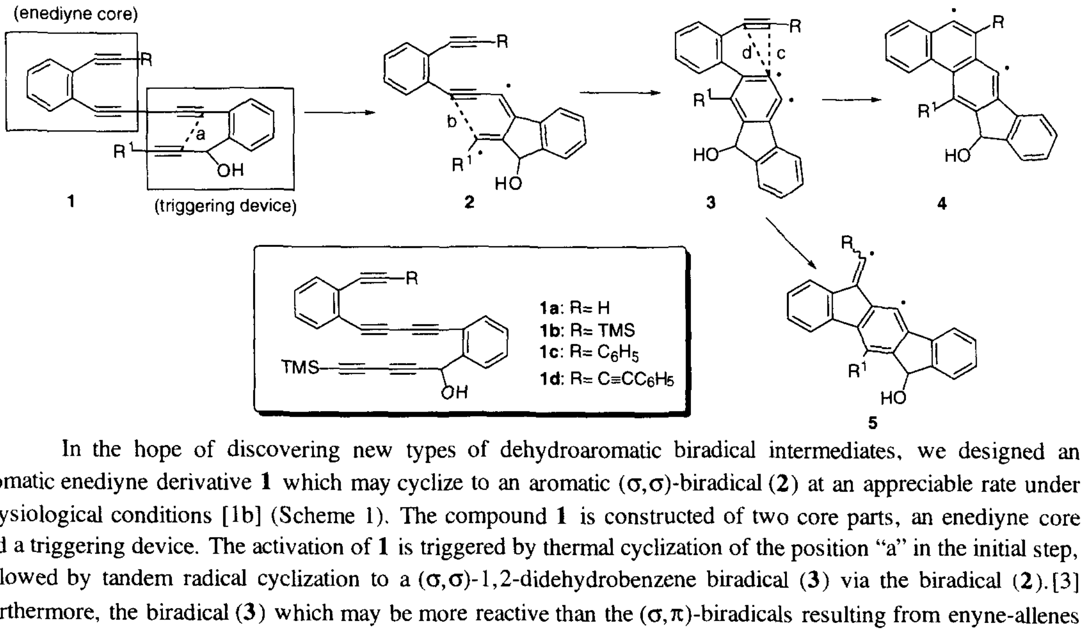
Received 5 June 1998; revised 2 July 1998; accepted 10 July 1998

Abstract: Aromatic enediynes (**1**) bearing a triggering device on the terminal acetylene carbon undergo thermal cyclization at 25 °C to yield polyphenylene ring systems (**6**, **9**, **13**, and **15**(**16**)) giving radical intermediates, dehydrobenzene monoradical (**12**) and didehydrobenzene biradicals (**4** and **14**) which may serve as a DNA-cleaving reagent.

Since the disclosure of the spectacular structures and mode of action of the natural enediyne antitumor antibiotics, much current research has been directed toward two areas: one involves the preparation of simple model compounds with analogous antitumor and antibiotic activity [1], and the other involves the synthesis of new types of polycyclic ring systems by a combination of biradical cyclization protocols and subsequent radical cyclization.[2]

Scheme 1.



In the hope of discovering new types of dehydroaromatic biradical intermediates, we designed an aromatic enediyne derivative **1** which may cyclize to an aromatic (σ,σ)-biradical (**2**) at an appreciable rate under physiological conditions [1b] (Scheme 1). The compound **1** is constructed of two core parts, an enediyne core and a triggering device. The activation of **1** is triggered by thermal cyclization of the position "a" in the initial step, followed by tandem radical cyclization to a (σ,σ)-1,2-didehydrobenzene biradical (**3**) via the biradical (**2**).[3] Furthermore, the biradical (**3**) which may be more reactive than the (σ,π)-biradicals resulting from enyne-allenes

