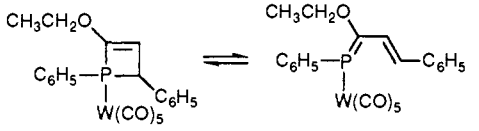
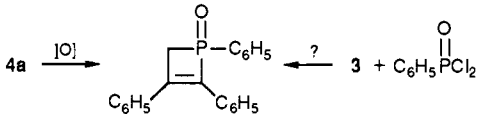
in determining the ground-state metrical parameters of the uncomplexed heterocycle, **4a**.



Although our first preparation of **4a**, in which workup was carried out in air rather than under nitrogen, gave **4a** contaminated with significant amounts of what appears to be the dihydrophosphete oxide,[10] **5**, we find that pure **4a** is remarkably inert toward oxidation. Solutions of **4a** in perdeuteriobenzene show only traces of the putative **5** after storage for several weeks under an atmosphere of pure oxygen. Attempted independent preparation of oxide **5** through the reaction of the titanacyclobutene **3** with phenyldichlorophosphine oxide gave inconclusive results.



The reaction of titanacyclobutene **3** with dichlorophosphines appears quite general.[8] Ethyldichlorophosphine gives dihydrophosphete **4b**, though **4b** appears unstable and has not yet been isolated or fully characterized. *tert*-Butyldichlorophosphine also reacts, though this reaction is considerably slower. Workup after 24 h affords the product, **4c**, in 30–50% yield. Ethyl phosphorodichloridite also reacts readily to produce the corresponding dihydrophosphete **4d**, as a stable white solid in 73% yield. In only one case have we failed to observe formation of the dihydrophosphete product. (Diisopropylamino)dichlorophosphine does not react with titanacycle **3** at room temperature; elevation of the temperature to ca. 50 °C results in decomposition.

We are currently extending this chemistry to titanacyclobutenes bearing substituents other than the phenyl groups present in **3** and are also exploring the use of other main-group electrophiles to remove the organic fragment from these titanacyclobutenes and other metallacyclic complexes prepared in our laboratories. The electrocyclic ring-opening of the 1,2-dihydrophosphetes is also being explored.[11]

Acknowledgment. This work was supported by the National Institutes of Health (Grant GM39494).

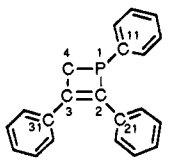
Registry No. **3**, 74834-09-6; **4a**, 123751-84-8; **4b**, 123751-85-9; **4c**, 123751-86-0; **4d**, 123751-87-1; **5**, 123751-88-2; $C_6H_5PCl_2$, 644-97-3; $CH_3CH_2PCl_2$, 1498-40-4; $(CH_3)_3CPCl_2$, 25979-07-1; $CH_3CH_2OPCl_2$, 1498-42-6.

Supplementary Material Available: Details of the preparation of **4a**, spectral characterizations of **4a–d**, and crystallographic data tables for **4** (9 pages); tables of observed and calculated structure factors for **4a** (8 pages). Ordering information is given on any current masthead page.

(10) ^1H NMR shows a new pair of dd at δ 3.38 and 3.43; MS displays the parent ion at m/z = 316.

(11) Electrocyclic ring-opening of a putative dihydrophosphete to a vinylphosphinidene has been postulated by Bestmann et al.: Bestmann, H. J.; Schmid, G.; Sandmeier, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 53-54. Mathey has reported similar reactivity for the $W(CO)_5$ complex of a dihydrophosphete: Tran Huy, N. H.; Mathey, F. *Tetrahedron Lett.* **1988**, *29*, 3077.

(12) Atom numbering scheme:



Design and Dynamics of a Chemically Triggered Reaction Cascade Leading to Biradical Formation at Subambient Temperature

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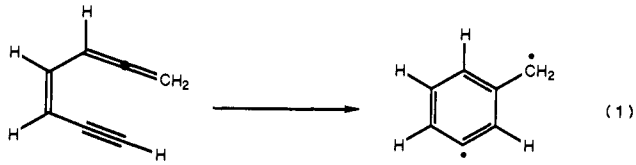
Received September 11, 1989

Mechanistic studies of the antitumor agents neocarzinostatin,[1] calichemicin,[2] and esperamicin[3] suggest, at a minimum, three common features essential to the operation of these antibiotics: (1) nondestructive high-affinity binding to DNA and (2) a chemical triggering mechanism leading to a high-energy intermediate capable of (3) rapid biradical formation at physiological temperatures. We describe herein the design, synthesis, and reactivity of a molecule that exhibits the latter two features and can be readily adapted to incorporate the first.[4]

