= 15.0 Hz, HCHPh), 4.39 (d, 1 H, J = 5.1 Hz, C_3H), 4.30 (d, 1 H, J = 15.0 Hz, HCHPh), 4.26 (dd, 1 H, J = 7.2 Hz, J' = 8.6 Hz, HCHO-CO), 3.86 (dd, 1 H, J = 5.0 Hz, J' = 12.3 Hz, HCHOH), 3.68 (dd, 1 H, J = 5.0 Hz, J' = 12.3 Hz, HCHOH), 3.56-3.51 (m, 1 H, C_4H), 3.17 (s_b, 1 H, OH). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.00; H, 5.88; N, 8.12.

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Supplementary Material Available: Listings of experimental details and spectral data for **4a-d**, **7a,b**, **8a-d**, **11a-d**, **14a-d**, **15a**, **16a**, **22**, **23**, **28**, and **29**, tables of X-ray data and structures for **6a**, **38**, and **39**, and ^{1}H NMR spectra for **4c**, **7a,b**, and **19-21** (18 pages); table of observed and calculated structure factors (19 pages). Ordering information is given on any current masthead page.

Studies on the Thermal Generation and Reactivity of a Class of (σ,π)-1,4-Biradicals

Andrew G. Myers,* Peter S. Dragovich, and Elaine Y. Kuo

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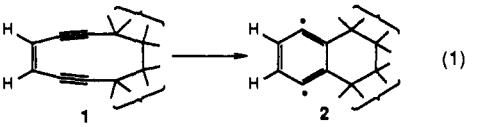
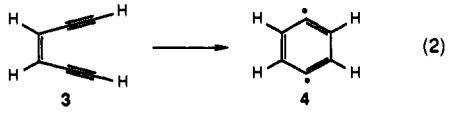
Abstract: (*Z*)-1,2,4-Heptatrien-6-yne and compounds that contain the (*Z*)-allene-ene-yne functional group or that form it in a serial reaction sequence were prepared and shown to undergo a mild thermal reaction to form aromatic products. All observations suggest that the initial step in the formation of these products is an electrocyclization reaction that forms α,3-dehydrotoluene in the parent case or the corresponding α,3-dehydroalkylbenzene in other examples. These dehydroaromatic intermediates are not observed directly but react to form products conventionally ascribed to both free radical and polar species. For example, (*Z*)-1,2,4-heptatrien-6-yne forms both 2-phenylethanol and phenyl methyl ether when heated in methanol. Mechanistic studies suggest that both products arise from a common intermediate, the so-called α,3-dehydrotoluene, that is best described as a singlet σ,π-biradical with substantial polar character. The partitioning between polar and free radical reaction pathways is influenced by biradical substitution and by the reaction medium in which the intermediate is generated. These results are discussed with reference to electrocyclization reactions occurring within the enediyne family of natural antitumor agents. The possibility that an α,3-dehydrotoluene intermediate might function as a DNA damaging agent and criteria for the design of molecules to implement such a strategy are discussed.

Introduction

Several lines of evidence now support the intermediacy of 1,4-biradicals as a common feature in the mechanism of action of the class of natural antitumor antibiotics comprising neocarzinostatin, calichemicin, esperamicin, and, most recently, dynemicin (the enediyne antibiotics).[1] These biradical intermediates are proposed to arise by electrocyclization of highly unsaturated precursors, formed from the native antibiotic as the result of a prior chemical "activation" step.[1] In the case of the natural products calichemicin, esperamicin, and dynemicin, cyclization may be generally represented by the transformation of the (*Z*)-enediyne **1** to the dehydrobenzene derivative **2** (eq 1) and is recognized to be a cyclic version of a hydrocarbon thermal rearrangement studied extensively by Bergman and co-workers (**3** → **4**, eq 2), now known as the Bergman reaction.[2]

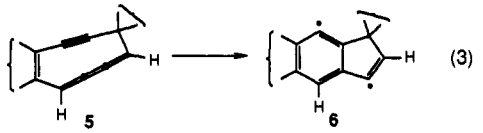


(1)

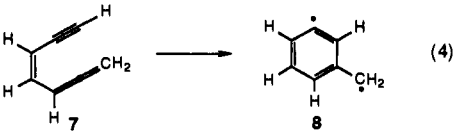


(2)

Cyclization of the (*Z*)-cumulene-ene-yne **5** to form the biradical **6** (eq 3) is proposed as the key step in the mechanism of action of the antitumor agent neocarzinostatin.[1a-c] This reaction



(3)



(4)

shares many features of reactions 1 and 2 but lacks precedent in known hydrocarbon thermal rearrangements. These factors led us to consider the feasibility of the related rearrangement of the acyclic hydrocarbon **7** to the biradical **8** (eq 4).[3,4] Though inspired

(1) Neocarzinostatin: (a) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 4493. (b) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (c) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 1146. Calichemicin: (d) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (e) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. Esperamicin: (f) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (g) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462. Dynemicin: (h) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. Review: (i) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

(2) (a) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (c) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091.

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

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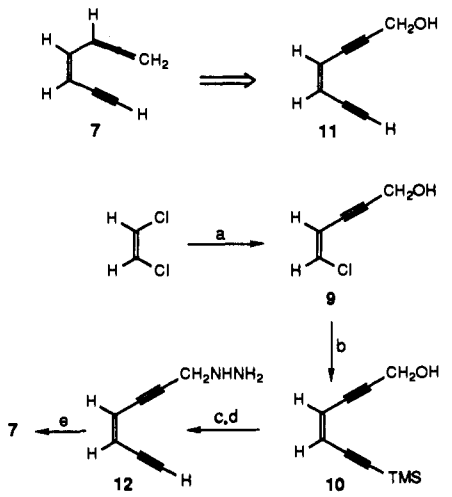
Scheme I[a]



[a] Reagents and conditions (TMS = $Si(CH_3)_3$): (a) 0.2 equiv $HC{\equiv}CCH_2OH$, 1.0 equiv n-$PrNH_2$, 0.03 equiv CuI, 0.01 equiv $Pd(PPh_3)_2Cl_2$, Et_2O, 0 → 23 °C, 6 h, 78%; (b) 1.4 equiv $HC{\equiv}CSi(CH_3)_3$, 4.0 equiv n-$PrNH_2$, 0.2 equiv CuI, 0.05 equiv $Pd(PPh_3)_4$, Et_2O, 0 °C, 1 h, 83%; (c) 2.0 equiv $KF{\cdot}2H_2O$, CH_3OH, 0 °C, 2.5 h, 96%; (d) 3.0 equiv CH_3SO_2Cl, 5.0 equiv Et_3N, CH_2Cl_2, 0 °C, 20 min; 14.3 equiv H_2NNH_2, 8:1 CH_2Cl_2:CH_3OH, 0 °C, 2 h; (e) 1.3 equiv MTAD, benzene-d_6, 23 °C, 20 min, 30% from **11**.

by reaction 3, the latter proposal differs significantly in that the ground-state structure of the product **8** is almost certain to be that of a σ,π-biradical, whereas **6** is constrained by geometry to be a σ,σ-biradical.[5] As discussed below, this distinction has important consequences in terms of thermochemistry and reactivity.

In this work we describe the preparation and cyclization behavior of (*Z*)-1,2,4-heptatrien-6-yne (**7**) and compounds that contain the (*Z*)-allene–ene–yne functional group or that form it in a serial reaction sequence.[3-5] Mechanistic studies are described which support the view that the (*Z*)-allene–ene–yne functional group undergoes a mild, thermal electrocyclization reaction to form an α,3-alkylbenzenediyl, a biradical intermediate with substantial polar character. These observations are discussed in light of mechanistic work concerning the enediyne antibiotics. The possibility that an α,3-dehydrotoluene intermediate might function as a DNA damaging agent and criteria for the design of molecules to implement such a strategy are also assessed.

Synthesis of (*Z*)-1,2,4-Heptatrien-6-yne (7)

The principal challenge in the development of a synthetic route to the hydrocarbon **7** is to construct the vinylallene with proper stereochemistry in a target molecule that is both thermally and chemically sensitive. Toward this end, a method for the synthesis of allenes from propargylic alcohols was devised which transforms, in the retrosynthetic sense, the target **7** into a more tractable precursor, the (*Z*)-enediyne **11** (Scheme I).[3,6] Stereospecific synthesis of this enediyne in a protected form (**10**) is readily achieved from (*Z*)-1,2-dichloroethylene, following the precedent of Kende and Smith,[7] by sequential coupling reactions with propargyl alcohol and (trimethylsilyl)acetylene, respectively (Scheme I).[8] Although the two coupling reactions can be run in sequence in a single flask, **10** is formed in greater yield and is more readily purified when the intermediate (*Z*)-vinyl chloride **9** is isolated by flash column chromatography on silica gel. The indicated order of acetylene coupling is preferred for the greater ease of purification of the vinyl chloride **9**. Thus, reaction of propargyl alcohol (1 equiv) with (*Z*)-1,2-dichloroethylene (5 equiv), bis(triphenylphosphine)palladium(II) chloride (0.05 equiv), and cuprous iodide (0.15 equiv) in ethyl ether containing *n*-propylamine (5 equiv) at 23 °C for 6 h affords, after extractive isolation and flash column chromatography, the (*Z*)-vinyl chloride **9** in 78% yield.[7,8] Subsequent coupling of **9** with (trimethylsilyl)acetylene (1.4 equiv) under similar conditions, albeit employing tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) as the palladium catalyst, provides the (*Z*)-enediyne **10** (83%).[8] Desilylation of **10** with potassium fluoride in methanol at 0 °C affords **11** in 96% yield. Although this deprotection can be deferred to a later stage of the synthesis, the sequence described here minimizes the number of volatile intermediates and ultimately facilitates the purification of **7**.

Transformation of the propargyl alcohol **11** to the allene **7** is initiated by hydroxyl activation with methanesulfonyl chloride (3.0 equiv) and triethylamine (5.0 equiv) in dichloromethane at 0 °C.[9] Following extractive isolation, the crude methanesulfonate ester (~0.3 M, CH_2Cl_2) is treated with a large excess of anhydrous hydrazine in methanol (14.3 equiv, 15 M) at 0 °C for 2 h to form the monoalkyl hydrazine **12**. Use of lesser quantities of hydrazine leads to competitive dialkylation, as anticipated given the greater nucleophilicity of alkylhydrazines versus hydrazine itself.[10] A simple aqueous extraction procedure serves to separate **12** from excess hydrazine. Treatment of crude **12** with a slight excess of diethyl azodicarboxylate (DEAD) or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) under anaerobic conditions at 0 °C then affords the allene **7**.[3,6] Mechanistic studies suggest that the latter reaction produces a mixture of (*E*)- and (*Z*)-diazenes; sigmatropic elimination of dinitrogen from the (*Z*)-diazene forms **7** directly while the (*E*)-isomer must first undergo rate-limiting $E \rightarrow Z$ isomerization.[11] Though several procedures have been found effective for purification of **7**, including preparative gas chromatography, the most straightforward entails the use of benzene-d_6 as solvent in the hydrazine oxidation step, followed by washing of the crude product solution with several portions of water, and separation and purification of the hydrocarbon layer by passage through a short column of silica gel. In this manner, solutions of the allene **7** in benzene-d_6 are obtained in >90% purity and ~30% yield (determined by addition of *m*-xylene as an internal standard and ^1H NMR analysis). Allene **7** is exceedingly volatile and must be stored anaerobically to avoid decomposition. Although the yield of **7** by this isolation method is modest, the simplicity of the procedure and purity of the product obtained recommend it above other methods of purification proceeding in higher yield.

A Surprisingly Facile Cyclization Reaction Forming α,3-Dehydrotoluene

Thermolysis of **7** in various solvents affords products consistent with the intermediacy of the biradical **8**, α,3-dehydrotoluene (Scheme II).[3] For example, heating solutions of **7** in deoxygenated benzene–1,4-cyclohexadiene forms toluene and the 1,4-cyclohexadiene adducts **14** and **15** as the only detectable volatile products. Preferential carbon–carbon bond formation at the

(4) For syntheses and study of other molecules which contain or form the (*Z*)-allene–ene–yne subunit, see: (a) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995. (b) Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907. (c) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825. (d) Toshima, K.; Ohta, K.; Ohtake, T.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 391. (e) Hirama, M.; Tokuda, M.; Fujiwara, K. *Synlett* **1991**, 694. (f) Toshima, K.; Ohta, K.; Ohtake, T.; Tatsuta, K. *J. Chem. Soc., Chem. Commun.* **1991**, 651. (g) Andemichael, Y. W.; Gu, Y. G.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 794. See also refs 5 and 1i.

(5) For syntheses and study of molecules which contain or form the (*Z*)-cumulene–ene–yne subunit, see: (a) Hirama, M.; Fujiwara, K.; Shigematu, K.; Fukazawa, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4120. (b) Fujiwara, K.; Kurisaki, A.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4329. (c) Fujiwara, K.; Sakai, H.; Hirama, M. *J. Org. Chem.* **1991**, *56*, 1688. (d) Myers, A. G.; Harrington, P. M.; Kwon, B.-M. *J. Am. Chem. Soc.* **1992**, *114*, 1086. See also refs 1a–c.

(6) Myers, A. G.; Finney, N. S.; Kuo, E. Y. *Tetrahedron Lett.* **1989**, *30*, 5747.

(7) (a) Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655. See also: (b) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631.

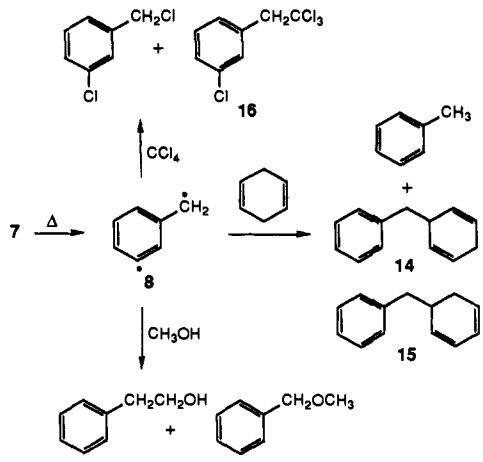
(8) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917. (c) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(9) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

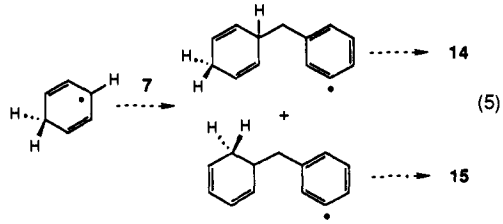
(10) Timberlake, J. W.; Stowell, J. C. In *The Chemistry of the Hydrazo, Azo and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975; p 70.

(11) Myers, A. G.; Finney, N. S. *J. Am. Chem. Soc.* **1990**, *112*, 9641.

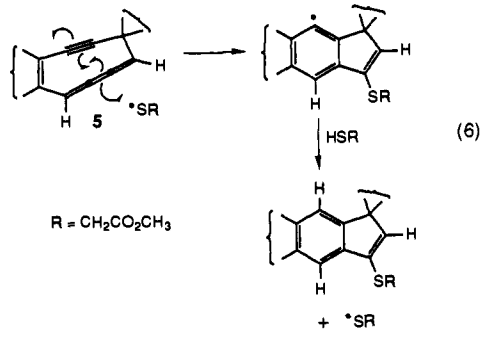
Scheme II



benzylic position (as opposed to the *m*-aryl position) in **14** and **15** is consistent with a scheme in which the more reactive σ-radical of **8** reacts initially by hydrogen atom abstraction from 1,4-cyclohexadiene, followed by recombination of the resulting pair of π-radicals (Scheme III). Products **14** and **15** can also be

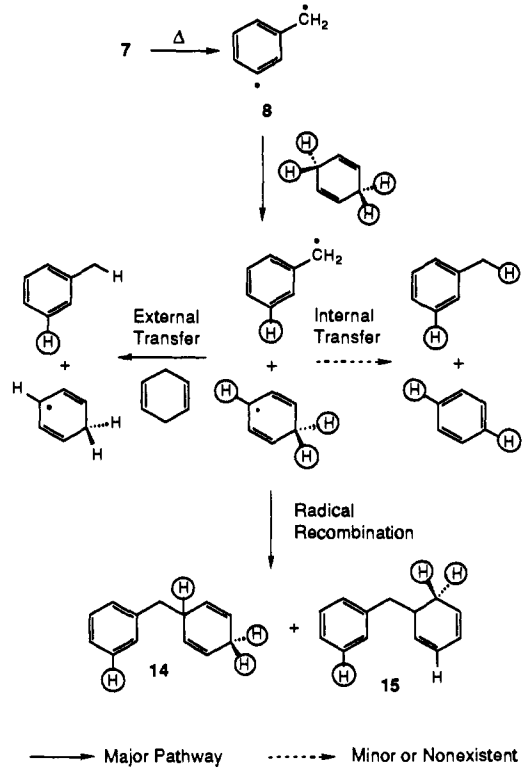


envisioned as arising by a sequence involving addition of cyclohexadienyl to the allenic terminus of **7**, cycloaromatization, and hydrogen atom abstraction (eq 5). Although precedent for such a radical chain aromatization exists (e.g., eq 6),[1c] the invariance of the ratio (**14** + **15**)/toluene with the concentration of **7** suggests that in the present case this pathway is at best a minor competitor with the simple recombination mechanism.



Further support for this contention is obtained from thermolysis experiments of **7** conducted in a mixture of 3,3,6,6-tetradeuterio-1,4-cyclohexadiene and unlabeled 1,4-cyclohexadiene (2:1, respectively, weighted to offset the isotope effect, 0.003 M **7**, 100 °C, 30 min, Scheme III). Under these conditions, the 1,4-cyclohexadiene addition products **14** and **15** are obtained as a 1:1 mixture in 55% yield.[12] The increased yield of the radical recombination products **14** and **15** versus toluene reflects the primary isotope effect in hydrogen atom transfer to the benzyl radical. Mass spectroscopic analysis of **14** and **15** shows that these products contain primarily four (d_4) or zero (d_0) deuterium atoms (36 and 55%, respectively, 91 ± 9% total) with ≤7% of crossover products

Scheme III



(d_1, d_3, average of two runs).[13] This result demonstrates that **14** and **15** arise primarily by radical cage recombination and not to any significant extent by a mechanism such as that shown in eq 5. In contrast, toluene produced in the above experiment is shown by mass spectroscopy to arise primarily by external hydrogen atom transfer (d_1:d_2 ~6:1, average of two runs, Scheme III).[12]

From several observations, it is clear that the efficient formation of stable volatile products in these thermolysis experiments depends critically upon the presence of high concentrations of a good radical trapping agent. In pyrolyses with 1,4-cyclohexadiene in benzene, for example, the combined yield of **14**, **15**, and toluene is found to increase with diminishing concentrations of **7** and with increasing concentrations of 1,4-cyclohexadiene (Table I, entries 1–3). These results are reasonably accounted for by invoking secondary reactions of **7** with the free radical products of its thermolysis.[14] While the nature of these secondary reactions is not known, due to our inability to detect byproducts by capillary gas chromatography or by ^{1}H NMR analysis it is presumed that such products are either oligomeric or highly unstable. As results below amply demonstrate, diminished chemical yields clearly correlate with the onset of free radical reactions. As a cautionary note, it is important to point out that the decomposition of **7** under conditions that produce less than quantitative yields of volatile products does not deviate appreciably from first-order behavior, albeit exhibiting a shorter half-life than that of **7** thermolyzed under ideal conditions.[15] Kinetic measurements under the latter conditions (combined yield of toluene, **14**, and **15** >95%, Table I, entry 3) are obtained over a 60-deg range (39–100 °C, Table II) using capillary gas chromatography and provide the following activation parameters: $\Delta H^{\ddagger}$ = 21.8 ± 0.5 kcal/mol, $\Delta S^{\ddagger}$ = −11.6 ± 1.5 eu (E_a = 22.5 kcal/mol, log A = 10.7).[3] The enthalpy of activation for the cyclization of **7** is some 10 kcal/mol lower than that for the cyclization of (*Z*)-hex-3-ene-1,5-diyne (**3**)[2a] and approximates that of strained cyclic (*Z*)-enediyne cyclizations (e.g.,

(12) The presence of toluene as a contaminant in the commercial 3,3,6,6-tetradeuterio-1,4-cyclohexadiene employed in this experiment prevents an accurate determination of the yield of toluene formed from **7**. The ratio of toluene-d_2:toluene-d_1 is estimated by correcting for contaminating natural-abundance toluene-d_1.

