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Highly Efficient Photochemical Synthesis of the Enediyne Functionality *via* a Norrish Type II Reaction

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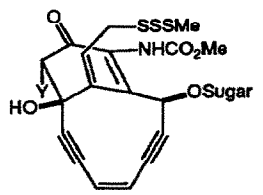
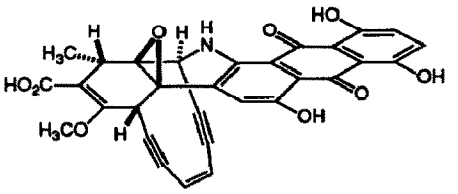
Summary: A photochemical synthesis of enediynes utilizing the Norrish Type II reaction is described. The application of this strategy to the synthesis of cyclic and acyclic enediynes from readily available precursors is discussed.

The potent anticancer properties, novel structures, and unique pharmacology of the enediyne antibiotics calicheamicin/esperamicin, **1**, and dynemicin, **2**, have engendered enormous interest in these compounds in the synthetic and biological chemistry communities.[1,2,3] These antibiotics manifest their considerable biological activity in the form of DNA damage; it is the product of aromatic cyclization[4] of the enediyne functionality present in each of these compounds (*ie.*, **3** to **5**) which brings about DNA strand scission by various hydrogen abstraction mechanisms.[3,4] Each of these antibiotics has a unique triggering mechanism which results in enforced propinquity of the two alkyne moieties (**3** to **4**); this change in conformation results in facile "Bergman" cyclization[4] and formation of the putative DNA damaging diradical **5**.[3] The triggering mechanism in the calicheamicin/esperamicin family involves bioreduction of the trisulfide functionality; the conformation change induced by the subsequent Michael reaction to the α,β-unsaturated carbonyl system by the mercaptan then results in aromatic cyclization of the enediyne to the reactive 1,4-biradical.[1,3] The biological activity of dynemicin is also triggered by a bioreduction of the aromatic nucleus; this results in fragmentation of the benzylic C-O bond, conformational change, and subsequently, biradical formation.[2,3]



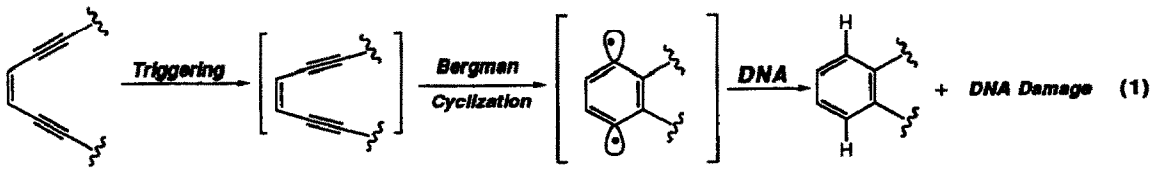
Calicheamicin Y = OSugar
Esperamicin Y = H

1



Dynemicin

2

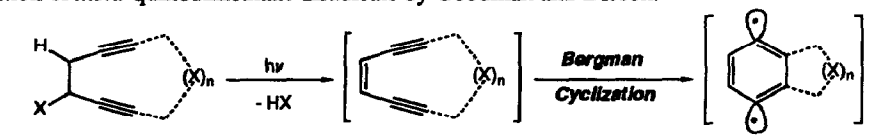


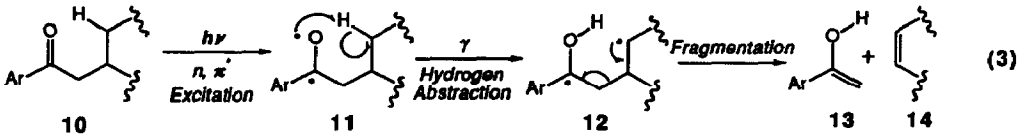
3 **4** **5** **6**

With the ultimate goal of developing functional analogues of these agents for potential use in chemotherapy or as tools for biotechnology, considerable attention has been given to the design of structurally simplified enediyne congeners retaining the impressive DNA cleaving properties of these molecules.[3,5] In addition, ingenious reports of alternative methods of triggering biradical formation from enediyne systems modeled loosely

