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pH Dependent Cycloaromatization of Enediyne Model Compounds *via* γ-Oxo Ketene Acetal Intermediates

Ichiro Suzuki,[a] Yoshimitsu Naoe,[a] Masahiko Bando,[b] Hisao Nemoto,[a] and Masayuki Shibuya[a]*

[a] Faculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1, Tokushima 770-8505, Japan

[b] Analytical Chemistry, 2nd Tokusima Institute of New Drug Research, Otsuka Pharmaceutical Co., Ltd., 463-10 Kagasuno, Kawauchi-cho, Tokushima 771-0192, Japan

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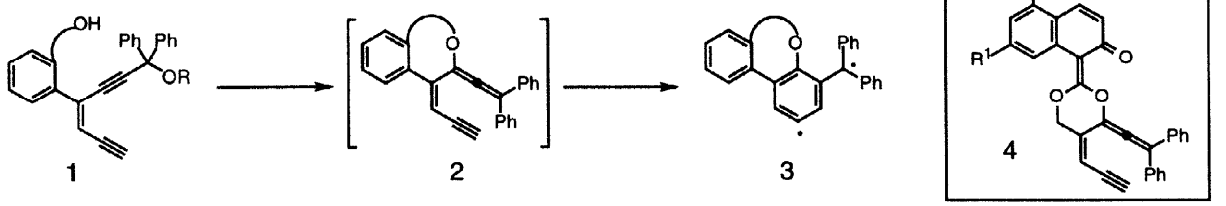
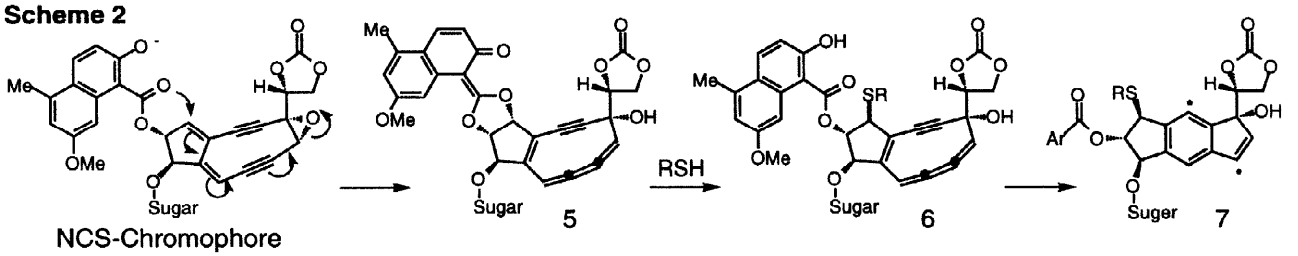
Abstract: The Myers-Saito-type cyclizations of enediyne derivatives *via* γ-oxo ketene acetal intermediates generated by the neighboring group participation of naphthoate ester groups in acidic media are described.

Various acyclic (*Z*)-1,2,4-heptatrien-6-ynes, which undergo cycloaromatization to produce reactive dehydrotoluene biradicals (Myers-Saito-type cyclization),[1] have been investigated as chemical models for a class of potent antitumor antibiotics, neocarzinostatin (NCS).[2] The preparation of enyne-allene models possessing characteristic triggering devices which initiate the generation of dehydrotoluene biradicals is a challenging current problem.[3] Recently, we reported that the *cis*-enediyne derivative **1** generates the toluene biradical **3** *via* the fixed s-*cis*-enyne-allene intermediate **2** by means of intramolecular triggering action of the hydroxy group under acidic conditions (**Scheme 1**).[4] For further development of this class of cascade reaction, we describe here the Myers-Saito-type cyclization *via* γ-oxo ketene acetal intermediates **4** generated by the neighboring group participation of the naphthoate ester moieties of enediyne derivatives in acidic media. Similar "anchimeric" assistance by the naphthoate ester moiety affording γ-oxo ketene acetal **5** was proposed by Fuchs as a potential intermediate in the conversion of NCS-chromophore to cumulene **6** which ultimately produces biradicals **7** (**Scheme 2**)[5], and Hirama[6] reported the photo-induced cycloaromatization *via* naphthoate participation.