(13) The yield of d_2 products is <2%.

(14) With benzene as solvent, the formation of addition products with the solvent cannot be ruled out.

(15) For this reason, the activation parameters of ref 4b must be regarded with caution.

Table I. Product Distributions Obtained upon Pyrolysis of **7** in Various Media at 100 °C

			products[a]						
entry	solvent	[7] (mM)	toluene	**14** + **15**	bibenzyl	3-chlorobenzyl chloride	**16**	methyl benzyl ether	2-phenyl-ethanol
1	CHD[b] (0.4 M)–benzene	9.0	16	10					
2	CHD (4.0 M)–benzene	4.5	34	15					
3	CHD	3.0	60	40					
4	CCl_4	8.0[c]				1	14		
5	CCl_4	8.0				5	18		
6	CCl_4	0.8				8	16		
7	CH_3OH	3.0			2			38	10
8	CH_3OH[d]	3.0			2			35	10
9	CH_3OH[e]	3.0			2			34	9
10	CD_3OH	3.0						70	
11	CH_3OD	3.0			3			18	21
12	CHD (0.2 M)–CH_3OH	3.0	19	9	1			25	1
13	CHD (1.0 M)–CH_3OH	3.0	32	19				12	
14	H_2O (5.6 M)–CH_3OH	3.0			1			47[f]	7
15	CF_3CH_2OH (1.4 M)–CH_3OH	3.0			1			51[g]	7

[a] Yields determined by GLC using *m*-xylene as an internal standard. [b] CHD = 1,4-cyclohexadiene. [c] 10^{-2} M. [d] Reaction glassware rinsed twice with 1,1,1,3,3,3-hexamethyldisilazane prior to pyrolysis. [e] Reaction glassware rinsed twice with glacial acetic acid prior to pyrolysis. [f] Benzyl alcohol also obtained in 6% yield. [g] 1,1,1-Trifluoroethyl benzyl ether also obtained in 3% yield.

Table II. Kinetic Parameters for the Thermal Cyclization of **7** (0.003 M) in 1,4-Cyclohexadiene

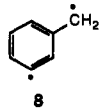
T (°C)	*k* (s^{-1})	$t_{1/2}$
39	$(9.40 \pm 1.50) \times 10^{-6}$	20.5 h
59	$(1.08 \pm 0.24) \times 10^{-4}$	1.8 h
77	$(4.92 \pm 0.01) \times 10^{-4}$	23.0 min
90	$(1.72 \pm 0.52) \times 10^{-3}$	6.7 min
100	$(3.40 \pm 1.20) \times 10^{-3}$	3.4 min

eq 11).[16] This cyclization also exhibits a rather large negative entropy of activation, a feature which further distinguishes it from reactions 1, 2, and 3.[17] This is thought to be due, in part, to the loss of rotational freedom about the C3–C4 σ-bond in the transition state for cyclization of **7**.

Thermolysis of **7** in oxygen-free carbon tetrachloride proceeds in analogy to experiments conducted in 1,4-cyclohexadiene, forming 3-chlorobenzyl chloride and the carbon tetrachloride adduct **16** in 15–24% combined yield (Scheme II). The lower yield of volatile products in these experiments, as compared with those conducted in 1,4-cyclohexadiene, presumably arises from slower trapping of the 3-chlorobenzyl radical by carbon tetrachloride, allowing secondary reactions with **7** to compete more effectively. Consistent with this idea, the yield of volatile products is found to rise with decreasing concentrations of **7** (Table I, entries 4–6).

Dichotomous Reactivity—Polar Chemistry of α,3-Dehydrotoluene (8)

Pyrolysis experiments conducted in protic media reveal an unanticipated complexity in the reactivity of the hypothesized intermediate **8**. For example, heating **7** (0.003 M, 100 °C) in deoxygenated methanol forms in addition to 2-phenylethanol (10%) and bibenzyl (2%) products anticipated from a biradical description of **8**, methyl benzyl ether (38%), a product more consistent with the zwitterionic structure **17**.[3] This product



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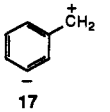


17

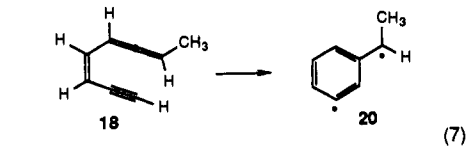
distribution is reproducible and is shown in control experiments to be insensitive to acidic or basic pretreatment of the glass reaction surface (Table I, entries 7–9), discounting the formation of methyl benzyl ether by adventitious acid or base. Mechanistic studies presented below support the notion that products from both polar and free radical reaction pathways arise from a single reactive intermediate or, indistinguishable by our experiments, a pair of rapidly equilibrating species rather than from discreet pathways involving slowly equilibrating or nonequilibrating intermediates, e.g., ground-state and electronically-excited forms of **8**. The latter cascade-type mechanisms are rendered less likely by the following observations. Heating **7** in CD_3OH (0.003 M, 100 °C) forms methyl-d_3 benzyl ether as the only detectable product in 70% yield (Table I, entry 10). A pathway involving formation of a short-lived "polar" species that decays irreversibly to an intermediate with radical reactivity is clearly inconsistent with the observed near-doubling of the yield of methyl benzyl ether. Conversely, pyrolysis of **7** in CH_3OD affords methyl benzyl-d_1 ether (18%) and 2-phenylethanol (21%) (Table I, entry 11), a distribution inconsistent with a cascade involving the inverse order of reactive intermediates, i.e., a short-lived biradical and ground-state polar species. Importantly, the kinetics of decomposition of **7** in CD_3OH, where methyl-d_3 benzyl ether is formed essentially exclusively, are first order and are indistinguishable, within experimental error, from those observed in pure 1,4-cyclohexadiene, where products anticipated from standard free radical reactions are formed ($k = (4.0 \pm 0.2) \times 10^{-4}$ and $(3.8 \pm 0.2) \times 10^{-4}$ s^{-1}, respectively, at 75 °C). This result strongly suggests that the two pathways, producing polar and free radical products, respectively, share a common rate-limiting step, proposed here to be the cyclization of **7** to **8**. It is further proposed that **8** partitions irreversibly in the next step, bond formation at the *m*-aryl position, in a manner predictable given the relevant homolytic bond strengths and acidity constants of the pyrolysis medium. In support of this proposal, it is found that addition of 1,4-cyclohexadiene to pyrolysis solutions of **7** in methanol leads to the formation of toluene, bibenzyl, and **14** and **15**, with a corresponding diminution in the production of methyl benzyl ether (Table I, entries 12 and 13). Similarly, increasing the acidity of the medium, by addition of water or trifluoroethanol, shifts the product distribution in favor of polar addition products (Table I, entries 14 and 15).

Simple Substitution and Further Reactivity Studies

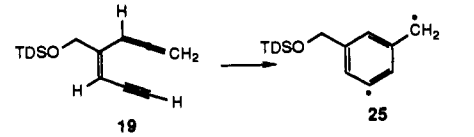
Substrates **18** and **19** probe the effect of simple substitution upon the cyclization reaction and provide important background information for studies of more elaborate substrates described later in this work. Cyclization of **18** is anticipated to form the biradical **20** in which the benzylic carbon bears a methyl substituent (eq 7). To the extent that this carbon is electron deficient in the transition state for cyclization, **18** is predicted to react more rapidly than the parent hydrocarbon **7**. The synthesis of **18** follows closely that described for the allene **7** (eq 8). Thermal reaction of **18**

(16) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. For a review, see ref 1i.

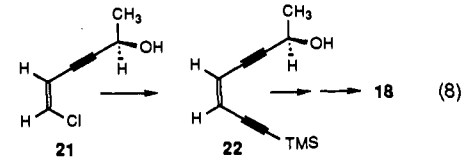
(17) The entropy of activation for the Bergman reaction has been assumed to be near 0 (ref 2a). The entropy of activation for cyclization of a complex synthetic (*Z*)-enediyne has been determined experimentally to be −7 eu: Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986.



(7)

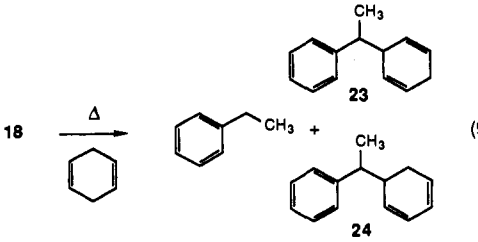


TDS = *t*-Bu(Ph)$_2$Si



(8)

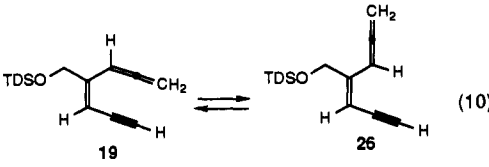
in deoxygenated 1,4-cyclohexadiene proceeds as with **7** to form the corresponding products ethylbenzene (45%) and addition products **23** and **24** (55%) (eq 9).[3] This product distribution



(9)

suggests that the relative rate of hydrogen atom abstraction from 1,4-cyclohexadiene versus cage recombination with cyclohexadienyl is lower for the 1-phenylethyl radical than for the more reactive benzyl radical. Kinetic analysis of the cyclization of **18** at 78 °C shows that methyl substitution does indeed accelerate the reaction by nearly 6-fold versus the cyclization of **7** (k = (3.24 ± 0.75) × 10^{-3} and (4.92 ± 0.01) × 10^{-4} s^{-1}, respectively). One tentative conclusion from this observation is that it may be possible to vary the rate of biradical formation in these systems through substitution of the allenic terminus, in contrast to the cyclizations of eqs 1 and 3 where substitution of the radical-bearing centers is not possible.

"Meta"-substitution, as exemplified by substrate **19**, is anticipated to have less of an impact upon the rate of cyclization to the biradical **25** (eq 7), barring an influence on the population of rotamers **19** and **26** (eq 10). The latter is reminiscent of the

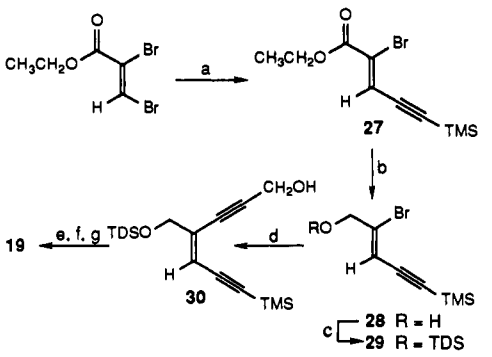


(10)

effect of butadiene 2-substitution in the Diels–Alder reaction. The ((*tert*-butyldiphenylsilyl)oxy)methyl group (TDSOCH$_2$) is chosen for the dual purpose of examining its effect as a substituent and its potential as a site for the attachment of auxiliary groups, e.g., DNA-binding moieties (vide infra). In order to employ the synthetic strategy used to prepare the allenes **7** and **18** in the synthesis of **19**, the trisubstituted enediyne **30** is required. The preparation of this substrate on a multigram scale is based on the development of a high-yield, β-selective coupling reaction of (*Z*)-ethyl 2,3-dibromopropenoate[18] with (trimethylsilyl)acetylene to form the bromo (*Z*)-enyne **27** (Scheme IV).[19] Ester reduction with diisobutylaluminum hydride in toluene at −78 °C and protection of the resulting alcohol **28** with *tert*-butyldiphenylsilyl chloride, triethylamine, and a catalytic quantity of 4-(di-

(18) Hall, R. G.; Trippett, S. *Tetrahedron Lett.* **1982**, *23*, 2603.
(19) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.

Scheme IV[a]



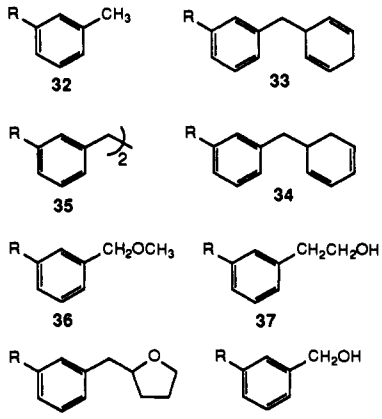
[a] Reagents and conditions (TMS = Si(CH$_3$)$_3$, TDS = SiPh$_2$-*t*-Bu): (a) 1.7 equiv HC≡CSi(CH$_3$)$_3$, 1.7 equiv *i*-Pr$_2$NEt, 0.2 equiv CuI, 0.05 equiv Pd(PPh$_3$)$_4$, DMF, 0 °C, 10 h, 86%; (b) 2.3 equiv *i*-Bu$_2$AlH, toluene, −78 → 0 °C, 30 min, 94%; (c) 1.2 equiv *t*-BuPh$_2$SiCl, 5.0 equiv Et$_3$N, 0.3 equiv DMAP, CH$_2$Cl$_2$, 0 → 23 °C, 3.5 h, 95%; (d) 2.0 equiv HC≡CCH$_2$OH, 4.0 equiv *n*-PrNH$_2$, 0.15 equiv CuI, 0.05 Pd(PPh$_3$)$_2$Cl$_2$, THF, 0 → 23 °C, 14 h, 86%; (e) 0.1 M NaOH, CH$_3$OH, 0 °C, 45 min; (f) 3.0 equiv CH$_3$SO$_2$Cl, 5.0 equiv Et$_3$N, CH$_2$Cl$_2$, 0 °C, 15 min; 30 equiv H$_2$NNH$_2$, CH$_3$OH, 12 h; (g) 1.2 equiv MTAD, Et$_2$O, 0 °C, 15 min, 40% from **30**.

Table III. Thermal Cyclization of **19** in Various Media[a]

		products[b]					
entry	medium	**32**	**33 + 34**	**35**	**36**	**37**	**38**
1	1,4-cyclohexadiene (4.0 M)–DMSO	50	40	1			
2	CH$_3$OH			1	39	7	
3	CH$_3$OD			1	19	12	
4	CD$_3$OH				52		
5	CH$_3$OH (4.0 M)–DMSO			1		10	
6	H$_2$O (11.0 M)–THF	6		1			23

[a] 0.01 M, 60 °C. [b] Yields determined by ^{1}H NMR analysis of crude reaction mixtures using (*Z*)-1,2-dichloroethylene as an internal standard.

Chart I



methylamino)pyridine furnishes the bromo (*Z*)-enyne **29** in 89% yield. Coupling of **29** and propargyl alcohol (2 equiv) in the presence of *n*-propylamine (4 equiv), cuprous iodide (0.15 equiv), and bis(triphenylphosphine)palladium(II) chloride (0.05 equiv) produces the enediyne **30** in 86% yield. Enediyne **30** is submitted to a sequence of steps similar to those outlined above for the synthesis of (*Z*)-allene–ene–ynes **7** and **18** to provide the target **19** in 40% yield. Heating **19** (0.01 M, 60 °C) in deoxygenated dimethyl sulfoxide (DMSO) containing 1,4-cyclohexadiene (4.0 M) affords 3-tolyl-*tert*-butyldiphenylsilyl ether (**32**) (50%), the 1,4-cyclohexadiene addition products **33** and **34** (40%), and the bibenzyl derivative **35** (1%) (Table III, entry 1). The kinetics

of cyclization of **19** (0.01 M in DMSO-d_6, 4.0 M 1,4-cyclohexadiene, determined by ^{1}H NMR analysis at 60 °C) are first order and are indistinguishable from those of **7** in 1,4-cyclohexadiene at the same temperature (k = (1.09 ± 0.01) × 10^{-4} and (1.08 ± 0.24) × 10^{-4} s^{-1}, respectively). Reacting **19** at 60 °C in oxygen-free CH_3OH, CH_3OD, and CD_3OH essentially replicates the distribution of polar (**36**) and free radical (**35** and **37**) addition products observed with **7** in the same solvents (Table III, entries 2–4), whereas heating **19** in 4.0 M methanol in DMSO forms only products of free radical addition, **35** and **37** (Table III, entry 5). The low yield of products in the latter experiment is consistent with the poorer ability of methanol to function as an effective radical trap versus, e.g., 1,4-cyclohexadiene. The decreased polar reactivity of **25** in methanol–DMSO mixtures versus neat methanol is presumably due to strong hydrogen bonding and decreased acidity of the methanolic hydroxyl group in the former medium. Heating solutions of **19** in deoxygenated 20% aqueous tetrahydrofuran at 60 °C (Table III, entry 6) affords the tetrahydrofuran adduct **38** as the major product (23%), as well as lesser amounts of free radical products **32** and **35** (6 and 1%, respectively) with <1% of benzyl alcohol **39**, the product of polar addition of water. The latter observation is significant in that it demonstrates the ability of biradicals such as **25** to undergo hydrogen atom transfer reactions, in lieu of polar trapping, in the presence of water.