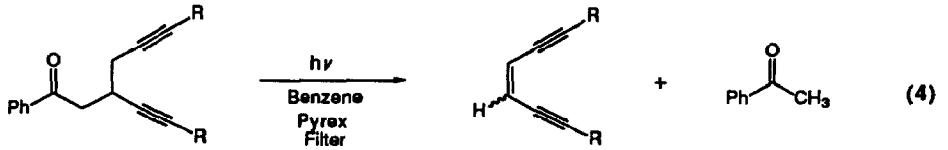
on **1** or **2**, including pH dependent rearrangements, redox based processes and photochemical strategies, have appeared from a number of laboratories.[3,6] Our interests in this area center on the design of photochemical methods for the generation of the enediyne functionality (Equation 2), and subsequently analogues of biradical **5**, from stable diyne precursors. We feel that this strategy has the potential to permit the generation of the DNA damaging diradicals under exceedingly mild conditions from stable progenitor diynes by introducing the double bond of the enediyne in a conformation which results in spontaneous aromatization to the biradical. We have chosen as our vehicle for photochemical enediyne generation the Norrish Type II fragmentation[7] (Equation 3), one of the most thorougly studied and general of photochemical reactions (HX in Equation 2 being the enol of acetophenone).

Several aspects of the Norrish Type II reaction are attractive as a means for enediyne synthesis: 1) this reaction generally proceeds with near unit efficiency; 2) an innocuous by-product is produced (acetophenone); 3) the wavelength required for this conversion is out of the range of both enediyne and DNA absorptions; and 4) the excitation wavelength can be tuned by adjusting the substutients on the aryl ring of the precursor.[7] We were also encouraged in these efforts by reports from other groups of the use of the Norrish Type II reaction for the *in situ* generation of highly reactive intermediates, such as the formation of unstable thioaldehydes by Vedejs[8a] and the generation of *meta*-quinodimethane diradicals by Goodman and Berson.[8b]





The feasiblility of this strategy is demonstrated in our initial efforts on simple phenyl ketone derivatives (Equation 4). Irradiation of diyne **15a** (R = H, Pyrex, benzene) affords a quantitative yield of acetophenone and a modest yield of the enediyne **16a** (the volatile nature of this hydrocarbon fragment precludes its efficient isolation); similarly, photolysis of **15b** (R = CH_2OCH_3) provides acetophenone and the less volatile enediyne **16b**, as a 1:1 mixture of olefin isomers,[7] in extremely high yield (95%).



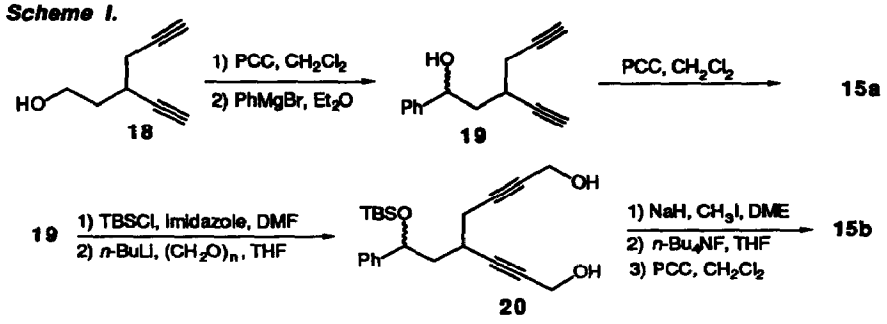
15a R = H
15b R = CH_2OCH_3

16a 45%
16b 95% (1 : 1 E : Z)

