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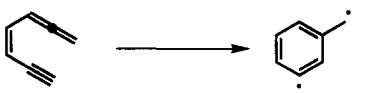
Cycloaromatization of Enediyne Model Compounds *via* a Reaction Cascade Triggered by Hydrolysis of the α-Alkynylmalonates

Masayuki Shibuya,* Masakazu Wakayama, Yoshimitsu Naoe, Tadaaki Kawakami,
Katsuya Ishigaki, Hisao Nemoto, Hisashi Shimizu, and Yoshimitsu Nagao
Faculty of Pharmaceutical Sciences, University of Tokushima,
Sho-machi 1, Tokushima 770, Japan

Abstract: Diethyl α-methoxy-α-alkynylmalotate derivatives of *cis*-enediynes were synthesized and they produced toluenebiradicals *via* the reaction cascade triggered by ester hydrolysis. Deuterium labeling studies suggested that the reaction involved the self quenching process by fairly fast disproportionation of toluene biradicals producing zwitterionic species.

Acyclic (Z)-1,2,4-heptatrien-6-ynes, which undergo cycloaromatization to produce the reactive toluene biradicals (Myers-type cyclization, **1** → **2**),[1] have been investigated as chemical models for the class of potent antitumor antibiotics neocarzinostatin (NCS)[2] and other natural enediyne drugs.[3] Currently challenges to prepare the enyne-allene models possessing characteristic triggering devices which initiate the generation of the DNA-damaging radicals, have been performed by many research groups.[4]

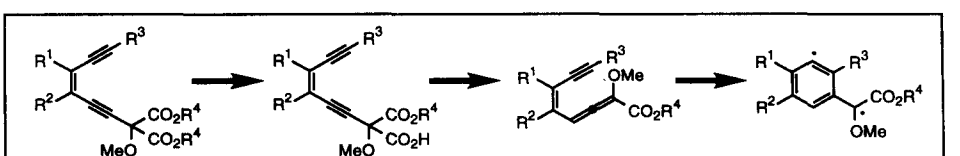


1 2

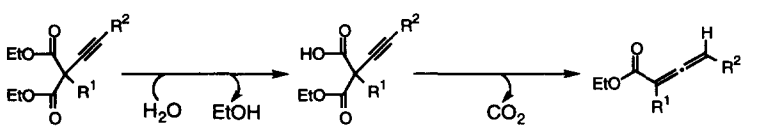
We describe herein development of the enediyne models which produce the reactive enyne-allenes and ultimately generate toluene biradicals *via* a reaction cascade triggered by hydrolysis of the malonyl ester group (Scheme 1). For production of the conjugated allenylester moiety, we utilized the hydrolytic decarboxylation reaction of diethyl α-alkynylmalonate derivatives developed by one of the authors (Y. Nagao) and his co-workers (Scheme 2).[5] For the desired acyclic Z-hex-3-ene-1,5-diyne derivatives depicted in Scheme 1, we synthesized the enediyne compounds possessing an aromatic group at olefinic carbon according to our new synthetic method.[6]

Benzoyl chloride was allowed to react with lithium salt of 3-(methoxymethyloxy)propyne[7] to give the alkynylketone **3**, which was then treated with propargyl bromide in the presence of zinc to provide the *tert*-