Scheme 1

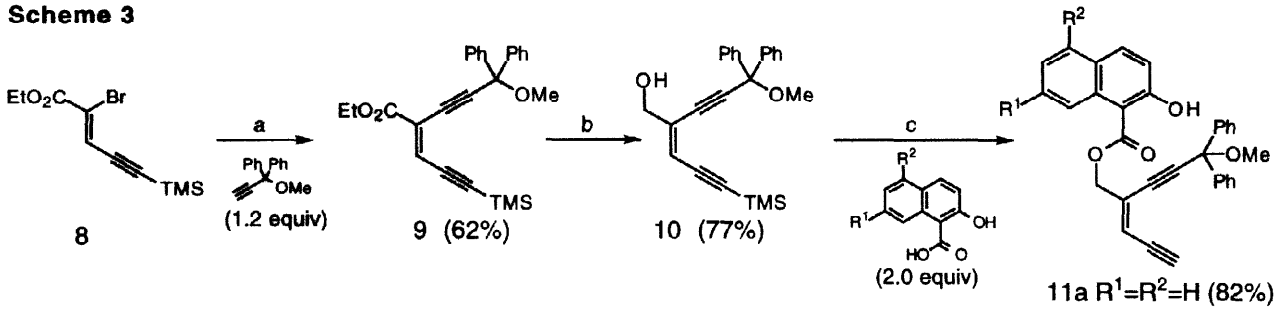


Scheme 2



PII: S0040-4039(98)00200-7

Scheme 3

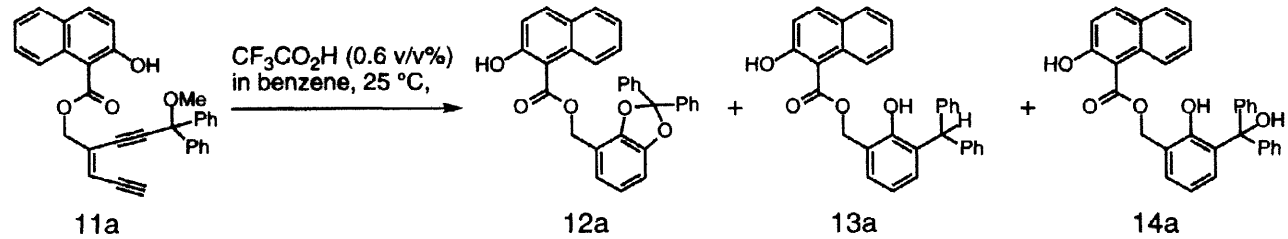


(a) $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.2 equiv), *n*-$PrNH_2$ (1.8 equiv), toluene, 60 °C; (b) DIBAL (2.1 equiv), THF, -78°C; (c) i) EDC (4.0 equiv), CH_2Cl_2, rt, ii) $(n\text{-}C_4H_9)_4NF$ (1.0 equiv), THF, 0°C

For typical examples, we synthesized the naphthoate ester **11a** as well as the ester **11b** having the α-hydroxy naphthoate moiety in NCS. Synthesis of naphthoate esters **11a,b** (**Scheme 3**) started with the known (Z)-bromoenyne **8**[7] which was condensed with 1-methoxy-1,1-diphenyl-2-propyne to give the enediyne **9**. Alcohol **10** was obtained by reduction of ester **9** with excess diisobutylaluminum hydride. A naphthoate group was introduced by the reaction of **10** with 2-hydroxy-1-naphthalenecarboxylic acid or 2-hydroxy-7-methoxy-5-methyl-1-naphthalenecarboxylic acid[8] in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and subsequent desilylation with tetra-*n*-butylammonium fluoride to afford the desired naphthoate esters **11a** and **11b**, respectively.

The reaction of naphthoate **11a** with trifluoroacetic acid (0.6 v/v%) in the presence of 1,4-cyclohexadiene (50 equiv) in benzene at room temperature afforded a mixture of several products from which diphenyl acetal **12a** (10% yield), the diol **13a** (5% yield) and the triol **14a** (28% yield) were isolated (**Scheme 4**). The structures of **12a**[9] and **14a**[10] were determined by X-ray crystallographic analysis (**Figure 1 and 2**), and the structure of **13a** was assigned by comparing its spectral data with those of **12a** and **14a**. These results suggest that the enediyne **11a** proceeded *via* an acid-catalyzed reaction to the enyne-allene intermediate followed by subsequent Myers-Saito-type reaction to form cyclized products. In order to examine the formation pathways of these products, particularly of the unusual acetal **12a**, we conducted the reaction in a degassed solvent as well as in oxygen atmosphere (**Table 1**). When the reaction of **11a** was carried out in a degassed solvent, the acetal