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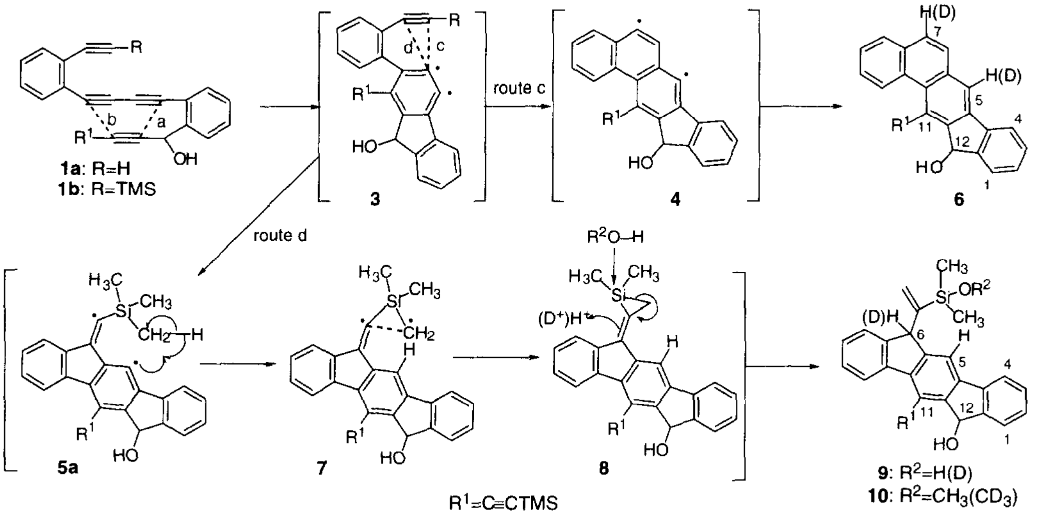
PII: S0040-4039(98)01454-3

(the Myers-Saito[4] and the Schmittel[5] cyclizations) undergoes thermal radical cyclization to yield two types of (σ,σ)-biradicals (**4** and **5**). These radical species will be transformed to the final products. We report herein the thermal behavior of **1**, the cyclization of which is the first example of generation of an aromatic 1,2-diyl which reacts with an acetylene bond to yield an aromatic ring system.

Compounds **1a-d** were synthesized from the corresponding benzaldehydes and commercially available 1,4-bis(trimethylsilyl)-1,3-butadiyne by a similar method to that described in the previous paper.[3]

Thermolysis of **1a** (50 mM, 25 °C, 121 h) in benzene in the presence of 1,4-cyclohexadiene (10 equiv.) resulted in triple cycloaromatization to afford **6**[1] along with a large amount of charcoal-like materials (Scheme 2). Despite extensive efforts we have been unable to increase the yield of **6** above about 10%. Thermolysis of methanol-d_4 led to the formation of **6**-d_2 containing deuterium atoms exclusively in the 5- and 7-positions (>55% by ^{2}H-NMR spectrometry).

Scheme 2.



Thermolysis of **1b** (50 mM, 25 °C, 85 h) in wet benzene afforded a mixture of diastereoisomers (**9a**; 18% and **9b**; 16%)[1] in a total yield of 34%.

