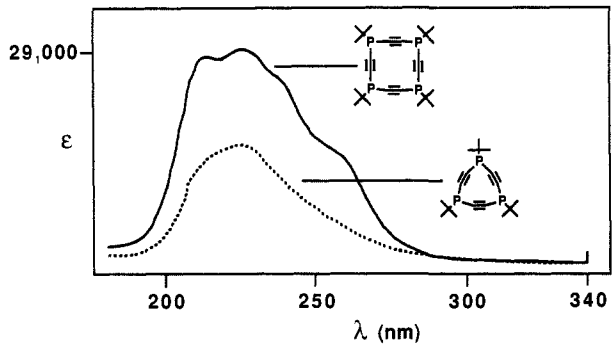

Figure 1. UV spectra of compounds **3b** and **4d** in cyclohexane.

of the *tert*-butyl groups for use as potential precursors to phosphocarbons **1** and **2**.

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DNA Cleavage and Antitumor Activity of Designed Molecules with Conjugated Phosphine Oxide-Allene-Ene-Yne Functionalities†

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Molecules with DNA-cleaving properties[1] and new anticancer agents[2] are of considerable current interest and value to molecular biology and medicine. As part of our program in these areas, we have designed, synthesized, and tested a series of compounds with conjugated phosphine oxide-allene-*cis*-ene-yne functionalities. In this communication we report our results, which include both of the above properties.

Scheme I depicts the mechanistic rationale for the formation and action of this new class of compounds. Thus, it was hypothesized that propargylic compounds of type I may be induced to rearrange to the conjugated allenic systems III under the influence of PhSCl or Ph_2PCl via intermediates II. Structures III were then expected to undergo a Myers[3] cyclization reaction[4] to

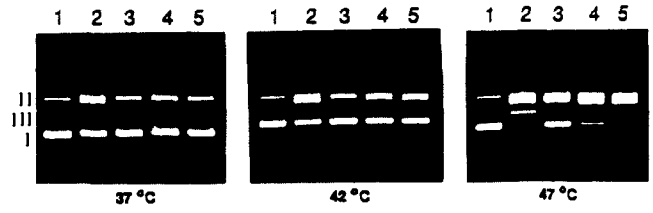
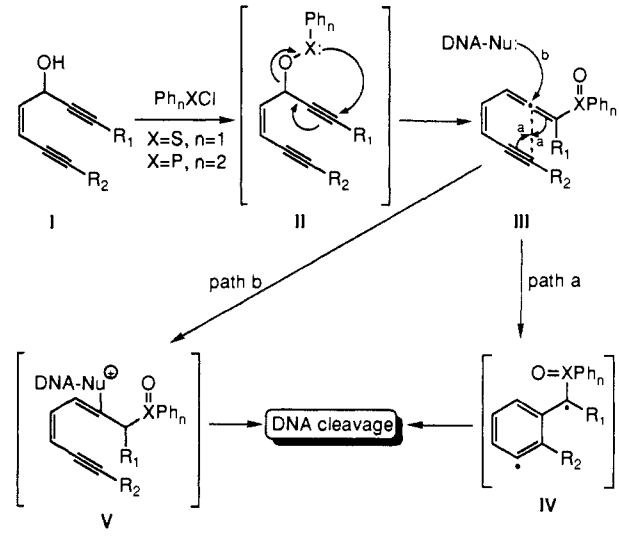