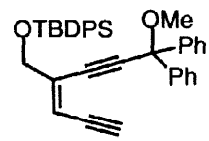
Scheme 4



11a 12a 13a 14a

Table 1 **Acid-catalyzed cyclization of naphthoates 11a and 11b [CF_3CO_2H (0.3 v/v%), cyclohexadiene (50 equiv), benzene, 25°C].**

Compound	Conditions	Reaction Time	Products (Yield)
11a	under Ar	14 h.	**13a** (7%), **14a** (24%)
11a	under O_2	24 h.	**12a** (65%)
11b	under Ar	15 min.	**14b** (14%)
11b	under O_2	30 min.	**12b** (55%)



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12a was not detected in the products. On the other hand, the reaction under oxygen atmosphere afforded **12a**, but not **13a** or **14a**. While the reactions of **11a** required more than 14 h at 25 °C, "NCS-model" **11b** reacted within 0.5 h under similar conditions. The latter reaction gave a more intricate mixture, from which **14b** (under Ar) and **12b** (under O_2) could be isolated. Compound **15**, when subjected to similar reaction conditions as shown in **Table 1**, was recovered unchanged under both aerobic and anaerobic conditions.

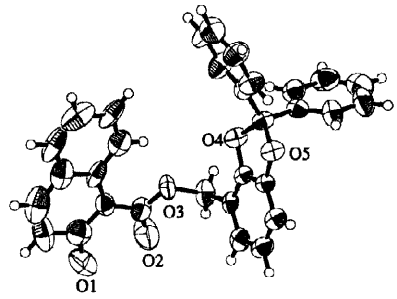


Figure 1. ORTEP Drawing of **12a**

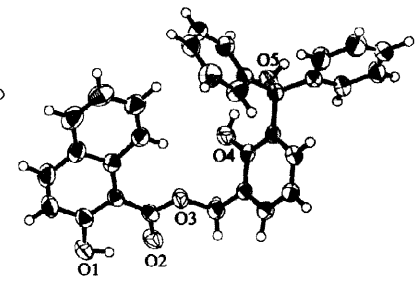
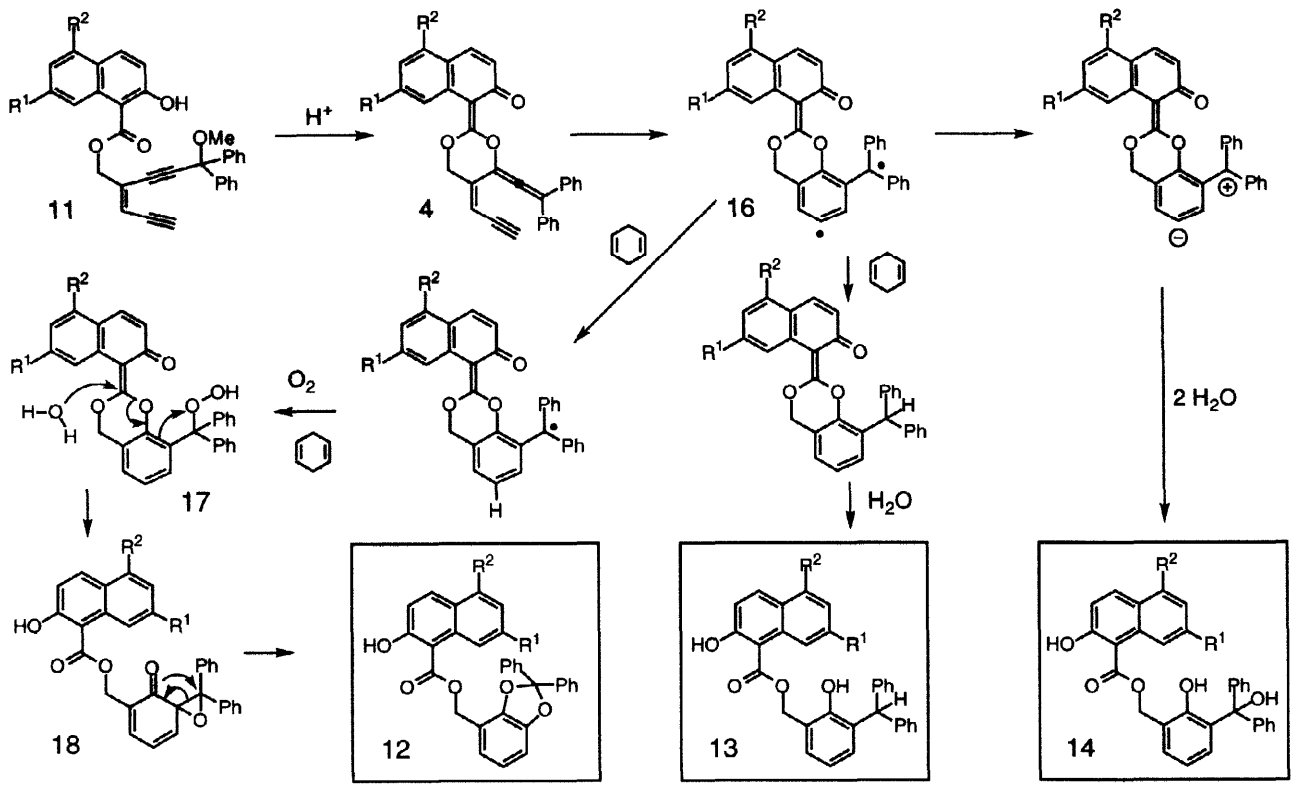