Chemical Activation in Biradical Formation—Design, Dynamics, and Reactivity

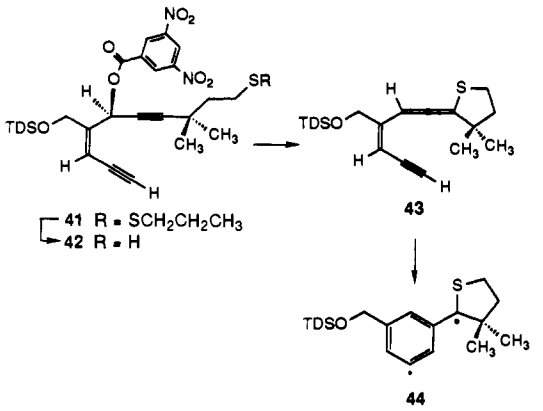
From activation parameters derived above, the half-life for formation of α,3-dehydrotoluene from (*Z*)-1,2,4-heptatrien-6-yne (**7**) can be calculated to be ~24 h at 37 °C. Comparable rates of biradical formation at this temperature from the cyclization of (*Z*)-enediynes are achieved only by ground-state destabilization, e.g., the strained (*Z*)-enediyne **40** is observed to cyclize with a half-life of 18 h at 37 °C (eq 11).[16] It is clear that the (*Z*)-

40 (11)

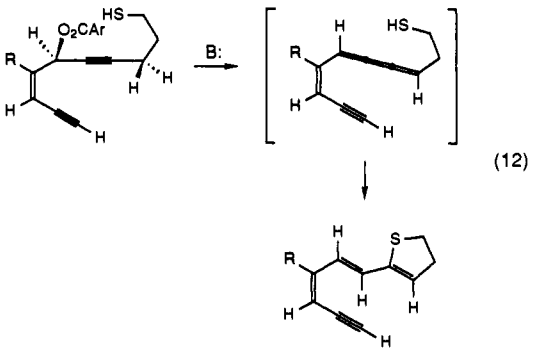
allene–ene–yne functional group offers the potential for biradical formation under exceedingly mild conditions, without additional ground-state destabilization. The simple model studies described above suggest that proper substitution, particularly of the "benzylic" carbon (see **18**), can accelerate biradical formation. Parenthetically, it should be mentioned that entropic factors can potentially be exploited for rate acceleration in this system as well. For example, by constraining the substrate in the proper orientation for cyclization (e.g., rotamer **19** versus **26**), perhaps by the introduction of a ring, rate acceleration of at least 1 order of magnitude should be possible, though this has not been addressed experimentally.[20] Given that biradical formation at or below physiological temperatures is a defining feature of the enediyne antitumor antibiotics (eqs 1 and 3), it is logical to ask whether the cyclization of substrates such as **7** or **19** could form the basis for the design of nonnatural antibiotics. A further defining feature of the enediyne antibiotics is the requirement for chemical activation prior to biradical formation. In the case of calichemicin, esperamicin, and dynemicin, this activation step removes a structural feature that impedes cyclization in the native antibiotics,[1d-h] while in the case of neocarzinostatin chromophore, chemical activation creates the functionality necessary for cyclization.[1a-c] In our initial efforts to design a chemically activated substrate for α,3-dehydrotoluene formation, we have chosen to adopt the latter strategy.[21,22]

Scheme V depicts such a substrate (**41**) and the sequence of chemical steps proposed to form the (*Z*)-1,2,4-heptatrien-6-yne

Scheme V



subunit (**41** → **42** → **43**) and, subsequently, the biradical **44**.[21] The allene is generated by disulfide bond cleavage and intramolecular S_N' cyclization, a sequence inspired by chemical activation steps occurring in the natural enediyne antibiotics, though differing somewhat in detail. Preliminary studies establish a requirement for the presence of the *gem*-dimethyl group; substrates bearing a proton at this position apparently undergo preferential 1,4-elimination to form a cumulene intermediate (eq 12). The



((*tert*-butyldiphenylsilyl)oxy)methyl substituent, as modeled in the allene **19**, provides a potential site for further structural elaboration (e.g., attachment of a DNA-binding group) while the sulfur and alkyl substituents on the allene terminus (of **43**) are anticipated to accelerate biradical formation, as suggested in studies with the substrate **18** above.

The target substrate **41** is synthesized by the convergent route previously described (Scheme VI).[21] Slow addition of the bromo (*Z*)-enyne **29**, described above, to a solution of *tert*-butyllithium (2.5 equiv, 0.14 M) in tetrahydrofuran–ethyl ether–pentane[23] (4:1:1) at −120 °C leads to its smooth transformation to the corresponding vinyllithium reagent, which is trapped at −120 °C with *N*,*N*-dimethylformamide (2.5 equiv) to produce the aldehyde **45** in 71% yield after aqueous workup and flash column chromatography. The use of very low temperatures in the halogen–metal exchange reaction is necessary to avoid elimination of the silyloxy group from the vinyllithium intermediate. Addition of methanesulfonyl chloride (1.2 equiv) to a solution of the known alcohol 3,3-dimethyl-4-pentyn-1-ol[24] (0.28 M) and triethylamine (1.3 equiv) in dichloromethane at 0 °C forms the corresponding methanesulfonate ester[9] which, after extractive isolation, is subjected to nucleophilic displacement with thiopivalic acid (6 equiv)–triethylamine (10 equiv) in tetrahydrofuran at 60 °C for 6 h to provide the thiol ester **46** in 85% yield. The pivaloyl thiol-protecting group is notable for its stability to the conditions of alkyne metalation, as demonstrated in the convergent step. Lithiation of **46** (1.2 equiv, 1.5 equiv LDA, THF, −78 °C, 10 min) and subsequent addition of anhydrous cerium(III) chloride (1.6

(20) For example, even a modest increase in $\Delta S^{\ddagger}$ of 5 eu leads to a rate increase of ~12 at 37 °C.

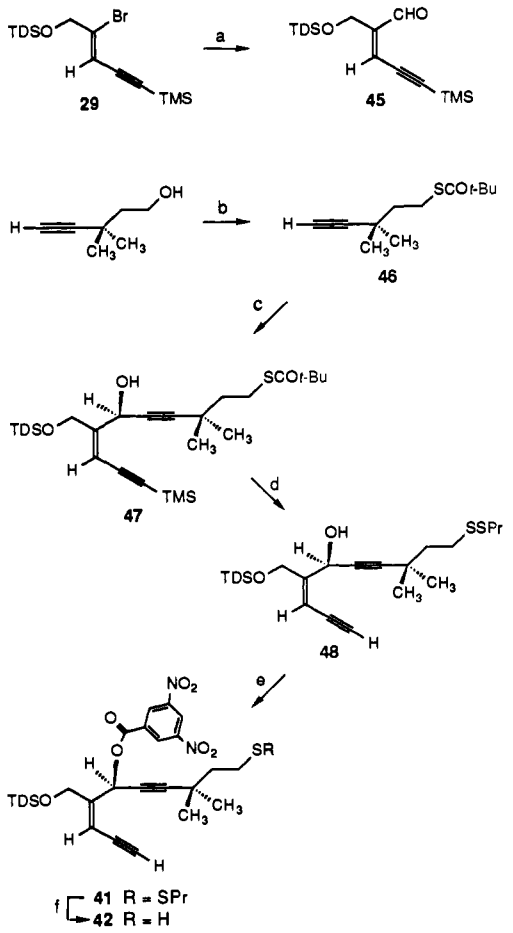
(21) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130.

(22) Other investigations directed toward this end: Nicolaou, K. C.; Skokotas, G.; Furuya, S.; Suemune, H.; Nicolaou, D. C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1064. See also refs 1i, 4b, c, e.

(23) (a) Köbrich, G.; Trapp, H. *Chem. Ber.* **1966**, *99*, 680. (b) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839.

(24) McMurry, J.; Matz, J. R.; Kees, K. L.; Bock, P. A. *Tetrahedron Lett.* **1982**, *23*, 1777.

Scheme VI[a]



[a] Reagents and conditions (TMS = $Si(CH_3)_3$, TDS = $SiPh_2$-*t*-Bu): (a) 2.5 equiv *t*-BuLi, 2.5 equiv DMF, 4:1:1 THF:Et_2O:pentane, −120 → −40 °C, 3 h, 71%; (b) 1.2 equiv CH_3SO_2Cl, 1.3 equiv Et_3N, CH_2Cl_2, 0 °C, 5 min; 10 equiv Et_3N, 6.0 equiv HSCO-*t*-Bu, THF, 0 → 60 °C, 6 h, 85%; (c) 1.5 equiv LDA, 1.2 equiv **46**, 1.6 equiv $CeCl_3$, then 1 equiv **45**, THF, −78 °C, 1 h, 90%; (d) 0.1 M NaOH, 4:1:1 THF:CH_3OH:propyl disulfide, 0 °C, 4 h, 70%; (e) 10 equiv 3,5-dinitrobenzoic acid, 10 equiv $CH_3CH_2N{=}C{=}N(CH_2)_3N(CH_3)_2$·HCl, 5.0 equiv DMAP, CH_2Cl_2, 0 °C, 30 min, 90%; (f) 10 equiv PBu_3, 4:1 DME:H_2O, 0 °C, 30 min, 82%.

equiv, −78 °C, 30 min incubation)[25] and the aldehyde **45** (1 equiv) affords the coupling product **47** in 90% yield. Although there are no enolizable protons in **45** or lithiated **46**, the acetylide addition proceeds in moderately higher yield (90 vs 75%) when cerium(III) chloride is present in the reaction mixture. Treatment of the coupling product **47** with sodium hydroxide (0.1 M) in THF–methanol–propyl disulfide (4:1:1) at 0 °C leads to rapid removal of the trimethylsilyl group (<20 min) and, more slowly, cleavage of the thiol ester (~4 h for completion) to form, after trapping the liberated thiol with propyl disulfide, the mixed disulfide **48** in 70% yield. The hydroxyl group of **48** is activated toward displacement by treatment with 3,5-dinitrobenzoic acid (10 equiv), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (10 equiv), and 4-(dimethylamino)pyridine (5 equiv) in dichloromethane at 0 °C for 30 min, affording the dinitrobenzoate **41** in 90% yield after purification by flash column chromatography. The 3,5-dinitrobenzoate ester represents a near optimum balance between chemical stability and reactivity toward displacement in this system. Accordingly, the corresponding methanesulfonate ester and chloride were too reactive to manipulate conveniently, while the acetate or benzoate esters proved to be too stable for subsequent facile displacement.

(25) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

Table IV. Reaction of Thiol **42** and Disulfide **41** in Various Media[a]

			products[b]			
entry	substrate	medium	**49**	**51**	**52**	**55**
1	**42**	1,4-cyclohexadiene (4.0 M)–DMSO	75			
2	**42**	1,4-cyclohexadiene-d_8 (4.0 M)–DMSO	45			
3	**41**	*p*-methoxythiophenol (0.02 M)–DMSO	22	75		
4	**42**	CH_3OH (4.0 M)–DMSO	33		33	
5	**42**	H_2O (11.0 M)–THF				40

[a] 0.01 M, 23 °C. [b] Yields determined by ^1H NMR analysis of crude reaction mixtures using (*Z*)-1,2-dichloroethylene as an internal standard.

Disulfide cleavage occurs under neutral conditions when **41** is treated with tributylphosphine (10 equiv) in 1,2-dimethoxyethane–water (4:1) at 0 °C, affording the thiol **42** in 82% yield.[26] The thiol **42** is stable to neutral or slightly acidic conditions and can be purified by chromatography on silica gel but undergoes rapid cyclization in the presence of base. Thus, addition of triethylamine (5.0 equiv) to a deoxygenated solution of the thiol **42** (0.01 M) in DMSO containing 1,4-cyclohexadiene (1.0 M) at 23 °C forms the tetrahydrothiophene derivative **49**, the product of addition of two hydrogen atoms to the putative biradical **44**, in 75% yield (Table IV, entry 1). Omission of 1,4-cyclohexadiene from the reaction medium leads to an intractable product mixture, suggesting that **43**, like **7**, is unstable to the free radical products of its cyclization but apparently not to cyclohexadienyl. The trapping sites are labeled by using 1,4-cyclohexadiene-d_8 (96% deuterium content at the allylic positions)[27] in the cyclization reaction (Table IV, entry 2). It is necessary to remove the *tert*-butyldiphenylsilyl group in **49** (tetrabutylammonium fluoride, THF, 23 °C) in order to resolve the newly-formed aromatic signals in the ^1H NMR spectrum; analysis of the resulting alcohol **50** shows the incorporation of deuterium at C5 (60%) and C1′ (90%). The source of residual protium at C5, the more reactive site in the biradical, is not known with certainty. As experiments described below rule out the thiol S–H bond as the source of protium (cyclization of **42** to **43** is more rapid than **43** to **44**), the only possible sources appear to be 3,5-dinitrobenzoic acid, triethylamine, or DMSO.[28] Though less than quantitative, the incorporation of deuterium at the indicated sites in **49** supports the intermediacy of the biradical **44** in the transformation **42** → **49**.

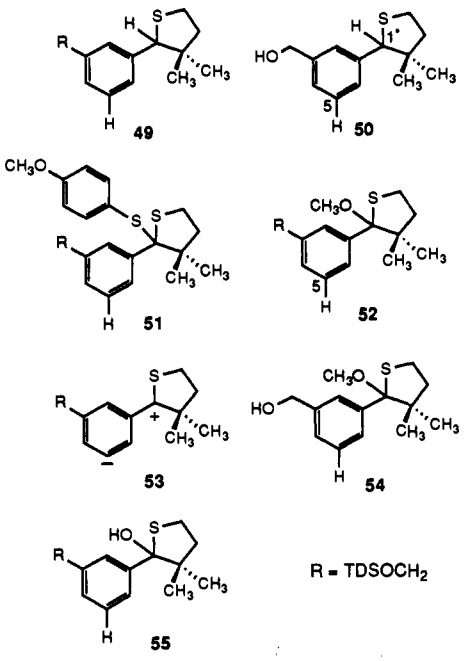
Due to a favorable ordering of rate constants, it is possible to observe the intermediate allene **43** by ^1H NMR spectroscopy and to follow its transformation to **49**. Addition of triethylamine (2.2 equiv) to a solution of **42** (0.02 M) and 1,4-cyclohexadiene (0.26 M) in deoxygenated DMSO-d_6–CD_2Cl_2 (2.3:1; CD_2Cl_2 is required to prevent freezing of the sample) at 10 °C causes rapid reaction of **42** (<30 min at 10 °C) to form an intermediate displaying signals consistent with structure **43**. This intermediate is observed to undergo first-order transformation to **49** in a slower step ($k = (3.6 \pm 0.5) \times 10^{-4}$ s^{-1} at 10 °C, two determinations). The entire cascade (**41** → **42** → **43** → **44** → **49**) can be brought about by treating the disulfide **41** (0.01 M) with triethylamine (5 equiv) and 4-methoxythiophenol (3 equiv) in oxygen-free DMSO, producing the tetrahydrothiophene derivative **49** and the thiophenol adduct **51** in excellent combined yield (Table IV, entry 3). This reaction is considerably slower than cyclization of the free thiol **42**, requiring 30 min at 23 °C for completion, and exhibits a rather large solvent dependence, slowing markedly in less polar media ($t_{1/2}$ = 6 h in 1.5:1 DMSO–THF). Control experiments with the

(26) Humphrey, R. E.; Potter, J. L. *Anal. Chem.* **1965**, *37*, 164. The fact that no cyclization is observed during disulfide cleavage suggests that free thiolate is not involved in this reaction.

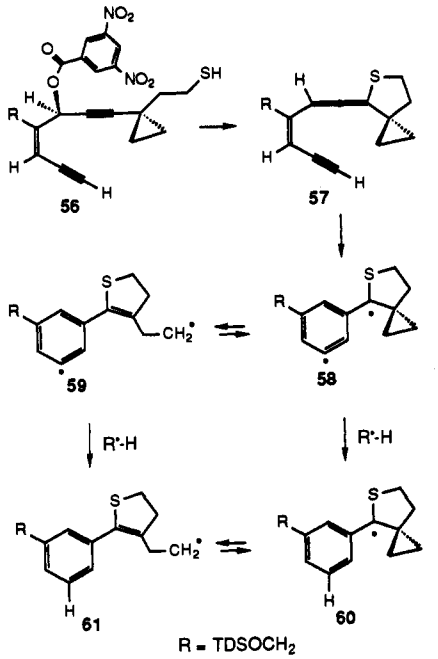
(27) Prepared by electrolysis of benzene-d_6 with D_2O, see: Kariv-Miller, E.; Swenson, K. E.; Lehman, G. K.; Andruzzi, R. *J. Org. Chem.* **1985**, *50*, 556. We are grateful to Drs. James Toth and David Blauch for their assistance with this procedure.

(28) 3,5-Dinitrobenzoic acid seems to be the most likely source of protium; electron transfer within the resulting ion pair may then occur, followed by trapping with 1,4-cyclohexadiene.

Chart II



Scheme VII



nonactivated disulfide **48** show that the rate of simple disulfide cleavage in this substrate follows closely the rate of formation of **49** from **41** in a given solvent, demonstrating that the rate-determining step in the latter reaction is likely to be disulfide cleavage.

Further trapping studies show that the biradical **44** displays enhanced polar reactivity as compared with the biradicals **8** and **25**. Attempts to cyclize the thiol **42** in neat methanol using triethylamine (5 equiv) lead to transesterification of the 3,5-dinitrobenzoate ester. This complication is avoided by treatment of **42** (1 equiv, 0.01 M) with methanol (4.0 M) in deoxygenated DMSO containing triethylamine (5 equiv) at 23 °C; cyclization produces equal amounts of the tetrahydrothiophene derivative **49** and the methyl ether **52** in good yield (Table IV, entry 4). Cursory consideration of these products suggests that both polar and free radical reaction pathways operate in this system. Further experiments show that this is not the case but implicate instead the exclusive operation of a polar reaction pathway (see resonance form **53**). Cyclization of the thiol **42** (1 equiv, 0.01 M) with triethylamine (5 equiv) in DMSO containing CD_3OD (4.0 M) demonstrates that both of the newly added hydrogen atoms in **49** are derived from methanol (>95% incorporation of deuterium at the C5 and C1′ positions, as determined by ^1H NMR analysis of alcohol **50**). The methyl ether **52** formed in the latter experiment also shows >95% incorporation of deuterium at C5, as determined by ^1H NMR analysis of the corresponding alcohol **54**. Use of CH_3OD leads to exclusive incorporation of deuterium at the C5 positions (>95%) of **49** and **52** with <5% incorporation at the C1′ position of **49**. These experiments support a scheme whereby **49** and **52** are formed by initial proton transfer from the hydroxyl group of methanol to C5 of the biradical **44**, with partitioning of the resultant ion pair by a (net) hydride transfer to form **49** (and presumably formaldehyde) or by simple recombination to form **52**. When compared with data from substrates **7** and **19** above, these results show that the biradical **44** exhibits a greater propensity to react as a polar species than intermediates **8** or **25**. In further support of this conclusion, it is found that treatment of the thiol **42** with triethylamine (5 equiv) in deoxygenated 20% aqueous tetrahydrofuran provides the hemithioketal **55** as the only isolable product (Table IV, entry 5, cf. Table III, entry 6).

A More Reactive Biradical—Another Step in the Cascade

Trapping studies described above confirm the expectation that the benzylic radical is less reactive than the phenyl radical within α,3-dehydroalkylbenzene biradicals. This difference in reactivity presents a concern with regard to the use of such a species to mimic biradicals generated from the enediyne antibiotics in the damage of double stranded DNA. The latter biradicals have been shown to induce double stranded lesions, as a subset of total DNA damage products, via the direct abstraction of hydrogen atoms from the ribose backbone of DNA by both radical sites.[29] It is questionable whether a benzylic radical is sufficiently reactive to abstract a ribose-bound hydrogen atom at a rate rapid with respect to alternative trapping pathways (e.g., reaction with molecular oxygen). To address this issue and to further probe the radical reactivity of α,3-dehydrotoluene intermediates, the cyclopropane-containing thiol **56** was prepared. As outlined in Scheme VII, thioallene formation and cyclization of the resultant (*Z*)-allene–ene–yne **57** is anticipated to form the biradical **58**. This cyclopropylcarbinyl radical is expected to enter into dynamic equilibrium with the corresponding homoallylic radical, either directly or, more likely, subsequent to hydrogen atom transfer to the phenyl radical (**58** ⇄ **59** and **60** ⇄ **61**, respectively).[30] Through this ring-opening process, a second highly reactive radical site is generated.

