DNA Cleavage Potency, Cytotoxicity, and Mechanism of Action of a Novel Class of Enediyne Prodrugs

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We have discovered a novel class of (*E*)-3-acyloxy-4-(arylmethylidene)cyclodeca-1,5-diynes such as **1** and **2** which exhibit promising enediyne-like DNA cleavage and cytotoxic activities.[1] LC-MS analysis of the incubation mixture of **1** (pH 8.5, 37 °C; Figure 1) confirmed formation of 10-membered ring enediyne **5** presumably via an allylic cation **4** and suggested that 1,4-benzenoid diradical **6** might be one of the active species for DNA damage and cytotoxicity. The proposed mechanism of action is given in Scheme 1.

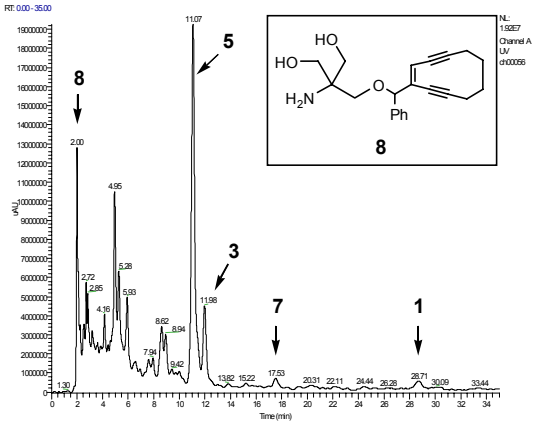
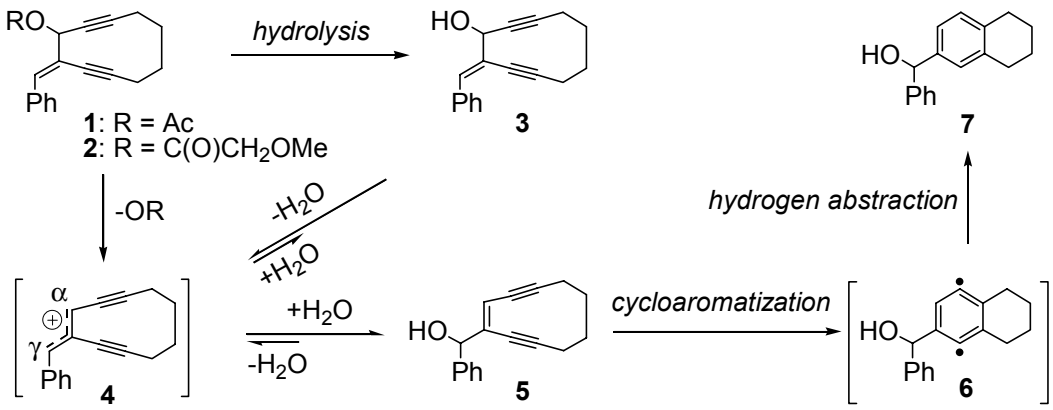


Figure 1. LC/MS data of the incubation mixture of **1** (MS charts not showed).



Scheme 1. Proposed mechanism of action of **1** and **2**.

1. Dai, W.-M.; Lai, K. W.; Wu, A.; Hamaguchi, W.; Lee, M. Y. H.; Zhou, L.; Ishii, A.; Nishimoto, S. *J. Med. Chem.* **2002**, *45*, 758-761.