Thiol **1** was envisioned to undergo a base-induced internal S_N2' displacement reaction to form the allenic sulfide **3** (Scheme I). This intermediate contains the (*Z*)-1,2,4-heptatrien-6-yne subunit, a functional group that has been shown to rearrange to the corresponding alkylbenzenediyl in the case of the parent substrate (*Z*)-1,2,4-heptatrien-6-yne ($\rightarrow\alpha$,3-dehydrotoluene, $t_{1/2} \sim 24$ h at 37 °C, eq 1).[5] In the latter study, it was demonstrated that



(1)

substitution of methyl for hydrogen on the allenic terminus leads to a 6-fold enhancement in the rate of biradical formation.[5] To the extent that the sulfur atom of **4** provides additional stabilization of a radical intermediate, the hypothetical cyclization **3** → **4** was anticipated to be even more rapid. The synthesis of **1** and **2** and the dynamics of their transformation to **3** and **4** are described below.

(*Z*)-Ethyl 2,3-dibromopropenoate underwent selective replacement of the β-bromide upon treatment with (trimethylsilyl)acetylene (1.7 equiv), *N,N*-diisopropylethylamine (1.7 equiv), cuprous iodide (0.20 equiv), and tetrakis(triphenylphosphine)-palladium (0.05 equiv) in *N,N*-dimethylformamide at 0 °C for 10 h, to produce the (*Z*)-bromo ester **5** in 90% yield.[6] Reduction of the ester group of **5** with diisobutylaluminum hydride (2.3 equiv) in toluene at −78 °C for 30 min and at 0 °C for 30 min formed the corresponding alcohol (94%), which was protected as its *tert*-butyldiphenylsilyl ether derivative [*tert*-butyldiphenylsilyl chloride (1.2 equiv), 4-(dimethylamino)pyridine (DMAP, 0.27 equiv), and triethylamine (5 equiv) in methylene chloride at 23 °C for 3.5 h, 95%]. Slow addition of bromide **6** to a solution of *tert*-butyllithium (2.5 equiv, 0.14 M) in tetrahydrofuran–ether–

(1) (a) Kappen, L. S.; Goldberg, I. H. *Nucleic Acids Res.* **1985**, *13*, 1637. (b) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146 and references therein.

(2) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198.

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(4) Dervan and co-workers have designed molecules that recognize DNA sequence specifically and can be chemically activated to cleave DNA by a free-radical mechanism: (a) Dervan, P. B. *Science* **1986**, *232*, 464. (b) Dervan, P. B. In *Nucleic Acids and Molecular Biology*; Eckstein, F., Lilley, D. M. J., Eds.; Springer-Verlag: Berlin, 1988; Vol. 2, p 49.

(5) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

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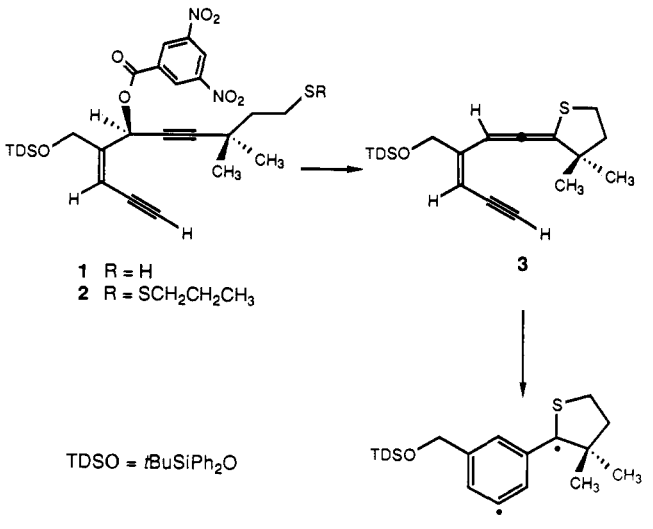
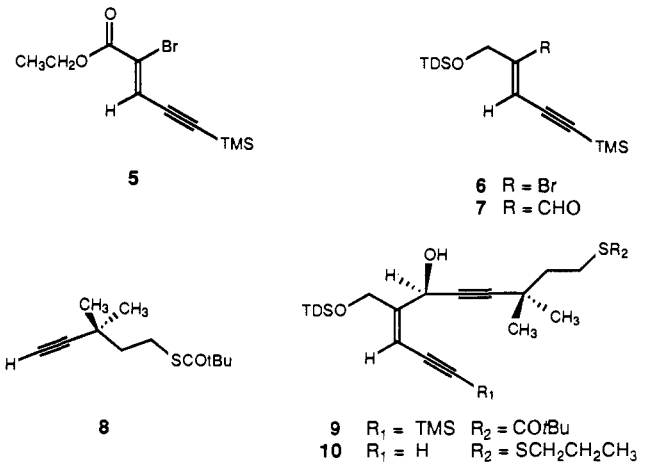
Scheme I