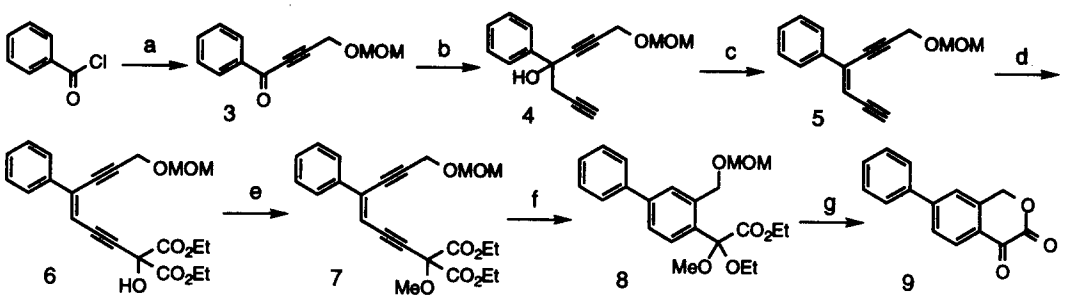
Scheme 1



Scheme 2

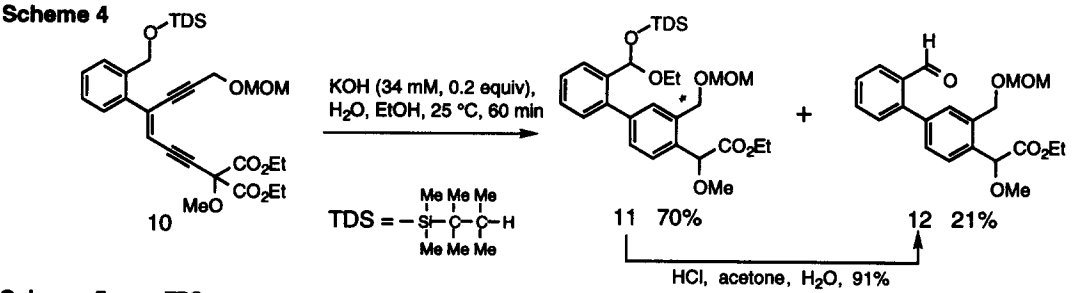


Scheme 3

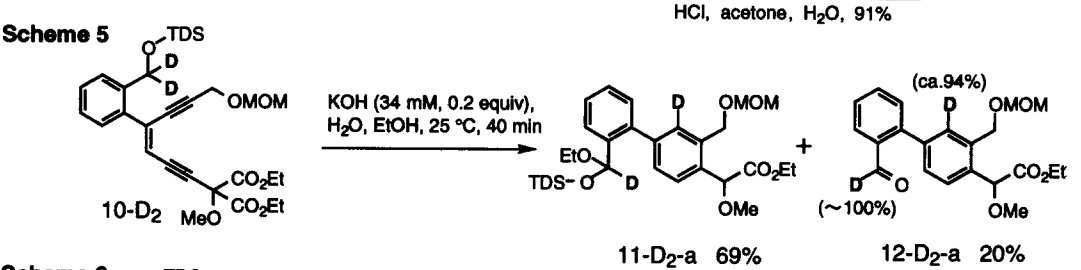


a) 1 equiv $HC{\equiv}CCH_2OCH_2OCH_3$, 1 equiv n-BuLi, THF, -78 °C, 60% yield; b) 2 equiv $BrCH_2C{\equiv}CH$, 3 equiv Zn, THF, 25 °C, 96% yield; c) 1.3 equiv MsCl, 3 equiv Et_3N, CH_2Cl_2, 0 °C, 94% yield (*trans* isomer, 4% yield); d) 1.05 equiv n-BuLi, 0.83 equiv $O{=}C(CO_2Et)_2$, THF, -78 °C, 49% yield; e) 3 equiv Ag_2O, 5 equiv $CaSO_4$, excess MeI, 25 °C, ~100% yield; f) 0.5 equiv KOH (42 mM), EtOH, H_2O (1:0.04 v/v), 25 °C, 78% yield; g) HCl (2M), acetone, H_2O (1:1 v/v), 55% yield