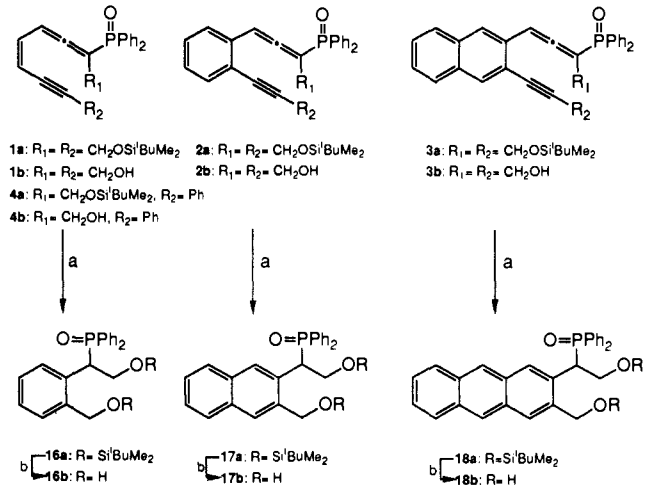
Figure 1. ΦX174 form I DNA (50 μM/base pair) was incubated for 48 h at the specified temperatures with various compounds (1 mM in 20% ethanol in phosphate buffers, pH 8.5, 50 mM) and analyzed by gel electrophoresis (1% agarose, ethidium bromide stain). Lane 1, DNA alone; lanes 2-5, compounds **1b**, **2b**, **3b**, and **4b**, respectively. I: form I DNA. II: form II DNA. III: form III DNA.

Scheme I[a]



[a] Mechanistic rationale for the design of DNA-cleaving molecules with, potentially, a dual mode of action: (a) radical mechanism; (b) alkylation mechanism.

Scheme II[a]



[a] Compounds synthesized and studied in this work: (a) 0.01 M in 1,4-cyclohexadiene, 37 °C, 0.01 M; **1a**, $t_{1/2}$ = 8 h; **2a**, $t_{1/2}$ = 23 h; **3a**, $t_{1/2}$ = 117 h; (b) 48% aqueous HF, acetonitrile, 20 °C, 15 min, quantitative.

form radicals IV (path a) or undergo nucleophilic attack originating from DNA to form species V (path b) as expected from our recent results with propargylic and allenic sulfones.[1d] Either pathway should cause cleavage of DNA. Sulfur compounds of

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‡ Recipient of a Ministerio de Educación y Ciencia Fulbright Fellowship, Spain, 1989-1990.

§ Department of Chemistry, The Research Institute of Scripps Clinic.

(1) For some selected examples, see: (a) Hertzberg, R. P.; Dervan, P. B. *J. Am. Chem. Soc.* **1982**, *104*, 313. (b) Moser, H. E.; Dervan, P. B. *Science* **1987**, *238*, 645. (c) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247. (d) Nicolaou, K. C.; Skokotas, G.; Maligres, P.; Zuccarello, G.; Schweiger, E. J.; Toshima, K.; Wendeborn, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1272. (e) Posvic, T. J.; Dervan, P. B. *J. Am. Chem. Soc.* **1989**, *111*, 3059. (f) Corey, D. R.; Schultz, P. G. *J. Am. Chem. Soc.* **1989**, *111*, 8523. (g) Pyle, A. M.; Long, E. C.; Barton, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 4520. (h) Sigman, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 4941. (i) Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781. (j) Ohno, M.; Otsuka, M. *J. Am. Chem. Soc.* **1990**, *112*, 838. (k) Natans, D.; Smith, H. O. *Annu. Rev. Biochem.* **1975**, *44*, 273.

(2) (a) Remers, W. A., Ed. *Antineoplastic Agents*; Wiley: New York, 1984. (b) Neidles, S., Waring, M. J., Eds. *Molecular Aspects of Anti-Cancer Drug Action*; Verlag Chemie: Weinheim, 1983. (c) Chagas, C., Pullman, B., Eds. *Molecular Mechanisms of Carcinogenic and Antitumor Activity*; Adenine Press: Schenectady, 1987. (d) Denny, W. A. *Drug. Des. Delivery* **1988**, *3*, 99.

(3) (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (b) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130.

(4) For similar cyclizations involving conjugated ketenes, see: Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975 and references cited therein.