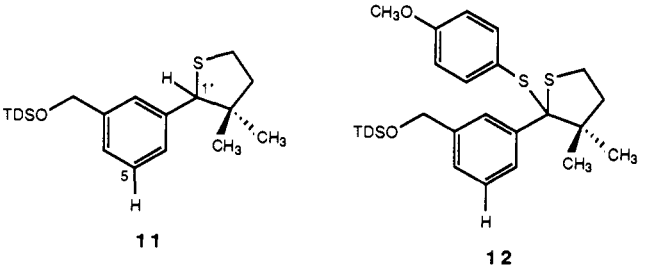


pentane (4:1:1) at −120 °C led to its smooth transformation to the corresponding vinyllithium reagent, which was trapped at −120 °C with *N*,*N*-dimethylformamide (2.5 equiv), to provide the



aldehyde **7** in 71% yield after aqueous workup and flash column chromatography.[6,7] Treatment of a solution of 3,3-dimethyl-4-pentyn-1-ol[8] (0.28 M) in methylene chloride containing triethylamine (1.3 equiv) at 0 °C with methanesulfonyl chloride (1.2 equiv, addition over 15 min)[9] formed the corresponding methanesulfonate ester, which, after extractive isolation, was subjected to nucleophilic displacement with thiopivalic acid (6 equiv)–triethylamine (10 equiv) in tetrahydrofuran at 50 °C for 6 h, to produce the thiol ester **8** in 85% yield. Lithiation of **8** (1.2 equiv of **8**, 1.5 equiv of lithium diisopropylamide, tetrahydrofuran, −78 °C, 10 min) and subsequent addition of anhydrous cerium(III) chloride (1.5 equiv, −78 °C, 30-min incubation)[10] and the aldehyde **7** (1 equiv) afforded the coupling product **9** in 90% yield. Exposure of **9** to 0.1 M sodium hydroxide in an ice-cooled solution of tetrahydrofuran–methanol–propyl disulfide (4:1:1) for 3 h brought about the following transformations: (1) removal of the acetylenic trimethylsilyl protecting group, (2) hydrolysis of the thiol ester, and (3) transdisulfidation of propyl disulfide with the resulting thiol to form the disulfide **10** (74% overall). Activation of the hydroxyl group of **10** as its 3,5-dinitrobenzoic acid ester was accomplished with 3,5-dinitrobenzoic acid (10 equiv), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (10 equiv), and DMAP (5 equiv) in methylene chloride at 0 °C for 30 min, to furnish **2** in 90% yield. Disulfide cleavage with tributylphosphine (10 equiv) in dimethoxyethane–water (4:1) at 0 °C for 30 min afforded the thiol **1** (82%), which was found to be stable for brief periods under neutral to slightly acidic conditions.

Addition of triethylamine (5.0 equiv) to a deoxygenated solution of thiol **1** (0.01 M) in dimethyl sulfoxide (DMSO) containing 1,4-cyclohexadiene (1.0 M) at 25 °C led to rapid formation of the aromatic sulfide **11**, the product of formal addition of dihydrogen to the biradical **4**, in 75% yield. When 1,4-cyclohexadiene was omitted from the latter experiment, an intractable product mixture was obtained, suggesting that oligomerization had occurred. Use of 1,4-cyclohexadiene-d_8 (96% deuterium content at the allylic positions, 1.0 M)[11] afforded **11** (45%) with incorporation of deuterium at C5 (60%) and C1′ (90%), sites of odd electron density in the biradical **4**.[12]