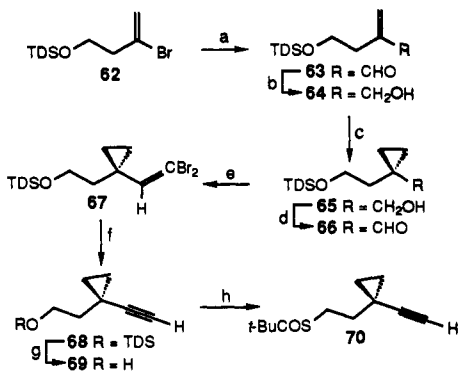
The synthesis of the cyclopropane thiol **56** parallels that of the thiol **42** (Scheme VIII), employing instead the alkyne **70** for coupling with the aldehyde **45**. The alkyne **70** is synthesized in eight steps from 3-bromo-3-butenyl *tert*-butyldiphenylsilyl ether **62**, obtained by treatment of the known bromo alcohol[31] with *tert*-butyldiphenylsilyl chloride (1.2 equiv), triethylamine (5.0 equiv), and 4-(dimethylamino)pyridine (0.62 equiv) in dichloromethane at 23 °C (95%). Addition of a solution of **62** in THF–ethyl ether–pentane[23] (4:1:1) to a solution of *tert*-butyllithium in the same solvent mixture at −120 °C, followed by the addition

(29) Neocarzinostatin: (a) Povirk, L. F.; Houlgrave, C. W.; Han, Y.-H. *J. Biol. Chem.* **1988**, *263*, 19263. (b) Chin, D.-H.; Zeng, C.-h.; Costello, C. E.; Goldberg, I. H. *Biochemistry* **1988**, *27*, 8106. (c) Meschwitz, S. M.; Goldberg, I. H. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 3047. Calichemicin: (d) Zein, N.; McGahren, W. J.; Morton, G. O.; Ashcroft, J.; Ellestad, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 6888. (e) Zein, N.; Poncin, M.; Nilakantan, R.; Ellestad, G. A. *Science* **1989**, *244*, 697. (f) De Voss, J. J.; Townsend, C. A.; Ding, W.-D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669.

(30) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. Rate of ring-opening of a benzylic cyclopropylcarbinyl radical: (c) Masnovi, J.; Samsel, E. G.; Bullock, R. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1044. (d) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Chem. Soc., Chem. Commun.* **1990**, 923. (e) Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992**, *57*, 4284.

(31) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621.

Scheme VIII[a]

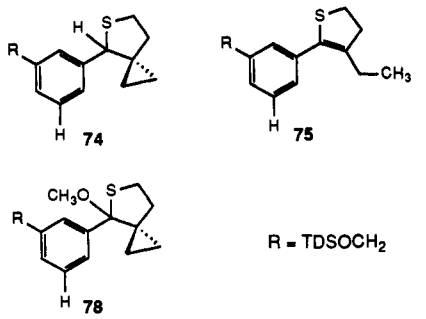


[a] Reagents and conditions (TDS = $SiPh_2$-*t*-Bu): (a) 2.5 equiv *t*-BuLi, 2.5 equiv DMF, 4:1:1 THF:Et_2O:pentane, −120 °C, 3 h, 91%; (b) 1.0 equiv $NaBH_4$, EtOH, 0 °C, 1 h, 88%; (c) 5.0 equiv Et_2Zn, 10 equiv CH_2I_2, Et_2O, 0 → 23 °C, 4 h, 68%; (d) 1.1 equiv $(COCl)_2$, 2.2 equiv DMSO, 5.0 equiv Et_3N, CH_2Cl_2, −78 → 0 °C, 87%; (e) 2.0 equiv Zn dust, 2.0 equiv PPh_3, 2.0 equiv CBr_4 (precomplexed for 24 h at 23 °C), CH_2Cl_2, then **66**, 23 °C, 5 h; (f) 2.2 equiv *n*-BuLi, THF, −78 °C, 3 h, 91% from **66**; (g) 3.0 equiv *n*-Bu_4NF, THF, 0 °C, 24 h, 86%; (h) 1.2 equiv CH_3SO_2Cl, 1.3 equiv Et_3N, CH_2Cl_2, 0 °C, 15 min; 10 equiv Et_3N, 5.0 equiv HSCO-*t*-Bu, THF, 0 → 50 °C, 6 h, 90% from **69**.

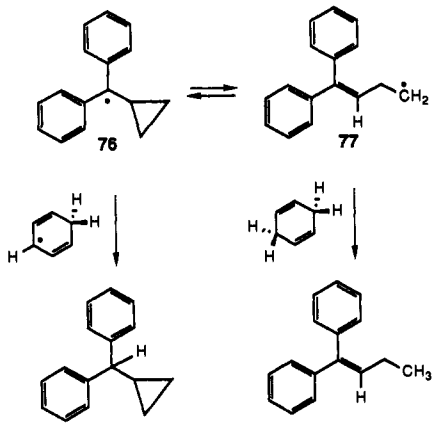
of a solution of *N*,*N*-dimethylformamide (2.5 equiv, 0.15 M) in tetrahydrofuran, affords the aldehyde **63** in 91% yield following aqueous workup and flash column chromatography. Reduction of **63** with sodium borohydride (1.0 equiv) in ethanol proceeds cleanly at 0 °C to provide the allylic alcohol **64** (88%). Cyclopropanation of this product with diethyl zinc (5.0 equiv) and diiodomethane (10.0 equiv) in diethyl ether at 23 °C affords the alcohol **65** in 68% yield after purification by flash column chromatography.[32] Swern oxidation of **65** (oxalyl chloride (1.1 equiv), dimethyl sulfoxide (2.2 equiv), triethylamine (5.0 equiv), dichloromethane, −78 → 0 °C) provides the cyclopropanecarboxaldehyde **66** in 87% yield.[33] Transformation of this aldehyde to the alkyne **68** is accomplished by the two-step homologation procedure of Corey and Fuchs.[34] Thus, addition of **66** to a suspension of triphenylphosphine (2.0 equiv), carbon tetrabromide (2.0 equiv), and zinc dust (2.0 equiv) in dichloromethane at 23 °C provides the corresponding 1,1-dibromo olefin **67** following workup and flash column chromatography. Subsequent treatment of a solution of **67** in tetrahydrofuran at −78 °C with *n*-butyllithium (2.2 equiv) affords the alkyne **68** in 91% yield after an aqueous quench and flash column chromatography. Exposure of **68** to a solution of tetrabutylammonium fluoride (3.0 equiv) in tetrahydrofuran at 23 °C cleanly removes the silyl protecting group to give the alcohol **69** in 86% yield. Addition of methansulfonyl chloride (1.2 equiv) and triethylamine (1.3 equiv) to a solution of **69** in dichloromethane at 0 °C provides the corresponding methanesulfoante ester,[9] which, without purification, is treated with thiopivalic acid (5.0 equiv) and triethylamine (10.0 equiv) in tetrahydrofuran at 50 °C, affording the thiol ester **70** in 90% yield from **69** after flash column chromatography. The remaining steps of the synthesis are virtually identical to those described above in the preparation of the thiol **42** and provide **56** in 28% yield from **70**.

The cyclopropane thiol **56** (0.01 M) cyclizes rapidly at 23 °C upon treatment with triethylamine (5 equiv) in deoxygenated DMSO containing 1,4-cyclohexadiene (4.0 M) to form products consistent with the intermediacy of the biradical **58**, i.e., the spirocyclopropyltetrahydrothiophene derivative **74** (28%) and the cyclopropane ring-opened product **75** (21%). The ratio of these products is highly dependent upon the concentration of 1,4-cyclohexadiene in the medium. For example, use of 4-fold less 1,4-cyclohexadiene (1.0 M) results in a sharp reduction in the yield

Chart III



Scheme IX



of the ring-opened product **75** (5%) with a corresponding increase in the yield of the spiro product **74** (50%). These results closely parallel the observations of Roberts et al. in their study of the trapping of the stabilized cyclopropylcarbinyl radical **76** with 1,4-cyclohexadiene.[35] These authors present data to support the reasonable hypothesis that the benzyl radical **76** and its ring-opened isomer **77** enter into a dynamic equilibrium; only the latter is capable of direct hydrogen atom abstraction from 1,4-cyclohexadiene, while the former is quenched exclusively with cyclohexadienyl (Scheme IX).[35]

Under conditions where the dimethyl-substituted thiol **42** reacts solely to form products described by a polar reaction mechanism (4.0 M methanol in DMSO, 0.05 M triethylamine, 23 °C), the cyclopropane-substituted analog **56** is found to react analogously, producing the spirotetrahydrothiophene derivatives **78** (67%) and **74** (13%). Trapping studies of **56** with CD_3OD and CH_3OD, as with **42** above, establish that a polar mechanism operates in this case as well. In contrast to the radical reaction pathway, polar trapping of **58** does not lead to cyclopropane ring-opened products.

Discussion

(*Z*)-1,2,4-Heptatrien-6-yne undergoes a mild thermal cyclization to form the biradical α,3-dehydrotoluene. It is instructive to compare the energetics of this process with the more familiar Bergman reaction (Figures 1 and 2). Through the innovative contributions of Squires and co-workers, the enthalpies of both reactions are now known;[36] kinetic measurements of Jones and Bergman[2a] and our own group[3] complete the energy diagrams of Figures 1 and 2. It can be seen that while the Bergman reaction is modestly endothermic, formation of α,3-dehydrotoluene from **7** is strongly exothermic ($\Delta H_r \sim -15 \pm 3$ kcal/mol). As reported in the work of Squires et al., the interaction of the two radical centers is stabilizing in each 1,4-biradical, worth 6 ± 3 kcal/mol in the case of **8** and 11 ± 3 kcal/mol for **4**.[36] The greater exo-

(32) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254.
(33) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(34) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(35) Halgren, T. A.; Howden, M. E. H.; Medof, M. E.; Roberts, J. D. *J. Am. Chem. Soc.* **1967**, *89*, 3051.
(36) (a) Wenthold, P. G.; Paulino, J. A.; Squires, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 7414. (b) Wenthold, P. G.; Wierschke, S. G.; Squires, R. R. *J. Am. Chem. Soc.* In press. We are grateful to Professor Robert Squires and co-workers for sharing their results prior to publication.

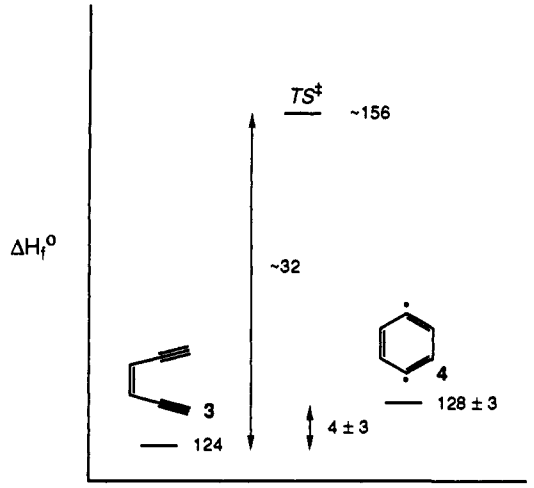


Figure 1. Enthalpy diagram for cyclization of (*Z*)-hex-3-ene-1,5-diyne (**3**). $\Delta H_f°$ (**3**): Calculated using revised group additivities (Benson, S. W.; Garland, L. J. *J. Phys. Chem.* **1991**, *95*, 4915). See also: Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1. $\Delta H^{\ddagger}$: ref 2a. $\Delta H_f°$ (**4**): ref 36a.

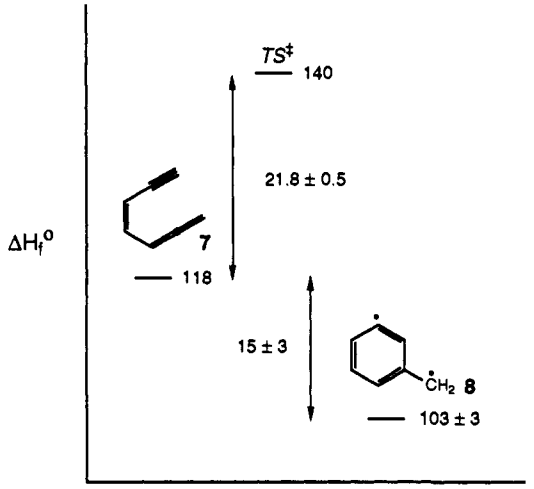


Figure 2. Enthalpy diagram for cyclization of (*Z*)-1,2,4-heptatrien-6-yne (**7**). $\Delta H_f°$ (**7**): see ref 3. Revision of this number downward by 1–2 kcal/mol may be warranted: Benson, S. W.; Garland, L. J. *J. Phys. Chem.* **1991**, *95*, 4915. $\Delta H^{\ddagger}$: ref 3. $\Delta H_f°$ (**8**): ref 36b.

thermicity of the α,3-dehydrotoluene-forming reaction is easily traced to the greater stability of a benzyl radical versus a phenyl radical. Given these thermodynamic data, it is perhaps not surprising that the barrier to cyclization of **7** is considerably lower than that of **3**. As demonstrated above, this barrier can be further reduced by appropriate substitution of the allenic terminus of **7** (and thus the benzylic site of **8**). In a calculated reaction pathway from **7** to **8**, Morokuma et al. find an early transition state, as expected given the exothermicity of the reaction, with no evidence of twisting of the incipient benzyl radical toward conjugation with the phenyl ring.[37] This radical nevertheless occupies an orbital of greater p character than the corresponding radical in cyclizations of eqs 2 or 3, a fact which may lead to a lower barrier to cyclizations of (*Z*)-allene–ene–yne systems. It is also true that the cyclizations of eqs 3 and 4 lack the repulsive interactions between the two in-plane p orbitals not involved in bonding, a feature which likely contributes to the enthalpy of activation of (*Z*)-enediyne cyclizations.[37] Regardless of the origin of the effect, it is clear that the (*Z*)-allene–ene–yne functional group cyclizes rapidly in the absence of additional ground-state destabilization, as required for the cyclization of (*Z*)-enediynes at comparable rates.[16]

(37) Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907.

Dichotomous (polar and free radical) reactivity is observed when **7** is pyrolyzed in the presence of polar reactants. Mechanistic studies suggest that both radical and polar products arise from a common intermediate or, if arising by a dynamic process, that this process must be rapid on the timescale of the trapping reactions. In the former case, the data support a description of the common intermediate as a polar biradical, that is, some linear combination of limiting structures **8** and the zwitterion **17**.[38] Little et al. have recently proposed and discussed in detail a similar description for a trimethylenemethane biradical intermediate.[39] Implicit in the "polar biradical" description is the fact that singlet species are involved, consistent with the work of Squires et al. supporting a singlet ground state for **8**.[36b] In light of the latter results and in consideration of the experimental data described herein, we presently favor a proposition to account for all products involving the single reactive intermediate **8**, best described as a polar, singlet biradical. A mechanism involving rapid equilibration between species (e.g., a singlet state and a low-lying triplet state) cannot, however, be ruled out. A third possibility involving the intermediacy of a chiral closed-shell allene structure (methylene-2,3,5-cyclohexatriene) is considered to be unlikely given the calculated energy of this species versus the planar, singlet biradical isomer[36b] and given the difficulty in reconciling the observed free radical and polar (orientation of methanol addition) products in terms of a species of this description.[40] The polar reactivity of **8** represents a departure from the known chemistry of the σ,σ-biradicals **2**, **4**, and **6**, which react exclusively by standard radical reaction paths.[41] Here again, the discriminating feature may well be the differential stabilities of the electron-deficient benzylic and phenyl carbons, in this instance with reference to the corresponding cations.

In light of this discussion of thermochemistry and reactivity, it is worthwhile to briefly consider the possibility that an α,3-dehydroalkylbenzene biradical might function as a DNA damaging agent, perhaps forming the basis for the design of a nonnatural antitumor agent, in analogy to the enediyne antitumor antibiotics. In this regard, several factors must be considered. First, will the cyclization reaction that forms a biradical such as **8** be sufficiently rapid? To answer this question, it must first be known what are optimum, or even adequate, rates of cyclization in a physiological system. Beyond certain obvious limitations defined by the biological system in question (e.g., the half-life for cell division), an optimum cyclization rate has yet to be determined. Given the high reactivity of the (*Z*)-allene–ene–yne functional group, one critical requirement is that the cyclization be rapid with respect to competing, nonproductive reactions. Even by these minimal criteria, the rate of the parent cyclization (**7** → **8**) would appear to be slow ($t_{1/2}$ (37 °C) ~ 1 day). As demonstrated in this work, substitution of the allenic terminus can dramatically accelerate the cyclization reaction. For example, the (*Z*)-allene–ene–yne **43** is found to cyclize with a half-life of ~1 h at 10 °C. Unfortunately, this example illustrates a further consideration with these systems in that the product biradical **44** favors a polar trapping mechanism in polar media. It remains to be established whether it is possible to accelerate cyclization by substitution of the allenic terminus without enhancing polar reactivity. As suggested above, an alternative strategy for rate acceleration in

(38) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92. The alternative zwitterionic structure is regarded to be too high in energy to contribute to a description of **8**.

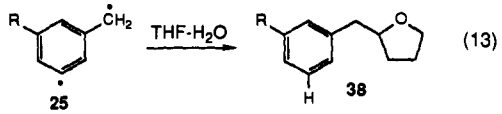
(39) (a) Little, R. D.; Brown, L. M.; Masjedizadeh, M. R. *J. Am. Chem. Soc.* **1992**, *114*, 3071 and references therein. Other potential examples: (b) Inglin, T. A.; Berson, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 3394. (c) Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975.

(40) See also: Angus, R. O., Jr.; Schmidt, M. W.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 532.

(41) We believe that instances where polar reactions of biradical **6** or closely related species have been invoked are due to misinterpretation of the experimental data: (a) Chin, D.-H.; Zeng, C-h.; Costello, C. E.; Goldberg, I. H. *Biochemistry* **1988**, *27*, 8106, discusses an "equilibrium" between diradical and polar resonance forms of **6**. (b) Sugiyama, H.; Yamashita, K.; Nishi, M.; Saito, I. *Tetrahedron Lett.* **1992**, *33*, 515 proposes a chemically implausible structure arising from a zwitterionic species related to **6**.

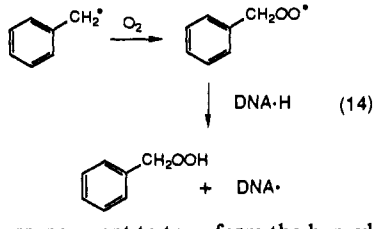
(*Z*)-allene–ene–yne cyclizations might exploit entropic factors. For example, by constraining the allene group in the proper orientation for cyclization, rate enhancements of perhaps more than 1 order of magnitude might be obtained.[20]

As illustrated with the biradical **44** and discussed in detail above, a second major issue in this system concerns the dichotomous (polar vs free radical) reactivity of these σ,π-biradicals. This feature necessarily introduces a mechanistic ambiguity into any DNA cleavage chemistry induced by biradicals such as **44**. However, in simple systems such as **25**, there is little doubt that radical reactions will predominate, even in the presence of water. For example, the major product from the trapping of **25** in 20% aqueous tetrahydrofuran is the adduct **38** (eq 13).