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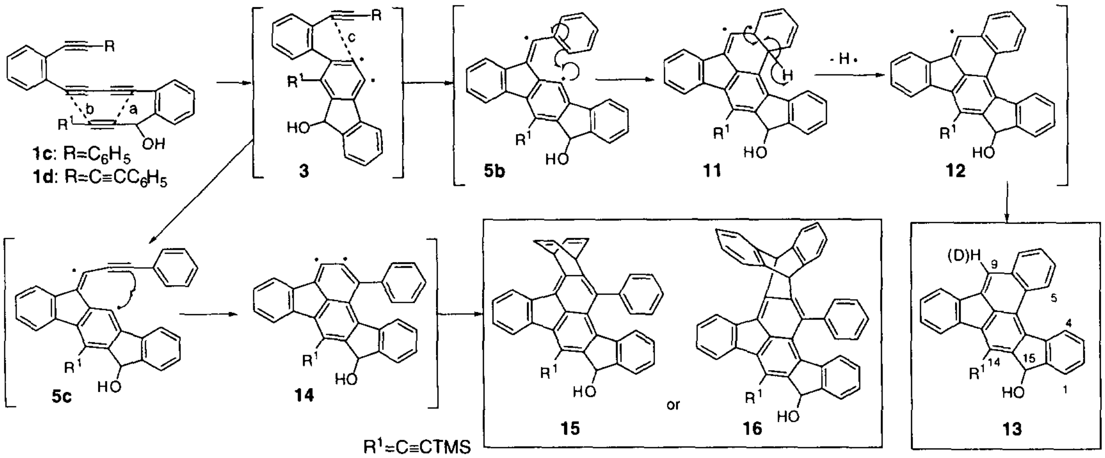
[1] **6**: Colorless needles (hexane/CH_2Cl_2); mp 93.5-94.7 °C; IR (KBr) 3530, 3430, 2140 cm^{-1}; UV ($CHCl_3$) λ max (log ε) 383 (3.8), 365 (3.8), 334 (4.4), 320 (4.5), 298 (4.9), 286 (4.8), 238 (4.5) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40-10.36 (m, 1H), 8.12 (s, 1H), 7.94-7.89 (m, 1H), 7.81 (d, *J*=7.1 Hz, 1H), 7.78 (s, 2H), 7.76 (d, *J*=7.3 Hz, 1H), 7.66-7.62 (m, 2H), 7.47-7.46 (m, 1H), 7.44-7.40 (m, 1H), 6.05 (d, *J*= 2.7 Hz, 1H), 3.86 (d, *J*= 2.9 Hz, 1H), 0.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 144.7, 138.9, 138.1, 133.9, 133.0, 131.0, 129.2, 129.1, 128.6, 128.4, 128.2, 127.6, 126.8, 126.0, 125.7, 125.6, 120.6, 120.5, 115.4, 106.5, 105.3, 75.0, -0.3; MS (Fab) m/z 378 (M$^+$); *Anal.* Cald for $C_{26}H_{22}OSi$: C, 82.50; H. 5.86%. Found: C, 82.30; H, 5.68%. **9a**: R_f=0.49 [(5:1) benzene-EtOAc]; Colorless powders (benzene); mp 196.3-196.6 °C; IR (KBr) 3320, 2160 cm^{-1}; UV ($CHCl_3$) λ max (log ε) 357 (4.3), 342 (4.2), 313 (4.6), 300 (4.5), 273 (4.5), 263 (4.4), 253 (4.5), 228 (4.6) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J*= 7.6 Hz, 1H), 7.70-7.65 (m, 3H), 7.46-7.33 (m, 5H), 6.22 (d, *J*= 2.7 Hz, 1H), 5.89 (d, *J*= 2.7 Hz, 2H), 4.64 (s, 1H), 3.21 (d, *J*= 3.7 Hz, 2H), 0.88 (s, 1H), 0.43 (s, 9H), -0.31 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 148.5, 148.2, 147.0, 144.8, 140.4, 140.3, 139.5, 139.3, 130.7, 129.0, 128.3, 127.9, 127.5, 127.4, 125.3, 125.1, 122.5, 120.0, 117.3, 112.8, 104.7, 101.3, 74.3, 57.1, 0.9, 0.7, -0.1; MS (Fab) m/z 466(M$^+$). *Anal.* Cald for $C_{29}H_{30}O_2Si_2$: C, 74.63; H, 6.48%. Found: C, 74.82; H, 6.30%. **9b**: R_f=0.40 [(5:1) benzene-EtOAc]; Colorless powders (benzene); mp 217.8-219.2 °C; IR (KBr) 3300, 2152 cm^{-1}; UV ($CHCl_3$) λ max (log ε) 357 (4.3), 342 (4.2), 3.13 (4.5), 300 (4.5) 272 (4.5), 263 (4.4), 253 (4.5), 227 (4.6) nm ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J*= 7.6 Hz, 1H), 7.70-7.66 (m, 3H), 7.46-7.34 (m, 5H), 6.21 (d, *J*= 2.9 Hz, 1H), 5.90 (d, *J*= 2.7 Hz, 1H), 5.88 (d, *J*= 3.9 Hz, 1H), 4.63 (s, 1H), 3.18 (d, *J*= 3.9 Hz, 1H), 0.91 (s, 1H), 0.43 (s, 9H), -0.30 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 148.5, 148.4, 147.1, 144.9, 140.4, 140.4, 139.3, 130.8, 129.1, 128.3, 128.0, 127.5, 127.4, 125.3, 125.1, 122.5, 120.0, 117.3, 112.9, 104.8, 101.3, 74.4, 57.3, 0.9, 0.8, -0.1; MS (Fab) m/z 464 [(M-2H)$^+$]. *Anal.* Cald for $C_{29}H_{30}O_2Si_2$: C, 74.63; H, 6.48%. Found: C, 74.38; H, 6.21%.