Further support for the formation of **11** by the pathway **1** → **3** → **4** → **11** was obtained in the following experiment. A deoxygenated solution of **1** (0.02 M) in DMSO-d_6–CD_2Cl_2 (2.3:1) containing 1,4-cyclohexadiene (0.26 M) and *trans*-1,2-dichloroethylene (internal reference) was cooled to 10 °C in the probe of a high-field NMR spectrometer. Addition of triethylamine (2.2 equiv) with subsequent monitoring by ^{1}H NMR spectroscopy showed complete transformation of **1** to a new compound within 30 min at 10 °C. Signals observed for this product were consistent with the proposed intermediate **3**.[13] In a slower step, resonances for **3** were observed to undergo first-order decay ($k = 3.6 \pm 0.5 \times 10^{-4}$ s^{-1} at 10 °C, two determinations) while signals corresponding to **11** increased (yield ~ 70%). These data are consistent with a mechanism in which intermediate **3** undergoes rate-limiting, first-order cyclization to the biradical **4** ($\Delta G^{\ddagger} = 21.0$ kcal/mol), which is then rapidly transformed to the product **11**.

Treatment of the disulfide **2** (0.007 M) with *p*-methoxythiophenol (3.0 equiv) in DMSO containing triethylamine (5.0 equiv) produced the thiol-addition product **12** (75%) along with the "dihydro" product **11** (22%) in a reaction requiring 30 min at 23 °C for completion. The regiochemistry of thiol addition is consistent with the orientational outcome of radical and polar additions to α,3-dehydrotoluene.[5] Dilution of the reaction medium with less polar organic solvents was found to considerably slow the reaction (e.g., $t_{1/2}$ ~ 6 h at 23 °C in 1.5:1 DMSO–tetrahydrofuran). Control experiments with the disulfide **10** established that the observed rate of reaction in each respective solvent was approximately equal to the rate of disulfide cleavage in that medium. The data suggest a change in rate-determining step from biradical formation (**3** → **4**) to disulfide cleavage (**2** → **1**) with the substrate **2**.[14]

(7) Köbrich, G.; Trapp, H. *Chem. Ber.* **1966**, *99*, 680.
(8) McMurry, J.; Matz, J. R.; Kees, K. L.; Bock, P. A. *Tetrahedron Lett.* **1982**, *23*, 1777.
(9) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(10) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(11) Prepared by electrolysis of benzene-d_6 with D_2O; see: Kariv-Miller, E.; Swenson, K. E.; Lehman, G. K.; Andruzzi, R. *J. Org. Chem.* **1985**, *50*, 556. We are grateful to Dr. James Toth and David Blauch for their assistance with this procedure.
(12) The poorer yield of **11** with perdeuteriocyclohexadiene is presumably a manifestation of the deuterium isotope effect. The labeling data are consistent with initial, less discriminating reaction at the vinylic position with subsequent trapping of the stable benzylic radical with cyclohexadiene or cyclohexadienyl radical (ref 5).
(13) Selected ^{1}H NMR spectral data for **1** and **3**: δ C=C*H* (**1**) 6.12 (d, $J = 2.2$ Hz), (**3**) 5.90 (d, $J = 1.5$ Hz); δ CH_2OTDS (**1**) 4.60 (AB, $J = 21.9$ Hz), (**3**) 4.21 (AB, $J = 19.8$ Hz); δ ArCO$_2$C*H* → C=C=C*H* (**1**) 6.72 (s), (**3**) 6.62 (s).

In summary, our experiments support a scheme whereby **1** and **2** are transformed upon treatment with various chemical agents to the intermediate **3** and then to the biradical **4**. The latter cyclization is rapid at 10 °C and is calculated to have a half-life of ~2 min at 37 °C.[15]

Acknowledgment. Financial support from the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

(14) Mechanisms that do not involve **1** as an intermediate in the formation of **11** and **12** from **2** can also be invoked.

(15) This calculation is based on an assumed $\Delta S^{\ddagger}$ of -11.6 ± 1.5 eu (ref 5).

Concave Functionality: Intracavity Phosphine Oxide as a Locus of Complexation

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The design of host molecules capable of binding neutral organic guests is an area of considerable current interest.[1] Our interest in macrocycles containing cavities bearing concave functionalities[2] led to our preparation of cages **2–5**. Since phosphine oxides have been demonstrated to serve as strong hydrogen-bond acceptors,[3] we chose to incorporate this functionality in the construction of macrocycles. We report the synthesis and preliminary binding studies of two exo–exo (**2** and **4**) and two endo–exo (**3** and **5**) bifunctional cages confirming that **3** and **5** exhibit intracavity complexation.