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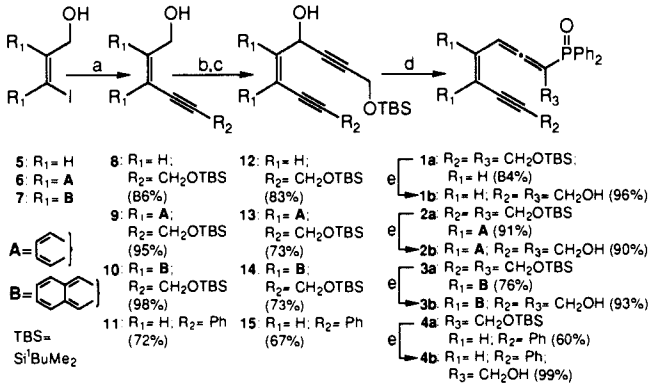
Scheme III[a]

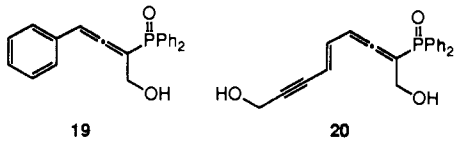


[a] Synthesis of compounds **1b**, **2b**, **3b**, and **4b**. Reagents and conditions: (a) 1.1 equiv of $R_2C{\equiv}CH$, 0.04 equiv of $Pd(PPh_3)_2Cl_2$, 0.16 equiv of CuI, 1.5 equiv of Et_2NH, benzene, 0 °C, 1 h; (b) excess MnO_2, benzene, 25 °C, 24 h; (c) 1.2 equiv of $Me_2{}^tBuSiOCH_2C{\equiv}CH$, 1.1 equiv of *n*-BuLi, THF, -10 °C, 0.5 h, then 1.0 equiv of aldehyde, THF, -20 °C, 1 h; (d) 1.0 equiv of Ph_2PCl, 1.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1 h; (e) 48% HF, MeCN, 25 °C, 15 min.

type III were found to be rather labile and not suitable for practical DNA or antitumor activity studies. The phosphorus series, however, proved to be easily prepared and handled and exhibited the expected properties of DNA cleavage and antitumor activity in the temperature range 37-47 °C.

Compounds **1a**,**b**-**4a**,**b** (Scheme II) were designed and synthesized as summarized in Scheme III.[5] The key operations involved (a) vinyl iodide-acetylene couplings via Pd(0)-Cu(I) catalysis (step a, Scheme III); (b) acetylide addition to aldehydes (step c, Scheme III); and (c) 2,3-sigmatropic rearrangements (step d, Scheme III).

Compounds **1a**, **2a**, and **3a** were sufficiently stable for isolation, but smoothly cyclized to aromatic systems [**16a** (60%), **17a** (75%), and **18a** (80%), respectively], presumably via diradicals, upon warming in the presence of cyclohexadiene (Scheme II).[6] The half-lives ($t_{1/2}$), of these systems at 37 °C (**1a**, $t_{1/2}$ = 8 h; **2a**, $t_{1/2}$ = 23 h; **3a**, $t_{1/2}$ = 117 h) indicated that they or their derivatives[7] may be good DNA and tumor cell damaging agents with prolonged periods of action. This expectation was reinforced when it was realized that **1a**-**4a** served as excellent acceptors of nucleophiles (e.g., *n*-$BuNH_2$, Et_2NH, $HSCH_2COOMe$)[8] at ambient temperatures, pointing to a possible nucleophilic scenario for reaction with DNA. Indeed, compounds **1b**-**4b** exhibited DNA-cleaving properties at 37, 42, and 47 °C in the absence of any additives. Thus incubation of compounds **1b**-**4b** with supercoiled DNA (form I) aerobically (or anaerobically)[9] at pH 8.5 and at various temperatures caused DNA rupture, leading initially to form II and finally to form III DNA as shown in Figure 1. Compounds **19** and **20**, which are incapable of undergoing the



19 **20**

cyclization reaction, showed considerably weaker DNA-cleaving properties than **1b** and **2b**, respectively,[9] supporting the notion of a dual mechanism of action for these compounds. On the other hand, compounds **1b**-**4b** exhibited lower potencies as DNA-cleaving agents at pH 6 than at pH 8.5 (suppression of nucleophilic mode of action), an observation also indicating a dual mode of action. As expected, the cyclized products **16b**-**18b** did not show any DNA-cleaving properties in control experiments.[9]

Compounds **1b**-**4b** exhibited potent, concentration-dependent cytotoxicity against human carcinoma cells, thus fulfilling the initial expectations that led to the design of these systems.[10] The reported results suggest new possibilities for the development of useful biotechnology tools[11] and novel therapeutic agents.