Figure 2. ORTEP Drawing of **14a**

These results strongly suggest the naphthoate participation and incorporation of molecular oxygen into the acetals **12a,b**. Thus, we propose the following mechanism for these cycloaromatization reactions as represented in **Scheme 5**. In the first step, the naphthoate migration to acetylenic carbon with the concomitant elimination of the methoxy group is likely to occur in acidic media. The γ-oxo ketene acetal intermediates **4**[11] thus formed should undergo the cycloaromatization to give the biradical intermediates **16**. Under anaerobic conditions, **16** would be converted into diol **13** by hydrogen abstraction from cyclohexadiene, followed by the addition of adventitious water or by hydrolysis under work-up conditions. Alternatively, biradicals **16** would be transformed into triol **14** *via* the ionization process.[12] When the reactions were carried out under oxygen atmosphere, hydrogenperoxy intermediates **17** would be formed by hydrogen abstraction, followed by molecular oxygen incorporation. Addition of water or trifluoroacetic acid to the ketene acetal **17** should

Scheme 5



provide **12** *via* the epoxy intermediates **18**. The final rearrangement pathway is similar to that of the well-known phenol synthesis from cumene hydroperoxide under acidic conditions.[13] The relatively fast reaction of **11b** compared with **11a** is presumably due to the presence of electron-releasing substituents on its naphthalene ring.

In summary, this study demonstrates that the naphthoate ester derivatives of *Z*-hex-3-ene-1,5-diyne can be used to generate biradicals *via* the γ-oxo ketene acetal intermediate. Studies on the analogues of this class of compounds and development of bio-active enediynes are continuing.[14]