25 **38** (13)

Finally, a third consideration is the stability of the benzylic site within α,3-dehydroalkylbenzene biradicals, given a radical reaction pathway. The enediyne antibiotics have been shown to produce double stranded lesions in B-form DNA wherein both radical sites within the biradical intermediate directly abstract hydrogen atoms from the ribose backbone.[29] It has been suggested that these lesions are the most lethal products of DNA damage in the case of the neocarzinostatin chromophore.[42] The stability of the benzylic site raises a concern as to whether the σ,π-biradicals described herein could participate directly in such a reaction. An indirect pathway with a similar outcome might involve a peroxyl intermediate, as illustrated in eq 14. The notion of using a



(14)

secondary rearrangement to transform the benzyl radical into a more reactive species is demonstrated above with the substrate **56** and represents one strategy for mimicking the more reactive biradicals of the enediyne antibiotics.

The preceding considerations follow rationally from the background studies described above. Clearly, however, the nature of the detailed interaction of double stranded DNA with α,3-dehydroalkylbenzene biradicals must await experimental determination.

Conclusion

In summary, (*Z*)-1,2,4-heptatrien-6-yne and related compounds which contain the (*Z*)-1,2,4-heptatrien-6-yne functional group or form it in a serial reaction sequence are shown to undergo a mild thermal rearrangement to form aromatic products. This transformation is best represented as a fundamentally new electrocyclization reaction forming α,3-dehydrotoluene in the parent case and the corresponding substituted derivative in all other examples. Mechanistic studies suggest that the intermediate α,3-dehydrotoluene is best described as a singlet σ,π-biradical with substantial polar character that partitions between polar and free radical reaction pathways in a manner influenced by biradical substitution and by the medium in which the intermediate is generated. Results from this work provide guidelines for the incorporation of the (*Z*)-1,2,4-heptatrien-6-yne subunit in the design of potential DNA damaging agents.

Experimental Section

General Procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation/argon-flush cycles (≥5 iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.[43] employing 230–400-mesh silica gel. Analytical and preparative thin-layer chromatography were performed using glass plates precoated with 0.25-mm 230–400-mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and ethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, *N,N*-diisopropylethylamine, propylamine, diisopropylamine, triethylamine, tributylphosphine, and pentane were distilled from calcium hydride at 760 Torr. *N,N*-Dimethylformamide and dimethyl sulfoxide were distilled from calcium sulfate at 20 Torr. Methanesulfonyl chloride was distilled from phosphorus pentoxide at 760 Torr. Oxalyl chloride was distilled at 760 Torr immediately prior to use. Anhydrous cerium(III) chloride was prepared from the heptahydrate by heating at 100 °C and 1 Torr for 12 h. 3,5-Dinitrobenzoic acid was recrystallized from water. Cuprous iodide was purified by continuous extraction (12 h) with tetrahydrofuran in a Soxhlet apparatus. Tetrakis(triphenylphosphine)palladium(0) was prepared according to the literature procedure[44] and was stored in a nitrogen-filled glovebox. The molarity of *n*-butyllithium was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[45] Solutions of lithium diisopropylamide in tetrahydrofuran (0.2–0.4 M) were prepared immediately prior to use by the addition of *n*-butyllithium (1.6 M in hexanes, 1 equiv) to a solution of diisopropylamine (1.1 equiv) in tetrahydrofuran at −78 °C with brief warming of the resultant mixture (5-min immersion of the reaction flask in an ice bath) and then cooling to −78 °C.

Instrumentation. Analytical gas–liquid chromatography (GLC) was carried out on a Hewlett–Packard 5890A gas chromatograph with a splitless mode capillary injection system and a flame ionization detector using a flexible fused silica capillary column (25-m × 0.20-mm) wall-coated with phenylmethyl silicone (0.5 μm, 5%). High performance liquid chromatography (HPLC) was conducted using a Waters 501 HPLC equipped with a Delta Pak C18 100-Å standard reverse phase analytical column (3.9-mm × 30-cm, 15 μm, spherical) and an Isco V^4 absorbance detector set to 255 nm. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment (when appropriate). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a JEOL JX-400 (400 MHz) or a Bruker AM-500 (500 MHz) NMR spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6HD_5, δ 7.15; $CHDCl_2$, δ 5.29). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in hertz (Hz), and assignment. High resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility.

(*Z*)-Vinyl Chloride 9. Cuprous iodide (0.62 g, 3.26 mmol, 0.15 equiv) and bis(triphenylphosphine)palladium(II) chloride (0.76 g, 1.08 mmol, 0.05 equiv) were added sequentially to an ice-cooled, deoxygenated solution of (*Z*)-1,2-dichloroethylene (8.41 mL, 107 mmol, 5.0 equiv), propargyl alcohol (1.21 g, 21.7 mmol, 1 equiv), and *n*-propylamine (8.90 mL, 108 mmol, 5.0 equiv) in ethyl ether (25 mL), and the resulting brown suspension was thoroughly degassed. After being stirred at 23 °C for 6 h, the reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (100 mL) and ethyl ether (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded the (*Z*)-vinyl chloride **9** (1.91 g, 78%) as a brown oil: R_f = 0.30 (20% ethyl acetate in hexanes); IR (neat) 3346 (br, OH), 3087 (m), 2917 (m), 2865 (m), 2209 (w, C≡C), 1592 (s), 1331 (s), 1126 (s), 1015 (s), 849 (s), 725 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 6.40 (d, 1 H, *J* = 7.3 Hz, C≡CCH=C*H*), 5.91 (dt, 1 H, *J* = 7.3, 2.0 Hz, C≡CC*H*=CH), 4.46 (d, 2 H, *J* = 2.0 Hz, CH_2OH); HRMS calcd for C_5H_5ClO (M^+) 116.0029, found 116.0029.

(*Z*)-Enediyne 10. A deoxygenated suspension of tetrakis(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 0.05 equiv) and the (*Z*)-vinyl chloride **9** (2.26 g, 19.0 mmol, 1 equiv) in ethyl ether (45 mL) at 23 °C was transferred via wide-bore cannula to an ice-cooled, deoxy-

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(43) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(44) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

(45) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

genated solution of cuprous iodide (0.74 g, 3.9 mmol, 0.20 equiv), (trimethylsilyl)acetylene (3.85 mL, 27.2 mmol, 1.4 equiv), and *n*-propylamine (6.4 mL, 76.0 mmol, 4.0 equiv) in ethyl ether (40 mL). The resulting brown suspension was thoroughly deoxygenated and was stirred at 0 °C for 1 h. The reaction mixture was poured into an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (100 mL), and the resulting biphasic solution was stirred under air at 23 °C for 45 min. The organic phase was separated, and the aqueous layer was extracted with ethyl ether (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the (*Z*)-enediyne **10** (2.87 g, 83%) as a brown oil: R_f = 0.38 (30% ethyl acetate in hexanes); IR (neat) 3353 (br, OH), 3048 (m), 2960 (s), 2144 (s, C≡C), 1574 (w), 1251 (s), 1134 (s), 1027 (s), 843 (s), 759 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 5.86 (s, 2 H, both C=C*H*), 4.47 (d, 2 H, *J* = 5.4 Hz, CH_2OH), 1.66 (t, 1 H, *J* = 5.4 Hz, CH$_2$O*H*), 0.22 (s, 9 H, Si(CH_3)$_3$); HRMS calcd for $C_{10}H_{14}OSi$ (M^+) 178.0814, found 178.0809.

Propargyl Alcohol 11. Potassium fluoride dihydrate (0.26 g, 2.76 mmol, 2.0 equiv) was added to an ice-cooled solution of the (*Z*)-enediyne **10** (0.248 g, 1.39 mmol, 1 equiv) in methanol (5.0 mL). After being stirred at 0 °C for 2.5 h, the reaction mixture was partitioned between brine (100 mL) and ethyl acetate (4 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to give the propargyl alcohol **11** (0.142 g, 96%) as a pale yellow oil: R_f = 0.38 (20% ethyl acetate in hexanes); IR (neat) 3327 (br, OH), 3287 (s, C≡CH), 2922 (m), 2209 (w, C≡C), 2097 (w), 1574 (w), 1391 (m), 1130 (s), 1015 (s), 751 (s); ^{1}H NMR (500 MHz, $CDCl_3$) 5.95 (dm, 1 H, *J* = 11.1 Hz, HC=C*H*C≡CCH$_2$OH), 5.83 (dd, 1 H, *J* = 11.1, 2.3 Hz, *H*C=CHC≡CCH$_2$OH), 4.48 (d, 2 H, *J* = 2.0 Hz, CH_2OH), 3.36 (d, 1 H, *J* = 2.3 Hz, C≡C*H*), 1.76 (s, 1 H, CH$_2$O*H*); HRMS calcd for C_7H_6O (M^+) 106.0419, found 106.0419.

(*Z*)-1,2,4-Heptatrien-6-yne (7). Methanesulfonyl chloride (0.26 mL, 3.31 mmol, 3.0 equiv) was added dropwise over 15 min to an ice-cooled solution of the propargyl alcohol **11** (0.12 g, 1.10 mmol, 1 equiv) and triethylamine (0.78 mL, 5.56 mmol, 5.0 equiv) in dichloromethane (5.0 mL). The resulting yellow suspension was stirred at 0 °C for 20 min and then was partitioned between brine (100 mL) and ethyl acetate (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The brown residue was dissolved in dichloromethane (4 mL) and was treated with a solution of anhydrous hydrazine (0.50 mL, 15.6 mmol, 14.3 equiv) in methanol (0.50 mL) at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was partitioned between water (100 mL) and a 9:1 mixture of dichloromethane and methanol (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide the crude hydrazine **12** which was diluted with deoxygenated benzene-d_6 (2.0 mL). The resulting suspension was treated with a deoxygenated solution of 4-methyl-1,2,4-triazoline-3,5-dione (0.162 g, 1.43 mmol, 1.3 equiv) in benzene-d_6 (5.0 mL, dropwise addition via cannula over 10 min). After being stirred at 23 °C for 10 min, the reaction mixture was washed with water (5 × 10 mL) and was dried over sodium sulfate. The crude solution of (*Z*)-1,2,4-heptatrien-6-yne in benzene-d_6 was purified by passage through a short column of flash-grade silica gel (2-cm × 1-cm, eluting with 5 mL of benzene-d_6). The yield of **7** was determined to be 30% by addition of 0.25 mmol *m*-xylene to the chromatographed solution and ^{1}H NMR analysis: R_f = 0.38 (hexanes); IR (C_6D_6 solution) 3291 (s, C≡CH), 2146 (w, C≡C), 1933 (s, C=C=C), 1604 (w), 787 (s); ^{1}H NMR (400 MHz, C_6D_6) 6.65 (dtd, 1 H, *J* = 11.0, 5.6, 1.0 Hz, C*H*=C=CH$_2$), 6.16 (td, 1 H, *J* = 11.0, 1.0 Hz, HC≡CCH=C*H*), 5.14–5.19 (m, 1 H, HC≡CC*H*=CH), 4.64–4.67 (dm, 2 H, *J* = 5.6 Hz, CH=C=CH_2), 2.89 (dd, 1 H, *J* = 1.7, 0.7 Hz, *H*C≡CCH=CH); HRMS calcd for C_7H_7 (MH^+) 91.0548, found 91.0552.

General Pyrolysis Procedure. Pyrolyses of (*Z*)-1,2,4-heptatrien-6-yne (**7**) were conducted in medium-walled NMR tubes (Wilmad 503 PS, 9 in) sealed at reduced pressure (ca. 0.015 Torr). Tubes were used as received or were washed twice with 1,1,1,3,3,3-hexamethyldisilazane or glacial acetic acid (so noted) and were dried in vacuo prior to use. Oxygen was removed prior to pyrolysis by three freeze–pump–thaw cycles.

Pyrolysis samples containing the allene **7** (0.8–80 mM) and *m*-xylene ($^1/_2$ concentration of **7**, internal reference) in an appropriate solvent were heated in boiling water (100 °C) or in a large, thermostatted oil bath (39, 59, 77, and 90 °C). In each case, samples were placed in a beaker fully submerged in the bath and were not allowed to contact the sides of the heating apparatus. During kinetic analyses, tubes were removed from the heating bath at appropriate time intervals and were immediately cooled to 0 °C, scored, and opened, and their contents were analyzed by GLC. GC parameters #1: initial temperature, 45 °C; initial time, 14.0 min; rate, 50 °C/min; final temperature, 70 °C; injector temperature, 90 °C; detector temperature, 110 °C; head pressure, 65 kPa; retention times, toluene, 9.6 min, allene **7**, 12.3 min, *m*-xylene, 16.9 min. GC parameters #2: initial temperature, 40 °C; initial time, 1.00 min; rate, 10 °C/min; final temperature, 175 °C; injector temperature, 225 °C; detector temperature, 250 °C; head pressure, 65 kPa; retention times, *m*-xylene, 7.9 min, methyl benzyl ether, 10.2 min, 2-phenylethanol, 12.6 min, bibenzyl, 21.8 min. GC parameters #3: initial temperature, 70 °C; initial time, 10.0 min; rate, 20 °C/min; final temperature, 200 °C; injector temperature, 119 °C; detector temperature, 154 °C; head pressure, 65 kPa; retention times, *m*-xylene, 8.8 min, **14** and **15**, 19.0 and 19.3 min. Product yields were determined by integration of the corresponding GLC signals and comparison to *m*-xylene with appropriate response factor corrections.

(*Z*)-Vinyl Chloride 21. A deoxygenated suspension of bis(triphenylphosphine)palladium(II) chloride (0.63 g, 0.89 mmol, 0.05 equiv) and (*Z*)-1,2-dichloroethylene (6.9 mL, 89 mmol, 5.0 equiv) in ethyl ether (15 mL) was transferred via wide-bore cannula to an ice-cooled, deoxygenated solution of cuprous iodide (0.51 g, 2.67 mmol, 0.15 equiv), 3-butyn-2-ol (1.25 g, 17.8 mmol, 1 equiv), and *n*-propylamine (7.50 mL, 89 mmol, 5.0 equiv) in ethyl ether (15 mL). After being stirred at 23 °C for 16 h, the reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (CH_2Cl_2) provided (*Z*)-vinyl chloride **21** (1.98 g, 70%) as a pale yellow oil: R_f = 0.50 (40% ethyl acetate in hexanes); IR (neat) 3332 (br, OH), 2985 (m), 1590 (s), 1329 (s), 1145 (s), 1077 (s), 1004 (s); ^{1}H NMR (400 MHz, C_6D_6) 5.69 (d, 1 H, *J* = 7.3 Hz, C≡CCH=C*H*), 5.36 (dd, 1 H, *J* = 7.3, 1.7 Hz, C≡CC*H*=CH), 4.23–4.31 (m, 1 H, C*H*(CH$_3$)OH), 1.37 (d, 1 H, *J* = 5.4 Hz, O*H*), 1.21 (d, 3 H, *J* = 6.6 Hz, CH(CH_3)OH); HRMS calcd for C_6H_7ClO (M^+) 130.0185, found 130.0174.

(*Z*)-Enediyne 22. A deoxygenated suspension of bis(triphenylphosphine)palladium(II) chloride (0.38 g, 0.54 mmol, 0.05 equiv) and the (*Z*)-vinyl chloride **21** (1.40 g, 10.8 mmol, 1 equiv) in tetrahydrofuran (10 mL) at 23 °C was transferred via wide-bore cannula to a deoxygenated, ice-cooled solution of cuprous iodide (0.31 g, 1.6 mmol, 0.15 equiv), (trimethylsilyl)acetylene (2.30 mL, 16.2 mmol, 1.5 equiv), and *n*-propylamine (4.4 mL, 54.0 mmol, 5.0 equiv) in tetrahydrofuran (10 mL). The resulting brown suspension was stirred at 0 °C for 2 h and then was added to an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (40 mL) and was stirred under air at 23 °C for 1 h. The organic phase was separated, and the aqueous layer was extracted with a 1:1 mixture of ethyl acetate and hexanes (2 × 20 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford (*Z*)-enediyne **22** (1.66 g, 81%) as a pale yellow oil: R_f = 0.55 (40% ethyl acetate in hexanes); IR (neat) 3378 (br, OH), 2961 (s), 2146 (s, C≡C), 1251 (s), 1149 (s), 1083 (s), 1028 (m), 987 (m); ^{1}H NMR (400 MHz, C_6D_6) 5.52 (d, 1 H, *J* = 11.0 Hz, HC=C*H*C≡CCH(CH$_3$)OH), 5.47 (d, 1 H, *J* = 12.2 Hz, *H*C=CHC≡CCH(CH$_3$)OH), 4.38 (dt, 1 H, *J* = 6.6, 5.4 Hz, C≡CC*H*-(CH$_3$)OH), 1.41 (d, 1 H, *J* = 5.4 Hz, O*H*), 1.29 (d, 3 H, *J* = 6.6 Hz, C≡CCH(CH_3)OH), 0.17 (s, 9 H, Si(CH_3)$_3$); HRMS calcd for $C_{11}H_{15}OSi$ (M^+) 192.0970, found 192.0974.

Allene 18. Methanesulfonyl chloride (0.28 mL, 3.66 mmol, 3.0 equiv) was added dropwise over 15 min to an ice-cooled solution of the (*Z*)-enediyne **22** (0.23 g, 1.22 mmol, 1 equiv) and triethylamine (0.85 mL, 6.10 mmol, 5.0 equiv) in dichloromethane (5.0 mL). The resulting yellow suspension was stirred at 0 °C for 20 min and then anhydrous hydrazine (6.0 mL, 189 mmol, 155 equiv) in methanol (6.0 mL) was added dropwise via syringe. After being stirred at 0 °C for 23 h, the reaction mixture was partitioned between a saturated aqueous solution of sodium bicarbonate (30 mL) and a 9:1 mixture of dichloromethane and methanol (2 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide the crude hydrazine, which was diluted with deoxygenated ethyl ether (10 mL).[46] The resulting suspension was treated with a deoxygenated solution of 4-methyl-1,2,4-triazoline-3,5-dione (0.162 g, 1.43 mmol, 1.3 equiv) in ethyl ether (5.0 mL, dropwise addition via cannula over 10 min). After being stirred at 0 °C for 10 min, the reaction mixture was added to a saturated, aqueous ammonium chloride solution (10 mL) and was washed with water (3 × 5.0 mL). The organic phase was dried over sodium sulfate and was concentrated at −24 °C to a volume of 2.5 mL. The concentrate was purified by flash column chromatography (pentane, fractions concentrated at 0 °C) to give the allene **18** as a solution in pentane. The yield

(46) Desilylation accompanied hydrazine formation in this instance.

of **18** was determined to be 46% by addition of 0.25 mmol of *m*-xylene to the chromatographed solution and ^{1}H NMR analysis: R_f = 0.46 (hexanes); IR (neat) 2161 (w, C≡C), 1940 (s, C=C=C); ^{1}H NMR (400 MHz, C_6D_6) 6.60–6.70 (m, 1 H, C*H*=C=CHCH$_3$), 6.18 (dd, 1 H, J = 10.5, 1.0 Hz, HC≡CCH=C*H*), 5.15 (dd, 1 H, J = 10.5, 2.4 Hz, HC≡CC*H*=CH), 5.00–5.10 (m, 1 H, CH=C=C*H*CH$_3$), 2.86 (d, 1 H, J = 2.4 Hz, *H*C≡CCH=CH), 1.37 (dd, 3 H, J = 7.1, 3.2 Hz, CH=C=CHC*H*$_3$); HRMS calcd for C_8H_9 (MH^+) 105.0705, found 105.0705.