Thermolysis of **1b** in benzene containing 90% deuterium oxide (100 mM) under the same conditions afforded a diastereomixture (**9a**-d_1 and **9b**-d_1) deuterated at the 6-position in 28% yield (Scheme 2). Compound **9** deuterated at the 5-position was not detected in these reactions, indicating that the hydrogen atom abstraction of **5a** may be an intramolecular reaction. Thermolysis in dry benzene in the presence of molecular sieves 4Å afforded only unidentified decomposition materials. A proposed mechanism for the unprecedented radical cyclization of **1b** is illustrated in Scheme 2. Biradical intermediate (**5a**) yielded by triple cycloaromatization of **1b** is converted to a key intermediate (**8**) via **7**, which is generated by intramolecular hydrogen atom abstraction of the biradical **5a** from the methyl group on the trimethylsilyl moiety. Nucleophilic attack at the silicon atom of **8** with water and methanol affords the final products (**9** and **10**).

As seen in Scheme 3, thermolysis of **1c** (50 mM, 25 °C, 65 h) in benzene afforded **13**[2] in 27% yield. Thermolysis in benzene containing 2-propanol-d_8 led to the formation of **13**-*d* containing a deuterium atom exclusively in the 9-position (>85% by ^{2}H-NMR spectrometry). Thermolysis of **1d** (50 mM, 25 °C, 48 h) in benzene resulted in quartet cycloaromatization to afford **15**[2] in 60% yield. Thermolysis in benzene in the presence of anthracene (20 equiv.) as 1,2-dehydrobenzene biradical trapping agent led to a Diels-Alder-type adduct (**16**) in 63% yield.

Scheme 3.



In summary, a new method for ring annulation has been developed by using the 1,2-diyl as a radical precursor for further radical cyclization into polycyclic ring systems. It has been shown that the cyclization proceeds with a sterically demanding functionality in the second acetylenic position.[5] The finding that multiple

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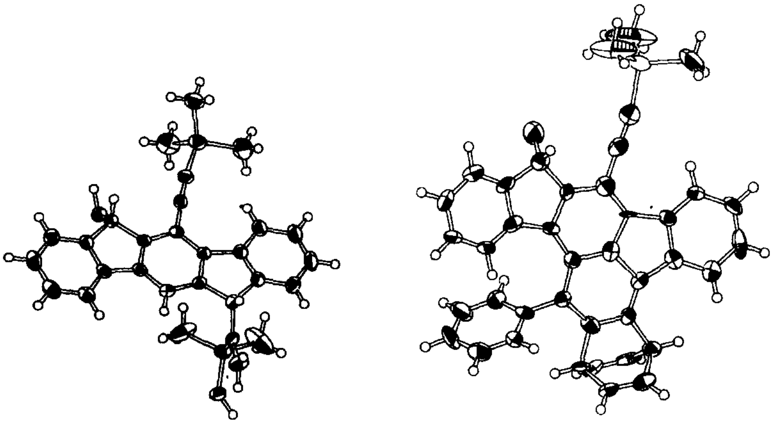
[2] **13**: Yellow powders (hexane/CH_2Cl_2); mp 86.3-87.2 ℃; IR (KBr) 3560, 2150 cm^{-1}; UV ($CHCl_3$) λ max (log ε) 410 (4.2), 389 (4.2), 342 (4.3), 316 (4.6), 305 (4.6), 294 (4.6), 260 (4.7) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01-8.99 (m, 1H), 8.37-8.31 (m, 2H), 7.98 (s, 1H), 7.90-7.88 (m, 1H), 7.84-7.80 (m, 1H), 7.77-7.73 (m, 1H), 7.58-7.51 (m, 2H), 7.40-7.33 (m, 4H), 5.92 (d, J= 1.7 Hz, 1H), 3.53 (d, J= 2.9 Hz, 1H), 0.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 146.0, 140.5, 139.3, 138.7, 137.0, 136.0, 135.0, 134.4, 134.2, 130.0, 130.0, 128.3, 128.2, 127.7 (x3), 127.4, 125.7, 125.2, 125.1, 123.9, 123.1, 122.3, 121.5, 111.8, 105.5, 101.5, 74.6, -0.1; MS (Fab) m/z 452 (M^+); *Anal.* Cald for $C_{32}H_{24}OSi$: C, 84.92; H, 5.34%. Found: C, 84.65; H, 5.35%. **15**: Yellow plates (benzene); mp 265.3-267.8 ℃ (dec.); IR (KBr) 3500, 2250 cm^{-1}; UV ($CHCl_3$) λ max (log ε) 409 (4.3), 380 (4.3), 328 (4.3), 302 (4.7), 249 (4.7) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55-8.53 (m, 1H), 8.28 (d, J= 7.1 Hz, 1H), 7.57-7.40 (m, 7H), 7.34 (d, J= 7.3 Hz, 1H), 7.07 (t-like, J= 7.5 Hz, 1H), 7.08-6.96 (m, 2H), 6.88-6.85 (m, 1H), 6.82-6.78 (m, 1H), 6.68 (t-like, J= 7.8 Hz, 1H), 5.96 (t, J= 5.9 Hz, 1H), 5.84 (d, J= 3.2 Hz, 1H), 5.60 (d, J= 8.1 Hz, 1H), 5.17 (t, J= 6.1 Hz, 1H), 3.56 (d, J= 3.4 Hz, 1H), 0.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.1, 145.0, 142.0, 140.9, 140.3, 139.4, 139.2, 139.0, 138.7, 138.3, 138.2, 137.5, 137.0, 132.3, 132.2, 131.5 (x2), 128.9 (x2), 127.9, 127.8, 127.6, 127.2, 126.3, 125.5, 124.0, 123.8, 123.3, 122.9, 111.8, 105.7, 101.8, 74.3, 46.2, 45.0, -0.1; MS (Fab) m/z 554 (M^+). *Anal.* Cald for $C_{40}H_{28}OSi$: C, 86.60; H, 5.45%. Found: C, 86.32; H, 5.17%.