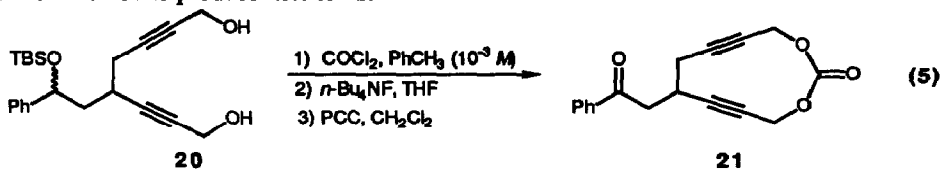
17 97%
17 98%

Photolysis substrates **15a** and **15b** are assembled quite easily beginning with the product of the reaction between the trianion of 1,5-hexadiyne and ethylene oxide, **18**, first reported by Vollhardt.[9] Oxidation of **18** and reaction of the resulting aldehyde with phenyl magnesium bromide affords **19**, which upon oxidation gives the first substrate **15a**. Protection of **18** as its *tert*-butyldimethylsilyl (TBS) ether followed by reaction with 2.1 equivalents of *n*-BuLi and paraformaldehyde produces the diol **20** in good yield. Elaboration to the acyclic diyne precursor **15b** is quite straightforward and involves alkylation of the propargyl alcohols (CH_3I, NaH, DME), deprotection of the benzylic carbinol, and oxidation.

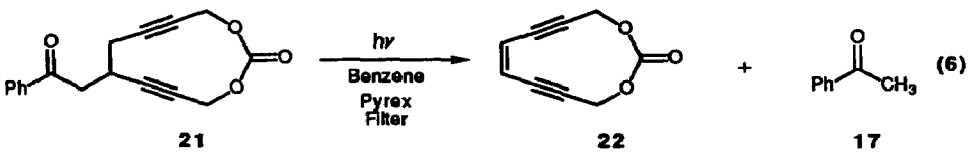
Scheme I.



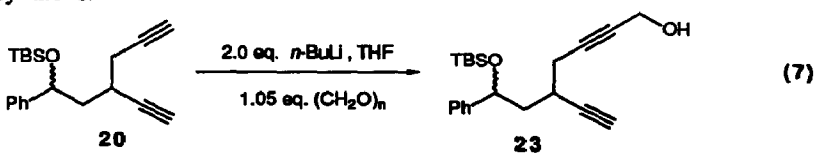
Following the success of this strategy in the acyclic systems, we have begun to examine the photochemistry of cyclic diyne precursors.[10] The requisite cyclic diyne precursor **21** can be constructed efficiently from diol **20** (Equation 5). Formation of the macrocyclic carbonate proceeds efficiently under high dilution (2×10^{-3} *M*) conditions, affording an eleven-membered macrocyclic carbonate in 71% yield. This was deprotected and oxidized to produce ketone **21**.



Photolysis of **21** also proceeds efficiently, affording acetophenone and cyclic enediyne (Z)-**22** as the only photoproducts (98% and 87%, respectively). This eleven membered ring enediyne, as expected from previous work, does not undergo aromatic cyclization at ambient temperature.[3] Attempts are currently underway to design a system which incorporates a smaller ring in the progenitor diyne and would lead to cyclization at room temperature upon Norrish Type II cleavage. This should be possible in a nine or ten membered diyne analogue of **21**, given paradigms which have been previously developed correlating ring size with ease of cyclization.[3]



Toward this end, we have found that the two seemingly indistinguishable alkyne functionalities present in acyclic diyne precursors such as **20** can be selectively functionalized; for example, treatment of the dianion generated by reaction of diyne **20** with 2.0 equivalents of *n*-BuLi with only 1.0 equivalent of paraformaldehyde affords a single alcohol **23**, in high yields (70-78%). The reasons for this high selectivity are unclear at this time, but nonetheless should allow us to easily fashion more highly functionalized progenitors from these simple, readily available synthons.



In summary, we report here our initial efforts devoted towards the development of a photochemically initiated enediyne synthesis. We show the viability of such an approach in the formation of both acyclic and cyclic enediynes. We feel that these are the first steps towards the development of new, potentially useful photochemically triggered DNA cleaving reagents.