Pyrolysis of Allene 18. Pyrolyses of the allene **18** (0.003 M) were conducted as described in the general procedure above using *N,N*-dimethylaniline (0.0015 M) as an internal reference. During kinetic analyses, tubes were removed from the heating bath at appropriate time intervals and were immediately cooled to 0 °C, scored, and opened, and their contents were analyzed by HPLC. HPLC conditions: solvent, 43% H_2O in methanol; flow rate, 0.8 mL/min; retention times, *N,N*-dimethylaniline, 28.8 min, allene **18**, 37.2 min. Product yields were determined by GLC analysis of pyrolysis reaction mixtures. GC parameters #4: initial temperature, 40 °C; initial time, 4.00 min; rate, 40 °C/min; final temperature, 120 °C; injector temperature, 200 °C; detector temperature, 200 °C; head pressure, 65 kPa; retention times, ethylbenzene, 7.2 min, *N,N*-dimethylaniline, 11.5 min. GC parameters #5: initial temperature, 120 °C; initial time, 7.0 min; rate, 40 °C/min; final temperature, 160 °C; injector temperature, 200 °C; detector temperature, 200 °C; head pressure, 65 kPa; retention times, *N,N*-dimethylaniline, 6.5 min, **24**, 16.2 and 16.6 min (1:1 mixture of diastereomers), **23**, 17.7 min. Product yields were determined by integration of the corresponding GLC signals and comparison to *N,N*-dimethylaniline with appropriate response factor corrections.

Bromo (*Z*)-Enyne 27. Cuprous iodide (1.48 g, 7.76 mmol, 0.20 equiv) and tetrakis(triphenylphosphine)palladium(0) (2.24 g, 1.94 mmol, 0.05 equiv) were added sequentially to a deoxygenated, ice-cooled solution of (*Z*)-ethyl-2,3-dibromopropenoate[25] (10.0 g, 38.8 mmol, 1 equiv), (trimethylsilyl)acetylene (9.32 mL, 66.0 mmol, 1.7 equiv), and *N,N*-diisopropylethylamine (11.5 mL, 66.0 mmol, 1.7 equiv) in *N,N*-dimethylformamide (60 mL). The resulting brown solution was thoroughly degassed and was stirred at 0 °C for 10 h. The reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The brown residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the bromo (*Z*)-enyne **27** (9.19 g, 86%) as a brown oil: R_f = 0.42 (5% ethyl acetate in hexanes); IR (neat) 2962 (m), 2901 (w), 2131 (w), 1732 (s, C=O), 1717 (s), 1584 (m), 1446 (w), 1367 (m), 1253 (s), 1083 (s), 1044 (m), 846 (s), 760 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 7.29 (s, 1 H, C=C*H*), 4.30 (q, 2 H, J = 7.1 Hz, CH$_3$C*H*$_2$O), 1.34 (t, 3 H, J = 7.1 Hz, C*H*$_3$CH$_2$O), 0.25 (s, 9 H, Si(C*H*$_3$)$_3$); HRMS calcd for $C_{10}H_{15}BrO_2Si$ (M^+) 274.0025, found 274.0024. Anal. Calcd for $C_{10}H_{15}BrO_2Si$: C, 43.64; H, 5.49. Found: C, 43.74; H, 5.26.

Alcohol 28. Diisobutylaluminum hydride (75.0 mL, 1.0 M solution in hexanes, 75.0 mmol, 2.27 equiv) was transferred via cannula over 15 min to a solution of the bromo (*Z*)-enyne **27** (9.10 g, 33.1 mmol, 1 equiv) in toluene (100 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then was maintained at 0 °C for 30 min. After the reaction was quenched with water (75 mL) at 0 °C, the cloudy mixture was stirred with tartaric acid (2 g) at 23 °C for 20 min and the resulting biphasic solution was extracted with a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5 → 30%) to give the alcohol **28** (7.23 g, 94%) as a yellow oil: R_f = 0.12 (10% ethyl acetate in hexanes); IR (neat) 3333 (br, OH), 2960 (m), 2900 (m), 2140 (m), 1409 (w), 1250 (s), 1082 (m), 1011 (m), 843 (s), 760 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 6.31 (s, 1 H, C=C*H*), 4.31 (d, 2 H, J = 5.4 Hz, HOC*H*$_2$), 2.57 (t, 1 H, J = 6.5 Hz, *H*OCH$_2$), 0.23 (s, 9 H, Si(C*H*$_3$)$_3$); HRMS calcd for $C_8H_{13}BrOSi$ (M^+) 231.9919, found 231.9923. Anal. Calcd for $C_8H_{13}BrOSi$: C, 41.21; H, 5.62. Found: C, 41.03; H, 5.58.

Bromo (*Z*)-Enyne 29. *tert*-Butyldiphenylsilyl chloride (4.68 mL, 18.0 mmol, 1.2 equiv) was added to a solution of the alcohol **28** (3.50 g, 15.0 mmol, 1 equiv) and triethylamine (10.5 mL, 75.3 mmol, 5.0 equiv) in dichloromethane (100 mL) at 0 °C. After the solution was warmed to 23 °C, 4-(dimethylamino)pyridine (0.5 g, 4.09 mmol, 0.27 equiv) was added, and the solution was stirred at 23 °C for 3.5 h. The reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the bromo (*Z*)-enyne **29** (6.73 g, 95%) as a yellow oil: R_f = 0.62 (20% ethyl acetate in hexanes); IR (neat) 3072 (m), 2959 (s), 2858 (m), 2144 (m, C≡C), 1472 (m), 1428 (m), 1250 (s), 1114 (s), 1091 (s), 1034 (m), 843 (s), 760 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 7.64–7.67 (m, 4 H, *Ph*Si), 7.38–7.48 (m, 6 H, *Ph*Si), 6.57 (t, 1 H, J = 2.0 Hz, C=C*H*), 4.33 (d, 2 H, J = 2.0 Hz, SiOC*H*$_2$), 1.08 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.25 (s, 9 H, Si(C*H*$_3$)$_3$); HRMS calcd for $C_{24}H_{32}BrOSi_2$ (MH^+) 471.1175, found 471.1180. Anal. Calcd for $C_{24}H_{31}BrOSi_2$: C, 61.13; H, 6.63. Found: C, 61.47; H, 6.73.

Enediyne 30. Cuprous iodide (0.082 g, 0.43 mmol, 0.15 equiv) and bis(triphenylphosphine)palladium(II) chloride (0.10 g, 0.14 mmol, 0.05 equiv) were added sequentially to an ice-cooled solution of the bromo (*Z*)-enyne **29** (1.35 g, 2.86 mol, 1 equiv), propargyl alcohol (0.33 mL, 5.72 mmol, 2.0 equiv), and *n*-propylamine (0.94 mL, 11.4 mmol, 4.0 equiv) in tetrahydrofuran (40 mL), and the resulting brown suspension was thoroughly degassed. After being stirred at 23 °C for 14 h, the reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford the enediyne **30** (1.10 g, 86%) as a pale yellow oil: R_f = 0.23 (20% ethyl acetate in hexanes); IR (neat) 3348 (br, OH), 3071 (w), 2958 (m), 2138 (m, C≡C), 1590 (w), 1428 (m), 1250 (m), 1112 (s), 846 (s), 703 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.63–7.65 (m, 4 H, *Ph*Si), 7.37–7.46 (m, 6 H, *Ph*Si), 6.28 (t, 1 H, J = 2.2 Hz, C=C*H*), 4.41 (s, 2 H, SiOC*H*$_2$), 4.22 (d, 2 H, J = 2.2 Hz, C≡CC*H*$_2$OH), 1.06 (s, 9 H, SiC(C*H*$_3$)$_3$), 0.23 (s, 9 H, Si(C*H*$_3$)$_3$); HRMS calcd for $C_{27}H_{35}O_2Si_2$ (MH^+) 447.2176, found 447.2182.

Allene 19. Sodium hydroxide (50% aqueous, 0.5 mL) was added via pipette to an ice-cooled solution of the enediyne **30** (1.10 g, 2.46 mmol) in methanol (30 mL). The colorless solution was stirred at 0 °C for 45 min and then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% hexanes in toluene) to give the propargyl alcohol **31** (0.89 g, 95%) as a colorless oil: R_f = 0.13 (20% ethyl acetate in hexanes); IR (neat) 3369 (br, OH), 3287 (m, C≡CH), 3071 (w), 2931 (m), 2857 (m), 1428 (m), 1112 (s), 824 (m), 704 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.64–7.66 (m, 4 H, *Ph*Si), 7.37–7.47 (m, 6 H, *Ph*Si), 6.24 (dd, 1 H, J = 4.4, 2.2 Hz, C=C*H*), 4.41 (s, 2 H, SiOC*H*$_2$), 4.24 (d, 2 H, J = 4.4 Hz, C≡CC*H*$_2$OH), 3.32 (d, 1 H, J = 2.2 Hz, C≡C*H*), 1.07 (s, 9 H, C(C*H*$_3$)$_3$); HRMS calcd for $C_{24}H_{30}NO_2Si$ (MNH_4^+) 392.2046, found 392.2059.

Methanesulfonyl chloride (0.10 mL, 1.33 mmol, 3.0 equiv) was added dropwise over 15 min to an ice-cooled solution of the propargyl alcohol **31** (0.17 g, 0.44 mmol, 1 equiv) and triethylamine (0.31 mL, 2.22 mmol, 5.0 equiv) in dichloromethane (10 mL). The resulting yellow suspension was stirred for 20 min at 0 °C and then anhydrous hydrazine (0.42 mL, 13.3 mmol, 30 equiv) in methanol (2 mL) was added dropwise via syringe over 2 min. The reaction mixture was stirred at 0 °C for 12 h and then was partitioned between water (100 mL) and ethyl acetate (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide the crude hydrazine. The crude hydrazine was diluted with deoxygenated ethyl ether (10 mL) at 0 °C, and the resulting suspension was treated with a deoxygenated solution of 4-methyl-1,2,4-triazoline-3,5-dione (0.60 g, 0.531 mmol, 1.2 equiv) in ethyl ether (20 mL, dropwise addition over 20 min). After being stirred at 0 °C for 5 min, the reaction mixture was partitioned between water (100 mL) and pentane (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated at 23 °C. The residue was purified by flash column chromatography (hexanes) to give the allene **19** (0.65 g, 41%) as a colorless oil: R_f = 0.53 (10% ethyl acetate in hexanes); IR (neat) 3297 (m, C≡CH), 3070 (w), 2931 (m), 2857 (m), 1934 (m, C=C=C), 1427 (m), 1112 (s), 828 (m), 703 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.66–7.68 (m, 4 H, *Ph*Si), 7.38–7.46 (m, 6 H, *Ph*Si), 6.51 (t, 1 H, J = 6.8 Hz, *H*C=C=CH$_2$), 5.93 (s, 1 H, C=C*H*), 4.88 (d, 2 H, J = 6.8 Hz, HC=C=C*H*$_2$), 4.32 (s, 2 H, SiOC*H*$_2$), 3.31 (s, 1 H, C≡C*H*), 1.07 (s, 9 H, C(C*H*$_3$)$_3$); HRMS calcd for $C_{24}H_{27}OSi$ (MH^+) 359.1831, found 359.1848.

Pyrolysis of Allene 19. Solutions of **19** (3.0–5.0 mg, 0.01 M) in a deoxygenated solvent (methanol, 4.0 M methanol in DMSO, 4.0 M 1,4-cyclohexadiene in DMSO or a 4:1 mixture of THF and water) were stirred at 60 °C for 18 h, and then each reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (3–5% ethyl acetate in hexanes). Product yields were determined prior to chromatography by addition of (*Z*)-1,2-dichloroethylene as an internal standard and ^{1}H NMR analysis.

3-Tolyl *tert*-butyldiphenylsilyl ether (32): R_f = 0.70 (5% ethyl acetate in hexanes); IR (neat) 3070 (w), 2932 (m), 2858 (m), 1590 (w), 1428 (m), 1157 (m), 1111 (s), 1079 (s), 824 (m), 703 (s); ^{1}H NMR (500 MHz, $CDCl_3$) 7.69–7.71 (m, 4 H, *Ph*Si), 7.36–7.44 (m, 7 H, *Ph*Si and *Ar*-2), 7.06–7.24 (m, 3 H, *Ar*-4, *Ar*-5, and *Ar*-6), 4.74 (s, 2 H, $SiOCH_2$), 2.34 (s, 3 H, CH_3), 1.09 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{24}H_{27}OSi$ ($M - H^+$) 359.1831, found 359.1838.

1,4-Cyclohexadiene addition products 33 and 34: R_f = 0.33 (hexanes); IR (neat) 3026 (w), 2930 (m), 2857 (m), 1590 (w), 1428 (m), 1156 (m), 1110 (s), 1081 (s), 702 (s); ^{1}H NMR (500 MHz, $CDCl_3$) 7.69–7.70 (m, *Ph*Si in both), 7.36–7.44 (m, *Ph*Si, *Ar*-2, *Ar*-4, *Ar*-5, and/or *Ar*-6 in both), 7.04–7.25 (m, *Ph*Si, *Ar*-2, *Ar*-4, *Ar*-5, and/or *Ar*-6 in both), 5.89–5.91 (m, C=C*H*), 5.69–5.76 (m, C=C*H*), 5.60–5.63 (m, C=C*H*), 4.76 (s, $SiOCH_2$ in both), 2.69–2.71 (m, CH_2 in either), 2.67 (d, J = 7.5 Hz, CH_2CH in **33**), 2.55–2.64 (m, CH_2CH in **33**), 1.97–2.04 (m, CH_2 in either), 1.09 (s, $SiC(CH_3)_3$ in both); HRMS calcd for $C_{30}H_{33}OSi$ (MH^+) 437.2301, found 437.2323.

Bibenzyl derivative 35: R_f = 0.40 (5% ethyl acetate in hexanes); IR (neat) 2927 (m), 2857 (m), 1468 (w), 1429 (m), 1109 (s), 822 (m), 701 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.68–7.71 (m, 8 H, *Ph*Si), 7.35–7.44 (m, 14 H, *Ph*Si and *Ar*-2), 7.17–7.23 (m, 6 H, *Ar*-4, *Ar*-5, and *Ar*-6), 4.76 (s, 4 H, $SiOCH_2$), 2.89 (s, 4 H, CH_2), 1.09 (s, 18 H, $SiC(CH_3)_3$); HRMS calcd for $C_{48}H_{54}O_2Si_2$ (M^+) 718.3662, found 718.3654.

Methyl ether 36: R_f = 0.33 (5% ethyl acetate in hexanes); IR (neat) 2931 (m), 2857 (m), 1428 (m), 1156 (m), 1109 (s), 823 (m), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.69–7.71 (m, 4 H, *Ph*Si), 7.38–7.43 (m, 7 H, *Ph*Si and *Ar*-2), 7.24–7.36 (m, 3 H, *Ar*-4, *Ar*-5, and *Ar*-6), 4.78 (s, 2 H, $SiOCH_2$), 4.45 (s, 2 H, CH_2OCH_3), 3.38 (s, 3 H, CH_2OCH_3), 1.10 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{25}H_{29}O_2Si$ ($M - H^+$) 389.1937, found 389.1931.

Alcohol 37: R_f = 0.07 (10% ethyl acetate in hexanes); IR (neat) 3349 (br, OH), 3072 (w), 2933 (m), 2854 (m), 1428 (m), 1110 (s), 701 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.68–7.70 (m, 4 H, *Ph*Si), 7.35–7.42 (m, 7 H, *Ph*Si and *Ar*-2), 7.11–7.29 (m, 3 H, *Ar*-4, *Ar*-5, and *Ar*-6), 4.76 (s, 2 H, $SiOCH_2$), 3.85 (t, 2 H, J = 6.6 Hz, CH_2CH_2OH), 2.86 (t, 2 H, J = 6.6 Hz, CH_2CH_2OH), 1.09 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{25}H_{34}NO_2Si$ (MNH_4^+) 408.2359, found 408.2342.

Tetrahydrofuran adduct 38: R_f = 0.18 (5% ethyl acetate in hexanes); IR (neat) 2931 (m), 2857 (m), 1428 (m), 1156 (w), 1110 (s), 823 (m), 741 (m), 702 (s); ^{1}H NMR (500 MHz, $CDCl_3$) 7.68–7.70 (m, 4 H, *Ph*Si), 7.36–7.44 (m, 7 H, *Ph*Si and *Ar*-2), 7.11–7.27 (m, 3 H, *Ar*-4, *Ar*-5, and *Ar*-6), 4.76 (s, 2 H, $SiOCH_2$), 4.03–4.08 (m, 1 H, one of $CHOCH_2$), 3.87–3.91 (m, 1 H, one of $CHOCH_2$), 3.71–3.76 (m, 1 H, one of $CHOCH_2$), 2.93 (dd, 1 H, J = 13.5, 6.8 Hz, CH_AH_BCH), 2.72 (dd, 1 H, J = 13.5, 6.8 Hz, CH_AH_BCH), 1.82–1.92 (m, 4 H, $CHCH_2CH_2$), 1.09 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{28}H_{38}NO_2Si$ (MNH_4^+) 448.2672, found 448.2661.

Benzyl Alcohol 39. *tert*-Butyldiphenylsilyl chloride (0.48 mL, 1.9 mmol, 1.0 equiv) was added to a solution of 1,3-benzenedimethanol (0.26 g, 1.9 mmol, 1 equiv), triethylamine (0.78 mL, 5.6 mmol, 3.0 equiv), and 4-(dimethylamino)pyridine (0.02 g, 0.16 mmol, 0.10 equiv) in dichloromethane (12 mL) at 23 °C. After being stirred at 23 °C for 2 h, the reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to give the benzyl alcohol **39** (0.41 g, 58%) as a colorless oil: R_f = 0.42 (30% ethyl acetate in hexanes); IR (neat) 3333 (br, OH), 3071 (m), 2931 (m), 2857 (m), 1472 (m), 1428 (s), 1112 (s), 824 (s), 740 (s), 701 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.68–7.70 (m, 4 H, *Ph*Si), 7.26–7.43 (m, 10 H, *Ph*Si, *Ar*-2, *Ar*-4, *Ar*-5, and *Ar*-6), 4.78 (s, 2 H, $SiOCH_2$), 4.68 (s, 2 H, CH_2OH), 1.10 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{24}H_{27}O_2Si$ ($M - H^+$) 375.1780, found 375.1764.