References and Notes

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9) X-Ray analysis of **12a**: $C_{31}H_{22}O_5$, Mr=474.51, triclinic, space group $P\bar{1}$, a=11.654(4)Å, b=12.230(4)Å, c=8.827(3)Å, α=108.64(2)°, β=95.13(3)°, γ=98.03(3)°, V=1168(7)Å^3, Z=2, Dc=1.349g/cm^3, F(000)=496 and μ=0.850cm^{-1}. Final R and Rw factors are 0.067 and 0.098, respectively.
10) X-Ray analysis of **14a**: $C_{31}H_{24}O_5$, Mr=476.53, triclinic, space group $P\bar{1}$, a=11.282(7)Å, b=11.489(8)Å, c=11.14(1)Å, α=117.37(6)°, β=110.79(5)°, γ=91.59(6)°, V=1167(2)Å^3, Z=2, Dc=1.356g/cm^3, F(000)=500 and μ=0.914cm^{-1}. Final R and Rw factors are 0.047 and 0.062, respectively.
11) Intermediate **4** is tentatively shown for the purposes of simplicity, since MM2 calculations (Macro Model V. 4.5) of **11** leading to **4** is more stable by 4.18 kJ/mol. over that leading to the other geometrical isomer.
12) Shibuya, M.; Wakayama, M.; Naoe, Y.; Kawakami, T.; Ishigaki, K.; Nemoto, H.; Shimizu, H.; Nagao, Y.; *Tetrahedron Lett.*; **1996**, *37*, 865-868.
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14) Selected data, **12a**: Colorless needles; mp 129-131 °C; IR($CHCl_3$) 3026, 1650, and 1468 cm^{-1}; ^{1}H-NMR(200MHz, $CDCl_3$): 12.28(1H, s), 8.80(1H, m), 7.90(1H, d, J = 9.0), 7.74(1H, m), 7.60-7.20(12H, m), 7.17(1H, d, J = 9.0), 6.99(1H, dd, J = 7.0 and 1.8), 6.91(1H, dd, J = 7.0 and 1.8), and 6.86(1H, t, J = 7.0), and 5.63(2H, s); MS(FAB): m/z calcd. for $C_{31}H_{23}O_5$: 475.1545(M^++H). found: 475.1496. **13a**: Yellow foam; IR($CHCl_3$) 3515, 3354, 3063, 3029, and 1635 cm^{-1}; ^{1}H-NMR(200MHz, $CDCl_3$): 11.83(1H, s), 8.73(1H, d, J = 9.0), 7.91(1H, d, J = 9.0), 7.75(1H, d, J = 8.0), 7.52(1H, ddd, J = 8.0, 7.0, and 1.0): 7.45-7.05(14H, m), 6.89(2H, d, J = 5.0), 5.91(1H, s), and 5.56(2H, s); MS(FAB): m/z calcd. for $C_{31}H_{25}O_4$(M^++H): 461.1753. found: 461.1722. **14a**: Colorless plates; mp 146-147 °C(decomp.); IR($CHCl_3$) 3331, 3020, and 1646 cm^{-1}; ^{1}H-NMR(200MHz, $CDCl_3$): 11.93(1H, s), 8.86(1H, s), 8.78(1H, dd, J = 8.0 and 1.0), 7.88(1H, d, J = 9.0), 7.72(1H, dd, J = 7.0 and 1.0), 7.42(1H, dd, J = 8.0 and 2.0), 7.40-7.20(12H, m), 7.15(1H, d, J = 9.0), 6.78(1H, t, J = 7.0), 6.58(1H, dd, J = 7.0 and 2.0), 5.61(2H, s), and 3.90(1H, s); MS m/z calcd. for $C_{31}H_{23}O_4$: 459.1596(M^++H-H_2O). found: 459.1593. **12b**: Colorless foam; IR($CHCl_3$) 3025, 1646, and 1616 cm^{-1}; ^{1}H-NMR(200MHz, $CDCl_3$): 12.29(1H, s), 8.04(1H, d, J = 9.0), 7.95(1H, d, J = 1.8), 7.60-7.10(10H, m), 7.05(1H, d, J = 9.0), 6.99(1H, dd, J = 7.0 and 1.0), 6.91(1H, dd, J = 7.0 and 1.0), 6.85(1H, t, J = 7.0), 6.78(1H, d, J = 1.8), 5.58(2H, s), 3.15(3H, s), and 2.61(3H, s); MS(FAB) m/z calcd. for $C_{33}H_{27}O_6$: 519.1808(M^++H). found: 519.1779. **14b**: Colorless foam; IR($CHCl_3$) 3315, 3024, 1645, and 1616 cm^{-1}; ^{1}H-NMR(200MHz, $CDCl_3$): 12.02(1H, s), 8.89(1H, s), 8.09(1H, d, J = 2.0), 8.01(1H, d, J = 9.0), 7.43(1H, dd, J = 7.0 and 1.6), 7.40-7.10(10H, m), 7.02(1H, d, J = 9.0), 6.83(1H, d, J = 2.0), 6.77(1H, t, J = 7.0), 6.59(1H, dd, J = 7.0 and 1.6), 5.58(2H, s), 3.84(1H, s), 3.56(3H, s), and 2.60(3H,s); MS m/z calcd. for $C_{33}H_{27}O_5$: 503.1858(M^++H-H_2O). found: 503.1815.