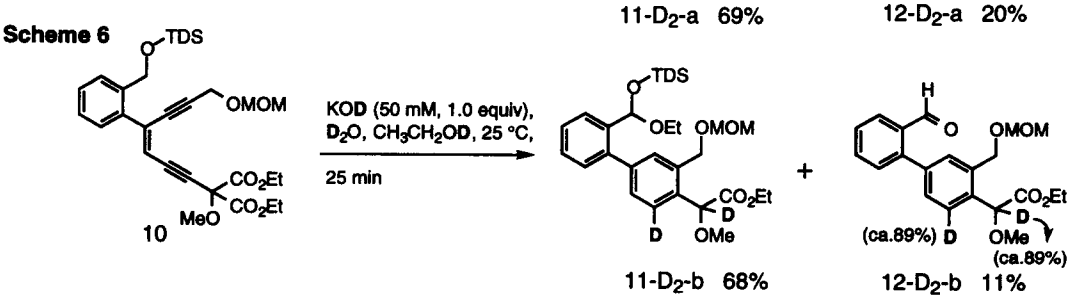
Scheme 4



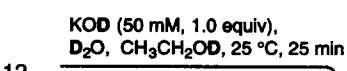
Scheme 5



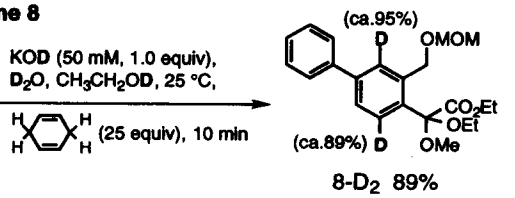
Scheme 6



Scheme 7



Scheme 8

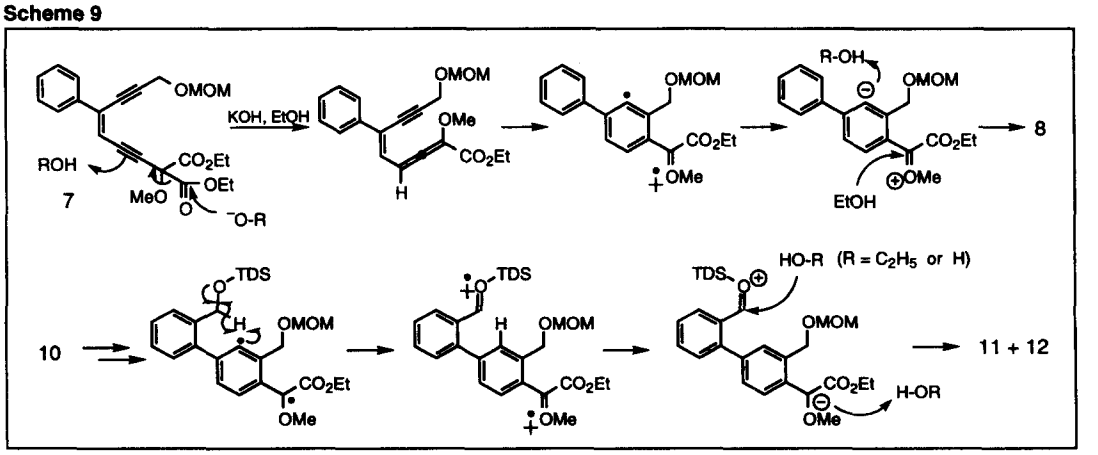


alcohol **4**. Reaction of **4** with MsCl and NEt_3 furnished predominantly the enediyne **5** having the *cis* geometry. Lithium salt of **5** was treated with diethyl ketomalonate followed by methylation of the resultant alcohol **6** to afford the desired α-alkynylmalonate **7**.

Decarboxylative cycloaromatization reaction was examined as follows. When treated with KOH (0.5 equiv) in EtOH containing 4 % (v/v) H_2O at room temperature, the α-alkynylmalonate **7** was converted to the acetal **8** in 78 % yield, in which the solvent EtOH was incorporated. Hydrolysis of **8** with HCl in aceton-H_2O (1:1) gave the isochromandione **9**, and the structures of **8** and **9** were determined by the spectroscopic analysis (Scheme 3). To confirm the formation of a toluene biradical intermediate and to clarify the mechanism of EtOH incorporation to the product, we examined the cycloaromatization reaction using compound **10**.[8] Hydrogen atoms at the benzylic position of **10** are favorably located in position which permit the abstraction by the predicted benzene σ-radical.[9] The similar reaction of **10** with KOH (0.2 equiv) in aqueous EtOH gave a 1:1 diastereomeric mixture of the acetal **11**, in which EtOH was incorporated into the benzylic position, and the aldehyde **12**. Acid catalyzed hydrolysis of the acetal **11** afforded the aldehyde **12** in a good yield (Scheme 4).

In order to clarify the mechanisms of above reactions, several labeling studies were conducted (Schemes 5-8). The experiment employing the compound **10-D_2** labeled at the benzylic position[10] produced compounds **11-D_2-a** and **12D_2-a**. A deuterium was incorporated onto the newly formed benzene ring of **11-D_2-a** and **12D_2-a** to the extent of >90%,[11] respectively, indicating the reaction involves the formation of toluene biradical intermediate (Scheme 5). When the cycloaromatization of **10** was carried out with KOD in CH_3CH_2OD and D_2O, compounds **11-D_2-b** and **12D_2-b** were obtained (extent of deuterium incorporation was ca. 89% for each position) (Scheme 6).[11] Deuterium atoms on the benzene ring of the products in the latter experiment (Scheme 6) are readily explained to be homolytically incorporated from CH_3CH_2OD in the decarboxylation pathway. (Scheme 1) On the other hand, the solvent incorporations in both experiments (Schemes 5 and 6) and deuterium incorporation in the latter experiment (Scheme 6) are somewhat intricate, because a homolytic solvent incorporation into the biradical intermediate must be ruled out from the reaction mechanism.[12] The product **12** when subjected to the same reaction conditions as Scheme 6 was recovered unchanged, ruling out the possibility that **12D_2-b** resulted by deuterium exchange after the cycloaromatization (Scheme 7). Furthermore, when the reaction of **7** was conducted in deuterated solvent with and without the presence of 1,4-cyclohexadiene, compound **8-D_2**, in which two deuterium atoms were incorporated, was obtained in a good yield (Scheme 8).