Aldehyde 45. A solution of the bromo (*Z*)-enyne **29** (2.50 g, 5.3 mmol, 1 equiv) in a mixture of THF, ethyl ether, and pentane (4:1:1, respectively, 10.3 mL) was added dropwise via cannula over 20 min to a solution of *tert*-butyllithium (7.80 mL, 1.70 M solution in pentane, 13.3 mmol, 2.5 equiv) in a mixture of THF, ethyl ether, and pentane (4:1:1, respectively, 37.5 mL) at −120 °C. Upon completion of the addition, a solution of *N,N*-dimethylformamide (1.03 mL, 13.3 mmol, 2.5 equiv) in tetrahydrofuran (3.0 mL) was added via cannula to the orange reaction mixture, and the resulting yellow solution was allowed to warm to −40 °C over 3 h. After the reaction was quenched with water (5 mL) at −40 °C, the product was partitioned between brine (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: toluene in hexanes, 10 → 50%) to give the aldehyde **45** (1.58 g, 71%) as a pale yellow oil: R_f = 0.55 (10% ethyl acetate in hexanes); IR (neat) 2959 (m), 2858 (m), 2130 (w), 1684 (s, C=O), 1472 (m), 1430 (m), 1303 (m), 1251 (m), 1192 (m), 1113 (s), 845 (s), 761 (m), 740 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 10.20 (s, 1 H, *CH*O), 7.61–7.63 (m, 4 H, *Ph*Si), 7.35–7.44 (m, 6 H, *Ph*Si), 6.99 (t, 1 H, J = 2.4 Hz, C=C*H*), 4.45 (d, 2 H, J = 2.4 Hz, $SiOCH_2$), 1.08 (s, 9 H, $SiC(CH_3)_3$), 0.25 (s, 9 H, $Si(CH_3)_3$); HRMS calcd for $C_{25}H_{33}O_2Si_2$ (MH^+) 421.2019, found 421.2011.

Thiol Ester 46. Methanesulfonyl chloride (0.39 mL, 5.1 mmol, 1.2 equiv) was added dropwise over 15 min to an ice-cooled solution of 3,3-dimethyl-4-pentyn-1-ol[24] (0.47 g, 4.2 mmol, 1 equiv) and triethylamine (0.77 mL, 5.5 mmol, 1.3 equiv) in dichloromethane (15 mL). The resulting yellow suspension was stirred at 0 °C for 5 min and then was partitioned between brine (40 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The remaining yellow oil was dissolved in tetrahydrofuran (6 mL) and the resulting solution was cooled to 0 °C. Triethylamine (5.9 mL, 42.2 mmol, 10.0 equiv) and thiopivalic acid (3.2 mL, 25.4 mmol, 6.0 equiv) were added sequentially at 0 °C. The mixture was heated at 60 °C for 6 h. After being cooled to 23 °C, the reaction mixture was partitioned between water (30 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give thiol ester **46** (0.72 g, 85%) as a colorless oil: R_f = 0.62 (20% ethyl acetate in hexanes); IR (neat) 3299 (m, C≡CH), 2972 (s), 2948 (m), 2870 (m), 2109 (w), 1680 (s, C=O), 1479 (m), 1365 (m), 1246 (w), 1037 (m), 953 (s), 810 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 2.94–2.98 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 2.15 (s, 1 H, C≡C*H*), 1.61–1.66 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 1.26 (s, 6 H, $SCH_2CH_2C(CH_3)_2$), 1.23 (s, 9 H, $C(CH_3)_3$); HRMS calcd for $C_{12}H_{21}OS$ (MH^+) 213.1313, found 213.1301.

Alcohol 47. A solution of lithium diisopropylamide in tetrahydrofuran (0.50 M, 10 mL, 1.5 equiv) was added via cannula to a solution of the thiol ester **46** (0.86 g, 4.04 mmol, 1.2 equiv) in tetrahydrofuran (40 mL) at −78 °C. After the mixture was stirred at −78 °C for 10 min, anhydrous cerium(III) chloride (1.33 g, 5.40 mmol, 1.5 equiv) was added to the reaction mixture, and the resulting orange suspension was stirred at −78 °C for 30 min. A solution of the aldehyde **45** (1.41 g, 3.36 mmol, 1 equiv) in tetrahydrofuran (10 mL) was then added via cannula over 2 min, and the reaction mixture was stirred at −78 °C for 30 min. After the reaction was quenched with water (3 mL) at −78 °C, sodium tartrate (0.5 g) was added, and the crude mixture was partitioned between water (400 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5 → 10%) provided the alcohol **47** (1.92 g, 90%) as a pale yellow oil: R_f = 0.24 (10% ethyl acetate in hexanes); IR (neat) 3506 (br, OH), 2965 (s), 2934 (m), 2859 (m), 2132 (w), 1679 (s, C=O), 1472 (m), 1364 (w), 1250 (m), 1110 (s), 952 (m), 846 (s), 704 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 7.64–7.68 (m, 4 H, *Ph*Si), 7.39–7.41 (m, 6 H, *Ph*Si), 5.85 (s, 1 H, C=C*H*), 5.56 (d, 1 H, J = 5.9 Hz, *CH*OH), 4.59 (dd, 1 H, J = 15.4, 2.0 Hz, $SiOCH_AH_B$), 4.36 (dd, 1 H, J = 15.4, 2.0 Hz, $SiOCH_AH_B$), 2.99 (d, 1 H, J = 6.4 Hz, CHO*H*), 2.80–2.84 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 1.52–1.57 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 1.20 (s, 9 H, $C(CH_3)_3$), 1.14 (s, 3 H, one of $SCH_2CH_2C(CH_3)_2$), 1.13 (s, 3 H, one of $SCH_2CH_2C(CH_3)_2$), 1.06 (s, 9 H, $SiC(CH_3)_3$), 0.22 (s, 9 H, $Si(CH_3)_3$); HRMS calcd for $C_{37}H_{53}O_3SSi_2$ (MH^+) 633.3254, found 633.3236.

Disulfide 48. Sodium hydroxide (50% aqueous, 0.5 mL) was added via pipette to an ice-cooled solution of the alcohol **47** (0.60 g, 0.97 mmol) in a mixture of tetrahydrofuran, methanol, and propyl disulfide (4:1:1, respectively, 18 mL). The yellow reaction mixture was stirred at 0 °C for 4 h and then was partitioned between water (30 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 70 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% hexanes in toluene) to give the disulfide **48** (0.37 g, 70%) as a pale yellow oil: R_f = 0.30 (toluene); IR (neat) 3428 (br, OH), 3289 (m, C≡CH), 3070 (w), 2961 (s), 2930 (s), 2857 (m), 2235 (w), 1427 (s), 1363 (m), 1249 (w), 1158 (m), 1112 (s), 1060 (m), 822 (m), 740 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.65–7.69 (m, 4 H, *Ph*Si), 7.40–7.42 (m, 6 H, *Ph*Si), 5.78 (s, 1 H, C=C*H*), 5.57 (s, 1 H, *CH*OH), 4.59 (d, 1 H, J = 15.1 Hz, $SiOCH_AH_B$), 4.36 (d, 1 H, J = 15.1 Hz, $SiOCH_AH_B$), 3.22 (s, 1 H, C≡C*H*), 2.66–2.70 (m, 2 H, $SSCH_2CH_2C(CH_3)_2$), 2.62 (t, 2 H, J = 7.21 Hz, $SSCH_2CH_2CH_3$), 1.65–1.74 (m, 4 H, $SSCH_2CH_2C(CH_3)_2$ and $SSCH_2CH_2CH_3$), 1.13 (s, 6 H, $SSCH_2CH_2C(CH_3)_2$), 1.08 (s, 9 H, $SiC(CH_3)_3$), 0.97 (t, 3 H, J = 7.33 Hz, $SSCH_2CH_2CH_3$); HRMS calcd for $C_{32}H_{43}O_2S_2Si$ (MH^+) 551.2474, found 551.2457. Anal. Calcd for $C_{32}H_{42}O_2S_2Si$: C, 69.77; H, 7.68. Found: C, 69.85; H, 7.52.

Dinitrobenzoate 41. 3,5-Dinitrobenzoic acid (2.86 g, 13.5 mmol, 10.0 equiv), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride

(2.58 g, 13.5 mmol, 10.0 equiv), and 4-(dimethylamino)pyridine (0.822 g, 6.73 mmol, 5.0 equiv) were added sequentially to a solution of the disulfide **48** (0.742 g, 1.35 mmol, 1 equiv) in dichloromethane (100 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 30 min and then was partitioned between water (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) afforded the dinitrobenzoate **41** (0.903 g, 90%) as a colorless oil: R_f = 0.31 (10% ethyl acetate in hexanes); IR (neat) 3286 (w, C≡CH), 3101 (w), 2961 (m), 2930 (m), 2857 (m), 1738 (m, C=O), 1547 (s, NO_2), 1428 (w), 1344 (s, NO_2), 1264 (m), 1156 (m), 1113 (s), 922 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 9.20 (t, 1 H, J = 2.1 Hz, Ph$(NO_2)_2H_p$), 9.02 (d, 2 H, J = 2.1 Hz, Ph$(NO_2)_2H_o$), 7.64–7.70 (m, 4 H, *Ph*Si), 7.35–7.43 (m, 6 H, *Ph*Si), 6.79 (s, 1 H, C=CC*H*(OR)C≡C), 6.19 (d, 1 H, J = 2.2 Hz, C=C*H*), 4.63 (d, 1 H, J = 16.7 Hz, SiOCH_AH_B), 4.51 (d, 1 H, J = 16.7 Hz, SiOCH_AH_B), 3.35 (d, 1 H, J = 2.4 Hz, C≡C*H*), 2.59–2.65 (m, 4 H, SSCH_2CH_2C$(CH_3)_2$ and SSCH_2CH_2CH_3), 1.62–1.72 (m, 4 H, SSCH_2CH_2C$(CH_3)_2$ and SSCH_2CH_2CH_3), 1.10 (s, 3 H, one of SSCH_2CH_2C$(CH_3)_2$), 1.09 (s, 12 H, SiC$(CH_3)_3$ and one of SSCH_2CH_2C$(CH_3)_2$), 0.96 (t, 3 H, J = 7.3 Hz, SSCH_2CH_2CH_3); HRMS calcd for $C_{39}H_{44}N_2O_7S_2Si$ (M^+) 744.2359, found 744.2377.

Thiol 42. Tributylphosphine (0.119 mL, 0.478 mmol, 10 equiv) was added to an ice-cooled solution of the disulfide **41** (0.360 g, 0.48 mmol, 1 equiv) in a 4:1 mixture of 1,2-dimethoxyethane and water (5 mL). The resulting purple solution was stirred at 0 °C for 30 min and then was partitioned between water (75 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the thiol **42** (0.262 g, 82%) as a colorless oil: R_f = 0.60 (toluene); IR (neat) 3286 (w, C≡CH), 2964 (w), 2851 (w), 1737 (m, C=O), 1547 (s, NO_2), 1344 (s, NO_2), 1265 (m), 1156 (m), 1113 (m), 702 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 9.21 (t, 1 H, J = 2.2 Hz, Ph$(NO_2)_2H_p$), 9.02 (d, 2 H, J = 2.2 Hz, Ph$(NO_2)_2H_o$), 7.65–7.70 (m, 4 H, *Ph*Si), 7.36–7.42 (m, 6 H, *Ph*Si), 6.79 (s, 1 H, C=CC*H*(OR)C≡C), 6.19 (d, 1 H, J = 2.3 Hz, C=C*H*), 4.61 (d, 1 H, J = 16.6 Hz, SiOCH_AH_B), 4.50 (d, 1 H, J = 16.6 Hz, SiOCH_AH_B), 3.35 (d, 1 H, J = 2.3 Hz, C≡C*H*), 2.43–2.49 (m, 2 H, HSCH_2CH_2C$(CH_3)_2$), 1.60–1.64 (m, 2 H, HSCH_2CH_2C$(CH_3)_2$), 1.29 (t, 1 H, J = 7.7 Hz, *H*SCH_2CH_2C$(CH_3)_2$), 1.09 (s, 9 H, SiC$(CH_3)_3$), 1.08 (s, 3 H, one of HSCH_2CH_2C$(CH_3)_2$), 1.07 (s, 3 H, one of HSCH_2CH_2C$(CH_3)_2$); HRMS calcd for $C_{36}H_{37}N_2O_7SSi$ (M − H^+) 669.2098, found 669.2115.

Allene 43. Triethylamine (0.005 mL, 0.036 mmol, 2.2 equiv) was added to a deoxygenated solution of the thiol **42** (0.011 g, 0.017 mmol, 1 equiv), 1,4-cyclohexadiene (0.016 mL, 0.17 mmol), and (*Z*)-1,2-dichloroethylene (0.072 mmol, internal standard) in a mixture of dimethyl sulfoxide-d_6 and dichloromethane-d_2 (2.3:1, respectively, 0.66 mL) contained in a septum-capped NMR tube at 0 °C. After rapid mixing, the tube was transferred without temperature increase to the probe of a high-field NMR spectrometer (400 MHz) that was maintained at 0 °C. The probe was warmed to 10 °C and, within 30 min, spectroscopic examination revealed the conversion (>95%) of the thiol **42** to the allene **43**. Selected ^{1}H NMR spectral data for **42** and **43**: C=C*H* (**42**) 6.12 (d, J = 2.2 Hz), (**43**) 5.90 (d, J = 1.5 Hz); CH_2OTDS (**42**) 4.60 (AB, J = 21.9 Hz), (**43**) 4.21 (AB, J = 19.8 Hz); ArCO_2C*H* → C=C=C*H* (**42**) 6.72 (s), (**43**) 6.62 (s).

General Cyclization Procedure (Thiol 42 and Dinitrobenzoate 41). Triethylamine (5 equiv) was added to a deoxygenated solution of the thiol **42** or the dinitrobenzoate **41** (each 0.01 M) and trapping agent (1,4-cyclohexadiene or methanol, each 4.0 M) in dimethyl sulfoxide at 23 °C. 4-Methoxythiophenol (3 equiv) was included in the reaction mixture when the dinitrobenzoate **41** was used as a substrate. After being stirred at 23 °C for 10 h, each reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (3–5% ethyl acetate in hexanes, 2 elutions). Product yields were determined prior to chromatography by addition of (*Z*)-1,2-dichloroethylene to the crude reaction mixtures as an internal standard and ^{1}H NMR analysis.

Tetrahydrothiophene derivative 49: R_f = 0.57 (5% ethyl acetate in hexanes); IR (neat) 3070 (w), 2959 (m), 2856 (m), 1472 (w), 1427 (m), 1364 (w), 1155 (w), 1113 (s), 1079 (m), 998 (w), 740 (m), 701 (s); ^{1}H NMR (500 MHz, CD_2Cl_2) 7.69–7.71 (m, 4 H, *Ph*Si), 7.36–7.45 (m, 7 H, *Ph*Si and *Ar*-2), 7.22–7.30 (m, 3 H, *Ar*-4, *Ar*-5, and *Ar*-6), 4.78 (s, 2 H, SiOCH_2), 4.17 (s, 1 H, SC*H*C$(CH_3)_2$), 3.02–3.07 (m, 1 H, one of SCH_2CH_2), 2.81–2.92 (m, 1 H, one of SCH_2CH_2), 1.99–2.04 (m, 1 H, one of SCH_2CH_2), 1.87–1.93 (m, 1 H, one of SCH_2CH_2), 1.09 (s, 9 H, SiC$(CH_3)_3$), 1.08 (s, 3 H, one of C$(CH_3)_2$), 0.74 (s, 3 H, one of C$(CH_3)_2$); HRMS calcd for $C_{29}H_{36}OSSi$ (MH^+) 460.2256, found 460.2243.

Thiophenol adduct 51: R_f = 0.28 (5% ethyl acetate in hexanes); IR (neat) 3057 (w), 2959 (m), 2927 (m), 1591 (m), 1492 (s), 1288 (m), 1246 (s), 1109 (s), 824 (m), 702 (s); ^{1}H NMR (500 MHz, $CDCl_3$) 7.69–7.71 (m, 4 H, *Ph*Si), 7.40–7.42 (m, 1 H, *Ar*-2), 7.34–7.38 (m, 6 H, *Ph*Si), 7.17–7.21 (m, 3 H, *Ar*-4, *Ar*-5, and *Ar*-6), 7.06–7.08 (m, 2 H, *p*-CH_3OPhH_o), 6.63–6.64 (m, 2 H, *p*-CH_3OPhH_m), 4.76 (d, 2 H, J = 1.7 Hz, SiOCH_2), 3.70 (s, 3 H, *p*-CH_3OPh), 2.99–3.04 (m, 2 H, SCH_2CH_2), 2.70–2.77 (m, 1 H, one of SCH_2CH_2), 2.00–2.06 (m, 1 H, one of SCH_2CH_2), 1.45 (s, 3 H, one of C$(CH_3)_2$), 1.09 (s, 9 H, SiC$(CH_3)_3$), 0.79 (s, 3 H, one of C$(CH_3)_2$); HRMS calcd for $C_{36}H_{41}O_2S_2Si$ (M − H^+) 597.2317, found 597.2343.

Methyl ether 52: R_f = 0.42 (5% ethyl acetate in hexanes); IR (neat) 3071 (w), 2959 (s), 2856 (s), 1472 (m), 1428 (s), 1112 (s), 1078 (s), 825 (m), 701 (s); ^{1}H NMR (500 MHz, $CDCl_3$) 7.69–7.71 (m, 4 H, *Ph*Si), 7.22–7.44 (m, 10 H, *Ph*Si, *Ar*-2, *Ar*-4, *Ar*-5, and *Ar*-6), 4.79 (s, 2 H, SiOCH_2), 3.16 (s, 3 H, CH_3O), 2.95–3.05 (m, 1 H, one of SCH_2CH_2), 2.82–2.90 (m, 1 H, one of SCH_2CH_2), 2.42–2.50 (m, 1 H, one of SCH_2CH_2), 1.84–1.96 (m, 1 H, one of SCH_2CH_2), 1.10 (s, 9 H, SiC$(CH_3)_3$), 1.04 (s, 3 H, one of C$(CH_3)_2$), 0.71 (s, 3 H, one of C$(CH_3)_2$); HRMS calcd for $C_{30}H_{37}O_2SSi$ (M − H^+) 489.2284, found 489.2278.

Hemithioketal 55: R_f = 0.49 (20% ethyl acetate in hexanes); IR (neat) 3484 (br, OH), 3065 (w), 2925 (m), 2855 (m), 1474 (m), 1427 (m), 1113 (s), 1078 (m), 822 (m), 700 (s); ^{1}H NMR (500 MHz, CD_2Cl_2) 7.69–7.75 (m, 5 H, *Ph*Si and *Ar*-2), 7.60–7.66 (m, 1 H, *Ar*-4 or *Ar*-6), 7.36–7.46 (m, 6 H, *Ph*Si), 7.27–7.29 (m, 2 H, *Ar*-5 and one of *Ar*-4 or *Ar*-6), 4.80 (s, 2 H, SiOCH_2), 3.09–3.14 (m, 1 H, one of SCH_2CH_2), 3.00–3.04 (m, 1 H, one of SCH_2CH_2), 2.47–2.54 (m, 1 H, one of SCH_2CH_2), 2.42 (s, 1 H, O*H*), 1.99–2.03 (m, 1 H, one of SCH_2CH_2), 1.09 (s, 9 H, SiC$(CH_3)_3$), 1.02 (s, 3 H, one of C$(CH_3)_2$), 0.78 (s, 3 H, one of C$(CH_3)_2$); HRMS calcd for $C_{29}H_{35}O_2SSi$ (M − H^+) 475.2127, found 475.2130.

General Desilylation Procedure. Tetrabutylammonium fluoride (2.0 mL, 1.0 M in tetrahydrofuran) was added to a solution of silyl ether (0.5–1.0 mg) in tetrahydrofuran (2 mL) at 23 °C. After being stirred at 23 °C for 30 min, each reaction mixture was partitioned between water (25 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 25 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (20% ethyl acetate in hexanes). Using the above procedure, the alcohols **50** and **54** were prepared from the tetrahydrothiophene derivative **49** and the methyl ether **52**, respectively.