Synthesis. Reaction of tris(4-hydroxyphenyl)phosphine oxide[4] with propargyl bromide and K_2CO_3 in acetone afforded tris(4-propargyloxyphenyl)phosphine oxide (**1**). Treatment of **1** in pyridine at 60 °C with $Cu(OAc)_2 \cdot H_2O$ for 2 h provided 14% and 7% yields of **2** and **3**, respectively, after isolation (Scheme I). Monoclinic crystals of **2** from chloroform were suitable for an X-ray structure determination. The space-filling representation (Figure 1), excluding solvent, confirms the exo orientation of both phosphine oxides, and a P–P distance of 10.85 Å was observed.

Hydrogenation of **2** afforded **4** in 47% yield, while hydrogenation of **3** provided **5** in 53% yield. The ^1H NMR spectra of **3** and **5** indicated four types of aromatic protons while **2** and **4** showed only two. Lanthanide shift reagents confirmed that the most downfield of the aromatic protons (**3**, 8.06 ppm; **5**, 7.86 ppm) in the two endo–exo hosts were those ortho to the exo phosphine oxide. The X-ray structure of **5** (Figure 2) obtained from triclinic crystals grown from wet ethyl acetate verifies the presence of the endo phosphine oxide. The water in the crystal structure was observed to exist in either of two locations: both showed hydrogen bonding to the exo phosphine oxide. The reduced intracavity space of **5** relative to **2** is apparent.

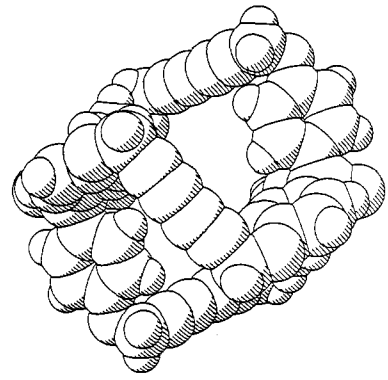

Figure 1. Space-filling representation of **2** generated by SHELXTL PLUS, based on X-ray data collected at −150 °C. Solvent molecules are excluded from the structure. The final R value after refinement was 0.108. The P–P distance is 10.85 Å.

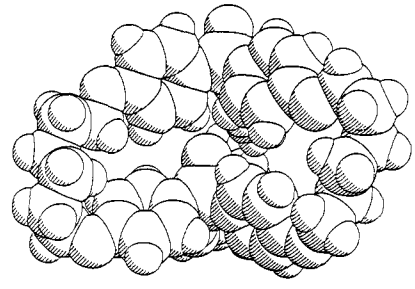

Figure 2. Space-filling representation of **5** generated by SHELXTL PLUS, based on X-ray data collected at −100 °C. Ethyl acetate and water molecules are excluded from the structure. The final R value after refinement was 0.0602.

Complexation. Titration of **3** or **5** with *p*-nitrophenol (PNP) in $CDCl_3$ results in a dramatic upfield shift of the protons ortho to the exo phosphoryl sites (**3**, 8.06 ppm; **5**, 7.86 ppm) in the ^1H NMR spectra. Similar treatment of **2** or **4** results in no substantial movement of host protons.[5] However, competition studies with **3** confirm the nonshifting exo complexation of PNP by **2** and **4**. The exo phosphoryl sites in **3** and **5** are proposed to bind similarly with an induced shift of host protons resulting only from endo complexation. The large shift of host protons ortho to the exo phosphine oxides upon endo complexation is attributed to the proximity of the guest's aromatic ring to these protons. Figures 3 and 4 illustrate the observed chemical shifts for the protons studied on **3** and **5** at various concentrations of PNP in addition to the curve fitted by Simplex.[6,7]

The two different phosphoryl sites on **3** and **5** indicate that initial complexation may occur at either the exo or the endo phosphoryl in 1:2 complex formation. Figure 3 is consistent with initial binding at the endo site, since the chemical shift of the 1:1 complex (7.42 ppm) derived from Simplex is substantially different from that of the free host, but identical with the derived shift of the 1:2 complex (7.42 ppm). The $^{endo}K_{assoc}$ is 354 M^{-1}, and the $^{exo}K_{assoc}$

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(4) Senear, A. E.; Valient, W.; Wirth, J. *J. Org. Chem.* **1960**, *25*, 2001–2006.

(5) No substantial movement indicates that less than 0.05 ppm shifting of any host proton occurred in the proton NMR on addition of 4 equiv of guest.

(6) A nonlinear-least-squares program was written by using the Simplex algorithm. It handles several complexation cases and has an attached PostScript and graphical user interface. The source (Turbo C) is available from the authors upon request.

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