Scheme 9



This experiment indicates that the hydrogen abstraction from CH_3CH_2OD or 1,4-cyclohexadiene does not occur during the cascade reactions. The results of above labeling studies strongly suggest that the reaction involves the self quenching process by fairly fast disproportionation of toluene biradicals producing zwitterionic species.[13] Thus, we propose the mechanisms for these cycloaromatization reactions as represented in Scheme 9.[14]

In summary, this study demonstrates that the diethyl α-alkynylmalonate derivatives of acyclic *Z*-hex-3-ene-1,5-diyne can be used to generate biradicals *via* the reaction cascade triggered by ester hydrolysis. We also provide a proposal and experimental evidence of a disproportionation pathway of biradicals that contribute to the mechanistic studies of DNA-cleaving antibiotics such as NCS Chromophore. Studies on the analogues of this class of compounds, involving enzyme induced biradical generation, are continuing.

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7. S. F. Martin and B. Benage, *Tetrahedron Lett.*, **25**, 4863 (1984).
8. Compound **10** was synthesized by condensation of the lithium salt of appropriate enediyne[6] with diethyl ketomalonate, followed by methylation.
9. Several examples of homolytic intramolecular 1,5-hydrogen atom shift have been reported in the field of enediyne chemistry. See, D.-H. Chin and I. H. Goldberg, *J. Am. Chem. Soc.*, **114**, 1914 (1992); P. A. Wender and M. J. Tebbe, *Tetrahedron*, **50**, 1419 (1994); H. Audrain, T. Skrydstrup, G. Ulibarri, C. Riche, A. Chiaroni, and D. S. Grierson, *Tetrahedron*, **50**, 1469 (1994); S. Kawata, T. Oishi, and M. Hirama, *Tetrahedron Lett.*, **35**, 4595 (1994); Z. Wang and K. K. Wang, *J. Org. Chem.*, **59**, 4738 (1994).
10. Compound **10-D_2** was prepared by our method[6] using dideuterio phthalide (96.5% deuterium contents at the benzylic position) as a starting material.
11. Extent of deuterium incorporation was determined by 400 MHz or 600 MHz ^{1}H NMR.
12. It is well established that homolytic hydrogen abstraction from EtOH is conducted from C-H bond exclusively, but not from O-H bond; e.g., F. Fontana, F. Minisci, Y. M. Yan, and L. Zhao, *Tetrahedron Lett.*, **34**, 2517 (1993).
13. Possibilities of intermolecular or intramolecular disproportionation of biradicals leading to zwitterionic intermediate have been suggested; H. Sugiyama, K. Yamashita, M. Nishi, and I. Saito, *Tetrahedron Lett.*, **33**, 515 (1992); A. G. Myers, P. S. Dragovich, and E. Y. Kuo, *J. Am. Chem. Soc.*, **114**, 9369 (1992); N. J. Turro, A. Evenzahav, and K. C. Nicolaou, *Tetrahedron Lett.*, **35**, 8089 (1994).
14. Selected data, **8**: IR (neat) 1752 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$): 1.21 (3H, t, J=7.1), 1.31 (3H, t, J=7.1), 3.23 (3H, s), 3.38-3.64 (2H, m), 3.42 (3H, s), 4.20 (2H, q, J=7.1), 4.72 (2H, s), 4.84 (2H, s), 7.35-7.65 (5H, m), 7.55 (1H, dd, J=8.3, and 1.7), 7.80 (1H, d, J=1.7), and 7.91 (1H, d, J=8.3); **9**: mp 160-162°C; IR (KBr) 1752 and 1698 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$): 8.23 (1H, d, J=8.3), 7.78 (1H, d, J=8.3), 7.49-7.67 (6H, m), and 5.79 (2H, s); **12**: IR (neat) 1748 and 1693 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$): 1.26 (3H, t, J=7.1), 3.42 (3H, s), 3.47 (3H, s), 4.19 (1H, dq, J=10.7, 7.1), 4.28 (1H, dq, J=10.7 and 7.1) 4.73 (2H, s), 4.73 (1H, d, J=12.7), 4.92 (1H, d, J=12.7), 5.17 (1H, s), 7.43-7.69 (6H, m), 8.04 (1H, d, J=8.4), and 9.99 (1H, s).

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