Acknowledgment. We express our many thanks to Drs. Dee H. Huang and Gary Siuzdak of the Research Institute of Scripps Clinic for their superb NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, the National Science Foundation, Hoffman-La Roche, and Merck Sharp and Dohme.

Supplementary Material Available: Listing of selected R_f, IR, ^1H and ^{13}C NMR, UV, and mass spectral data for compounds **1a**,**b**-**4a**,**b**, **4c**,**d**, **12**-**15**, **16a**-**18a**, **19**, and **20** as well as photographs of electrophoresis gels for control experiments (14 pages). Ordering information is given on any current masthead page.

(5) New compounds exhibited satisfactory spectral and/or analytical data.

(6) Under similar conditions, cyclization of compound **4a** to the corresponding aromatic system proceeded at a slower rate and lower yield.

(7) For a similar system, see: Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *29*, 4995.

(8) As expected, attack by N or S occurred at the central allene carbon, leading to the expected 1,4-adducts. Selected data for one adduct of $HSCH_2COOMe$ (**4c**) and one adduct of *n*-$BuNH_2$ (**4d**) with compound **4a** are given in the supplementary material. Details of these and related reactions will be reported in due course.

(9) Photographs of electrophoresis gels supporting this statement are included in the supplementary material.

(10) Although it is tempting to link DNA cleavage with cytotoxicity, proof of this connection will have to await further experimentation.

(11) It is noteworthy that compound **3a** upon cyclization leads to a fluorescent product (**18a**), a property that should enhance the potential of these systems as biological probes.

Reaction of Cyclohexene with Iodosylbenzene Catalyzed by Non-Porphyrin Complexes of Iron(III) and Aluminum(III). Newly Discovered Products and a New Mechanistic Proposal

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Iodosylbenzene has been widely used as a source of oxygen atoms in metal-catalyzed oxygenation reactions.[1] Until recently, it has been widely assumed that such reactions proceed exclusively via high-valent metal oxo intermediates. However, the recent discovery that olefin epoxidations by iodosylbenzene may be catalyzed by certain nonredox metal complexes incapable of forming high-valent metal oxo complexes[2] indicates that additional pathways for these oxygen-transfer reactions must exist. Iodine(III) compounds are known to react with olefins in the absence of metal catalysts, although epoxides have never been reported as products.[3] Nevertheless, the possibility, originally proposed

(1) McMurry, T. J.; Groves, J. T. In *Cytochrome P-450: Structure, Mechanism and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1986; pp 1-28 and references therein.

(2) Nam, W.; Valentine, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 4977.

(3) (a) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 2462. (b) Koser, G. F.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1981**, *46*, 4324. (c) Shah, M.; Taschner, M. J.; Koser, G. F.; Rach, N. L.; Jenkins, T. E.; Cyr, P.; Powers, D. *Tetrahedron Lett.* **1986**, *27*, 5437. (d) Zefirov, N. S.; Zhdankin, V. V.; Dan'kov, Y. V.; Sorokin, V. D.; Semerikov, V. N.; Koz'min, A. S.; Caple, R.; Berglund, B. A. *Tetrahedron Lett.* **1986**, *27*, 3971. (e) Zefirov, N. S.; Zhdankin, V. V.; Dan'kov, Y. V.; Koz'min, A. S. *J. Org. Chem. USSR (Engl. Transl.)* **1984**, *20*, 401. (f) Zhdankin, V. V.; Tykwinski, R.; Berglund, B.; Mullikin, M.; Caple, R.; Zefirov, N. S.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2609. (g) Hembre, R. T.; Scott, C. P.; Norton, J. R. *J. Org. Chem.* **1987**, *52*, 3650.

0002-7863/90/1512-7826$02.50/0