cycloaromatization of **1** proceeds at 25 °C, yielding an active arene radical species (**4**, **12** and **14**), may potentially serve to increase our fundamental knowledge for the design of artificial enediyne parts and to widen the range of enyne-type DNA-cleaving reagents to systems that have not previously been available. Studies on structure-radical formation relationships and biological properties are in progress.

Structure assignment: All new compounds in this paper gave satisfactory IR, NMR, Mass spectra and elementary analyses. The structure of **9b** and **15** was confirmed by X-ray crystal analysis. The ORTEP drawings of both compounds are shown in Figure 1.[3)] Finally, the structure of **6**, **13** and **16** was determined by comparing their NMR spectal data with that of **15**.



9b **15**

Figure 1. The ORTEP drawings of **9b** and **15**.

Acknowledgments

The authors are indebted to the Material Analysis Center of ISIR-Sanken for the elementary analyses. This work was supported in part by a Grant-in-Aid for The Joint Research between the Institute for Protein Research and the Institute of Scientific and Industrial Research, Osaka University, from the Ministry of Education Science, Sports and Culture.

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[3] The crystal data for **9b** (R=H): Crystal dimensions= 0.35x0.43x0.35 mm, Triclinic, Space group P-$\bar{1}$ (no. 2), a=11.554 (6)Å, b=13.058(4)Å, c=11.087(5)Å, α=98.21(3)°, β=100.28(4)°, γ=95.12(3)°; V=1617(1)Å^3; Z=2; F(000)=972; D_{calc} 1.879 g/cm^3; The final R and R_w were 0.062 and 0.069 for 4770 observed reflections (I>3.00 (σ) I). The crystal data for **15**: Crystal dimensions=0.43x0.63x0.20 mm, Monoclinic, Space group P2$_1$/a (no. 14), a=11.559 (7)Å, b=19.125(4)Å, c=16.021(4)Å, β=91.537(9)°; V=3540(1) Å^3; Z=4; F(000)=1336; D_{calc} 1.187 g/cm^3; The final R and R_w were 0.073 and 0.082 for 3368 observed reflections (I>3.00 (σ) I). The structure was solved by direct method (SIR92) and refined by full-matrix least-squares techniques. Diffraction data were obtained using Rigaku AFC5R diffractometer at -75°C for **9b** and using Rigaku RAXIS-IV imaging plate area detector at 15°C for **15**.