Acknowledgement:

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References:

1. References for the isolation of calicheamicin/esperamicin: (a) CAL: Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawakuch, H.; Konishi, M.; Krishinan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T.W. *J. Am. Chem. Soc.* **1987**, *109*, 3461; (b) ESP: Lee, M.D.; Dunne, T.S.; Siegel, M.M.; Chang, C.C.; Morton, G.O.; Borders, D.B. *J. Am. Chem. Soc.* **1987**, *109*, 3463, 3466. Mechanism of action: (a) Suguira, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T.W. *Proc. Nat. Acad. Sci. USA* **1989**, *86*, 7672; (b) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G.A. *Science* **1989**, *244*, 697.
2. The isolation and structural characterization of dynemicin: Konishi, M.; Ohkuma, H.; Matsumoto, K., Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; VanDuyne, G.D.; Clardy, J. *J. Antibiotics* **1989**, *42*, 1449. Mechanism of action: Semmelhack, M.F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, 1521.
3. Recent reviews: (a) Nicolaou, K.C.; Dai, W.-M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387; (b) Nicolaou, K.C.; Smith, A.L.; Yue, E.W. *Proc. Nat. Acad. Sci. USA* **1993**, *90*, 5881.
4. Bergman, R.G. *Acc. Chem. Res.* **1973**, *6*, 25. See also: Darby, N.; Kim, C.U.; Salaün, J.A.; Shelton, K.W.; Takada, S.; Masamune, S. *Chem. Commun.* **1971**, 1516; Wong, H.N.C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, 217.
5. A large number of groups have been involved in the synthesis of CAL/ESP or DYN models. For representative examples, see: (c) Magnus, P.; Lewis, R.; Huffman, J.C. *J. Am. Chem. Soc.* **1988**, *110*, 6921; (d) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J.P. *J. Am. Chem. Soc.* **1990**, *112*, 4986; (e) Nicolaou, K.C.; Ogawa, Y.; Schweiger, E.J.; Kumazawa, T. *J. Am. Chem.Soc.* **1988**, *110*, 4866; (f) Haseltine, J.N.; Danishefsky, S.J. *J. Org. Chem.* **1990**, *55*, 2576; (g) Mantlo, N.B.; Danishefsky, S.J. *J. Org. Chem.* **1989**, *54*, 2781; (h) Schoenen, F.J.; Porco, J.A., Jr.; Schreiber, S.L. *Tetrahedron Lett.* **1989**, 3765; (i) Snyder, J.P.; Tipsword, G.E. *J. Am. Chem. Soc.* **1990**, *112*, 4040.
6. For detailed discussions see References 3a, b. Examples of pH dependent triggering: (a) Nicolaou, K.C.; Skokota, G.; Maligres, P.; Zuccarello, G.; Scheweiger, E.G.; Toshima, K.; Wendeborn, S. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1272; (b) Semmelhack, M.F.; Date, T. Fourth Chemical Congress of North America Abstracts, American Chemical Society **1991**, ORGN 102. Photochemical triggering: Nicolaou, K.C.; Dai, W.-M.; Wendeborn, S.V.; Smith, A.L.; Torisawa, Y.; Maligres, P.; Hwang, C.-K. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1032. Redox triggering: (a) Maier, M.; Brandstetter, T. *Tetrahedron Lett.* **1991**, 3679; (b) Semmelhack, M.F.; Neu, T.; Foubelo, F. *Tetrahdron Lett.* **1992**, 3277; (c) Semmelhack, M.F.; Gallagher, J.J. *Tetrahedron Lett.* **1993**, 4121; (d) Myers, A.G.; Dragovich, P.S. *J. Am. Chem. Soc.* **1992**, *114*, 5859.
7. Review of the Norrish Type II Reaction: Wagner, P.J. *Accts. Chem. Res.*, **1971**, *4*, 168. For a reference detailing the abstraction of propargylic hydrogens, see: Kravitz, J.; Margaretha, P.; Agosta, W.C. *Tetrahedron Lett.* **1991**, 31.
8. (a) Generation of thioaldehydes: Vedejs, E.; Perry, D.A. *J. Am. Chem. Soc.* **1983**, *105*, 1683; Vedejs, E.; Eberlein, T.H.; Varie, D.L. *J. Am. Chem. Soc.* **1982**, *104*, 1445; (b) *meta*-Quinodimethane generation: Goodman, J.L.; Berson, J.A. *J. Am. Chem. Soc.* **1985**, *107*, 5409, 5425; Goodman, J.L.; Berson, J.A. *J. Am. Chem. Soc.* **1984**, *106*, 1867.
9. Funk R.L.;Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245.
10. For a review of medium ring cycloalkynes, see: Gleiter, R.*Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 27.

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