Alcohol 50: R_f = 0.18 (20% ethyl acetate in hexanes); IR (neat) 3326 (br, OH), 2954 (s), 2921 (s), 2862 (m), 1452 (m), 1359 (m), 1021 (m), 790 (m); ^{1}H NMR (500 MHz, CD_2Cl_2) 7.40 (s, 1 H, *Ar*-2), 7.33 (d, 1 H, J = 7.4 Hz, *Ar*-4 or *Ar*-6), 7.28 (t, 1 H, J = 7.4 Hz, *Ar*-5), 7.24 (d, 1 H, J = 7.4 Hz, *Ar*-4 or *Ar*-6), 4.69 (d, 2 H, J = 5.6 Hz, HOCH_2), 4.19 (s, 1 H, SC*H*C$(CH_3)_2$), 3.04–3.10 (m, 1 H, one of SCH_2CH_2), 2.89–2.94 (m, 1 H, one of SCH_2CH_2), 2.00–2.05 (m, 1 H, one of SCH_2CH_2), 1.88–1.96 (m, 1 H, one of SCH_2CH_2), 1.60 (t, 1 H, J = 5.6 Hz, O*H*), 1.09 (s, 3 H, one of C$(CH_3)_2$), 0.76 (s, 3 H, one of C$(CH_3)_2$); HRMS calcd for $C_{13}H_{18}OS$ (M^+) 222.1078, found 222.1072.

Alcohol 50 (d_1): ^{1}H NMR (500 MHz, CD_2Cl_2) 7.39 (s, 1 H, *Ar*-2), 7.32 (s, 1 H, *Ar*-4 or *Ar*-6), 7.24 (s, 1 H, *Ar*-4 or *Ar*-6), 4.65 (d, 2 H, J = 5.8 Hz, HOCH_2), 4.18 (s, 1 H, SC*H*C$(CH_3)_2$), 3.03–3.09 (m, 1 H, one of SCH_2CH_2), 2.88–2.92 (m, 1 H, one of SCH_2CH_2), 2.00–2.04 (m, 1 H, one of SCH_2CH_2), 1.88–1.94 (m, 1 H, one of SCH_2CH_2), 1.73 (t, 1 H, J = 5.8 Hz, O*H*), 1.08 (s, 3 H, one of C$(CH_3)_2$), 0.74 (s, 3 H, one of C$(CH_3)_2$).

Alcohol 50 (d_2): ^{1}H NMR (500 MHz, CD_2Cl_2) 7.40 (s, 1 H, *Ar*-2), 7.32 (s, 1 H, *Ar*-4 or *Ar*-6), 7.24 (s, 1 H, *Ar*-4 or *Ar*-6), 4.65 (d, 2 H, J = 5.8 Hz, HOCH_2), 3.03–3.09 (m, 1 H, one of SCH_2CH_2), 2.87–2.92 (m, 1 H, one of SCH_2CH_2), 2.00–2.04 (m, 1 H, one of SCH_2CH_2), 1.88–1.94 (m, 1 H, one of SCH_2CH_2), 1.74 (t, 1 H, J = 5.8 Hz, O*H*), 1.08 (s, 3 H, one of C$(CH_3)_2$), 0.74 (s, 3 H, one of C$(CH_3)_2$).

Alcohol 54 (d_1): R_f = 0.16 (20% ethyl acetate in hexanes); IR (neat) 3374 (br, OH), 2933 (m), 1426 (m), 1149 (w), 1077 (s), 822 (m), 790 (m), 708 (m); ^{1}H NMR (500 MHz, CD_2Cl_2) 7.58 (s, 1 H, *Ar*-2), 7.51 (s, 1 H, *Ar*-4 or *Ar*-6), 7.29 (s, 1 H, *Ar*-4 or *Ar*-6), 4.67 (d, 2 H, J = 5.8 Hz, HOCH_2), 3.14 (s, 3 H, CH_3O), 2.99–3.05 (m, 1 H, one of SCH_2CH_2), 2.81–2.85 (m, 1 H, one of SCH_2CH_2), 2.40–2.46 (m, 1 H, one of SCH_2CH_2), 1.90–2.04 (m, 1 H, one of SCH_2CH_2), 1.75 (t, 1 H, J = 5.8 Hz, O*H*), 1.04 (s, 3 H, one of C$(CH_3)_2$), 0.69 (s, 3 H, one of C$(CH_3)_2$).

Alcohol 54 (d_4): ^{1}H NMR (500 MHz, CD_2Cl_2) 7.58 (s, 1 H, *Ar*-2), 7.51 (s, 1 H, *Ar*-4 or *Ar*-6), 7.29 (s, 1 H, *Ar*-4 or *Ar*-6), 4.67 (d, 2 H, J = 5.8 Hz, HOCH_2), 2.99–3.05 (m, 1 H, one of SCH_2CH_2), 2.81–2.85 (m, 1 H, one of SCH_2CH_2), 2.40–2.46 (m, 1 H, one of SCH_2CH_2), 1.90–1.94 (m, 1 H, one of SCH_2CH_2), 1.76 (t, 1 H, J = 5.8 Hz, O*H*),

1.04 (s, 3 H, one of $C(CH_3)_2$), 0.69 (s, 3 H, one of $C(CH_3)_2$); HRMS calcd for $C_{14}H_{16}D_4O_2S$ (M^+) 256.1435, found 256.1426.

3-Bromo-3-butenyl *tert*-Butyldiphenylsilyl Ether (62). *tert*-Butyldiphenylsilyl chloride (2.07 mL, 7.96 mmol, 1.2 equiv) was added to a solution of 3-bromo-3-buten-1-ol[31] (1.00 g, 6.62 mmol, 1 equiv) and triethylamine (4.61 mL, 33.1 mmol, 5.0 equiv) in dichloromethane (75 mL) at 0 °C. The reaction mixture was allowed to warm to 23 °C, whereupon 4-(dimethylamino)pyridine (0.5 g, 4.09 mmol, 0.62 equiv) was added. After being stirred at 23 °C for 2 h, the product solution was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to afford the 3-bromo-3-butenyl *tert*-butyldiphenylsilyl ether (**62**) (2.50 g, 93%) as a yellow oil: R_f = 0.67 (20% ethyl acetate in hexanes); IR (neat) 3070 (w), 2931 (m), 2857 (m), 1630 (m), 1428 (m), 1112 (s), 888 (w), 701 (s), 622 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 7.70–7.72 (m, 4 H, *Ph*Si), 7.40–7.46 (m, 6 H, *Ph*Si), 5.68 (s, 1 H, one of C=CH_2), 5.51 (s, 1 H, one of C=CH_2), 3.87 (t, 2 H, J = 6.1 Hz, $SiOCH_2CH_2$), 2.67 (t, 2 H, J = 6.1 Hz, $SiOCH_2CH_2$), 1.09 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{20}H_{24}BrOSi$ ($M - H^+$) 387.0780, found 387.0757.

Aldehyde 63. A solution of the *tert*-butyldiphenylsilyl ether **62** (2.67 g, 6.86 mmol, 1 equiv) in a mixture of tetrahydrofuran, ethyl ether, and pentane (4:1:1, respectively, 9.0 mL) was added dropwise via cannula over 5 min to a solution of *tert*-butyllithium (9.74 mL, 1.76 M solution in pentane, 17.1 mmol, 2.5 equiv) in a mixture of tetrahydrofuran, ethyl ether, and pentane (4:1:1, respectively, 60 mL) at −120 °C. After the mixture was stirred at −120 °C for 5 min, a solution of *N*,*N*-dimethylformamide (1.33 mL, 17.1 mmol, 2.5 equiv) in tetrahydrofuran (4.0 mL) was added dropwise via cannula over 7 min to the orange reaction mixture. The resulting yellow solution was warmed to 0 °C over 3 h and then was quenched with water (5 mL). The product was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 3 → 20%) afforded the aldehyde **63** (2.11 g, 91%) as a pale yellow oil: R_f = 0.20 (5% ethyl acetate in hexanes); IR (neat) 3070 (w), 2958 (m), 2857 (m), 1961 (s, C=O), 1472 (m), 1112 (s), 823 (m), 738 (m), 702 (s), 613 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 9.49 (s, 1 H, C*H*O), 7.63–7.66 (m, 4 H, *Ph*Si), 7.37–7.43 (m, 6 H, *Ph*Si), 6.36 (s, 1 H, one of C=CH_2), 6.05 (s, 1 H, one of C=CH_2), 3.78 (t, 2 H, J = 6.5 Hz, $SiOCH_2CH_2$), 2.52 (t, 2 H, J = 6.5 Hz, $SiOCH_2CH_2$), 1.04 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{21}H_{27}O_2Si$ (MH^+) 339.1780, found 339.1765.

Allylic Alcohol 64. Sodium borohydride (powder, 0.235 g, 6.22 mmol, 1.0 equiv) was added in small portions over 10 min to an ice-cooled solution of the aldehyde **63** (2.11 g, 6.22 mmol, 1 equiv) in absolute ethanol (50 mL). After the mixture was stirred at 0 °C for 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, and the crude reaction mixture was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 10 → 40%) to give the allylic alcohol **64** (1.87 g, 88%) as a colorless oil: R_f = 0.25 (20% ethyl acetate in hexanes); IR (neat) 3348 (br, OH), 3070 (w), 2930 (m), 2857 (m), 1427 (m), 1111 (s), 823 (m), 738 (m), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.67–7.68 (m, 4 H, *Ph*Si), 7.38–7.44 (m, 6 H, *Ph*Si), 5.07 (s, 1 H, one of C=CH_2), 4.89 (s, 1 H, one of C=CH_2), 4.08 (d, 2 H, J = 5.9 Hz, CH_2OH), 3.77 (t, 2 H, J = 6.2 Hz, $SiOCH_2CH_2$), 2.35 (t, 2 H, J = 6.2 Hz, $SiOCH_2CH_2$), 2.30 (t, 1 H, J = 6.1 Hz, CH_2OH), 1.06 (s, 9 H, $SiC(CH_3)_3$); HRMS calcd for $C_{21}H_{29}O_2Si$ (MH^+) 341.1937, found 341.1917.

Alcohol 65. Diethylzinc (26.5 mL, 1.0 M solution in hexanes, 26.5 mmol, 5.0 equiv) was added via cannula over 5 min to a solution of the allylic alcohol **64** (1.80 g, 5.29 mmol, 1 equiv) in ethyl ether (40.0 mL) at 0 °C. Diiodomethane (4.26 mL, 52.9 mmol, 10.0 equiv) was added via syringe over 2 min, and the pale orange reaction solution was stirred at 23 °C for 4 h, during which time a white precipitate formed. After the reaction was quenched with water (5 mL), the reaction mixture was partitioned between brine (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5 → 40%) afforded the alcohol **65** (1.29 g, 68%) as a colorless oil: R_f = 0.45 (10% ethyl acetate in hexanes); IR (neat) 3383 (br, OH), 3071 (w), 2999 (w), 2931 (m), 1472 (m), 1112 (s), 823 (m), 701 (s), 688 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 7.67–7.71 (m, 4 H, *Ph*Si), 7.39–7.45 (m, 6 H, *Ph*Si), 3.78 (t, 2 H, J = 5.37 Hz, $SiOCH_2CH_2$), 3.44 (s, 2 H, CH_2OH), 1.60 (t, 2 H, J = 5.37 Hz, $SiOCH_2CH_2$), 1.07 (s, 9 H, $SiC(CH_3)_3$), 0.49 (t, 2 H, J = 5.0 Hz, two of *Cy*), 0.34 (t, 2 H, J = 5.0 Hz, two of *Cy*); HRMS calcd for $C_{22}H_{31}O_2Si$ (MH^+) 355.2093, found 355.2086.

Cyclopropanecarboxaldehyde 66. Dimethyl sulfoxide (0.541 mL, 7.62 mmol, 2.2 equiv) was added over 2 min to a solution of oxalyl chloride (0.330 mL, 3.81 mmol, 1.1 equiv) in dichloromethane (15 mL) at −78 °C. The resulting clear solution was allowed to stir at −78 °C for 5 min before addition of a solution of the alcohol **65** (1.23 g, 3.46 mmol, 1 equiv) in dichloromethane (15 mL, via cannula over 3 min). After 15 min, triethylamine (2.41 mL, 17.3 mmol, 5.0 equiv) was added to the reaction mixture, and the resulting solution was warmed to 0 °C and was stirred at that temperature for 30 min. The reaction was quenched at 0 °C with water (5 mL), and the product was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5 → 20%) to give the cyclopropanecarboxaldehyde **66** (1.06 g, 87%) as a colorless oil: R_f = 0.40 (20% ethyl acetate in hexanes); IR (neat) 3068 (w), 2997 (w), 2930 (m), 1710 (s, C=O), 1427 (m), 1110 (s), 903 (m), 739 (m), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 8.85 (s, 1 H, C*H*O), 7.64–7.66 (m, 4 H, *Ph*Si), 7.36–7.43 (m, 6 H, *Ph*Si), 3.76 (t, 2 H, J = 6.5 Hz, $SiOCH_2CH_2$), 1.89 (t, 2 H, J = 6.5 Hz, $SiOCH_2CH_2$), 1.13 (dd, 2 H, J = 7.2, 4.5 Hz, two of *Cy*), 1.04 (s, 9 H, $SiC(CH_3)_3$), 0.96 (dd, 2 H, J = 7.2, 4.5 Hz, two of *Cy*); HRMS calcd for $C_{22}H_{27}O_2Si$ ($M - H^+$) 351.1780, found 351.1783.

Alkyne 68. Zinc dust (1.09 g, 16.7 mmol, 2.0 equiv), triphenylphosphine (4.38 g, 16.7 mmol, 2.0 equiv), and carbon tetrabromide (5.53 g, 16.7 mmol, 2.0 equiv) were combined at 23 °C in dichloromethane (80 mL), and the resulting olive suspension was stirred at 23 °C for 24 h. A solution of the cyclopropanecarboxaldehyde **66** (2.94 g, 8.34 mmol, 1 equiv) in dichloromethane (10 mL) was added via cannula to the then-purple suspension, and the mixture was stirred at 23 °C for 5 h. Pentane (150 mL) was added, producing a white precipitate, and the reaction mixture was filtered through a coarse frit. The cloudy filtrate was clarified by the addition of dichloromethane (~10 mL). Addition of pentane (~50 mL) produced a precipitate, which was removed by filtration. After a third iteration of the above cycle, the filtrate was dried over sodium sulfate and was concentrated. The residue was purified by flash column chromatography (10% dichloromethane in hexanes) to give the 1,1-dibromo olefin **67** as a colorless oil (5.62 g).

n-Butyllithium (13.8 mL, 1.6 M solution in hexanes, 22.0 mmol, 2.2 equiv) was added over 5 min to a solution of **67** (5.62 g, 8.34 mmol, 1 equiv) in tetrahydrofuran (100 mL) at −78 °C. After being stirred at −78 °C for 3 h, the reaction mixture was quenched at −78 °C with saturated aqueous ammonium chloride solution (10 mL) and was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (gradient elution: toluene in hexane, 5 → 10%) provided the alkyne **68** (2.65 g, 91%) as a colorless oil: R_f = 0.51 (20% ethyl acetate in hexanes); IR (neat) 3310 (w, C≡CH), 3071 (w), 3015 (w), 2930 (m), 2112 (w), 1473 (m), 1427 (m), 1112 (s), 701 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.68–7.71 (m, 4 H, *Ph*Si), 7.36–7.42 (m, 6 H, *Ph*Si), 3.90 (t, 2 H, J = 6.8 Hz, $SiOCH_2CH_2$), 1.78 (s, 1 H, C≡C*H*), 1.63 (t, 2 H, J = 6.8 Hz, $SiOCH_2CH_2$), 1.05 (s, 9 H, $SiC(CH_3)_3$), 0.87 (dd, 2 H, J = 6.7, 4.3 Hz, two of *Cy*), 0.62 (dd, 2 H, J = 6.7, 4.3 Hz, two of *Cy*); HRMS calcd for $C_{23}H_{29}OSi$ (MH^+) 349.1988, found 349.1986.

Alcohol 69. Tetrabutylammonium fluoride (22.8 mL, 1.0 M sodium in tetrahydrofuran, 22.8 mmol, 3.0 equiv) was added via syringe to an ice-cooled solution of the alkyne **68** (2.65 g, 7.60 mmol, 1 equiv) in tetrahydrofuran (125 mL). After the mixture was stirred at 0 °C for 24 h, saturated aqueous ammonium chloride solution (10 mL) was added, and the mixture was partitioned between water (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 20 → 30%) to give the alcohol **69** (0.72 g, 86%) as a pale yellow oil: R_f = 0.38 (30% ethyl acetate in hexanes); IR (neat) 3352 (br, OH), 3297 (s, C≡CH), 3090 (w), 3009 (w), 2942 (m), 2882 (m), 2111 (m), 1426 (m), 1057 (s), 1026 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 3.88–3.91 (m, 2 H, $HOCH_2CH_2$), 1.91 (s, 1 H, C≡C*H*), 1.72–1.73 (m, 1 H, O*H*), 1.63 (t, 2 H, J = 6.2 Hz, $HOCH_2CH_2$), 0.95 (dd, 2 H, J = 6.5, 4.3 Hz, two of *Cy*), 0.67 (dd, 2 H, J = 6.5, 4.3 Hz, two of *Cy*); HRMS calcd for $C_7H_{10}O$ (M^+) 110.0732, found 110.0733.

Thiol Ester 70. Methanesulfonyl chloride (0.61 mL, 7.85 mmol, 1.2 equiv) was added dropwise via syringe over 15 min to an ice-cooled solution of the alcohol **69** (0.72 g, 6.54 mmol, 1 equiv) and triethylamine (1.19 mL, 8.50 mmol, 1.3 equiv) in dichloromethane (100 mL). The

resulting yellow suspension was stirred at 0 °C for 5 min and then was partitioned between brine (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The remaining yellow oil was dissolved in tetrahydrofuran (15 mL), and the resulting solution was cooled to 0 °C. Triethylamine (9.12 mL, 65.4 mmol, 10.0 equiv) and thiopivalic acid (4.16 mL, 32.7 mmol, 5.0 equiv) were added sequentially at 0 °C; the mixture was heated at 50 °C for 3 h. After being cooled to 23 °C, the reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (3% ethyl acetate in hexanes) to give the cyclopropyl thiol ester **70** (1.27 g, 90%) as a colorless oil: R_f = 0.47 (5% ethyl acetate in hexanes); IR (neat) 3293 (m, C≡CH), 2969 (s), 2933 (m), 2112 (w, C≡C), 1679 (s, C=O), 1477 (m), 1036 (m), 953 (s), 807 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 3.03–3.07 (m, 2 H, SCH_2CH$_2$), 1.89 (s, 1 H, C≡CH), 1.55–1.60 (m, 2 H, SCH$_2$CH_2), 1.22 (s, 9 H, C(CH_3)$_3$), 0.93 (dd, 2 H, J = 6.6, 4.4 Hz, two of *Cy*), 0.67 (dd, 2 H, J = 6.6, 4.4 Hz, two of *Cy*); HRMS calcd for $C_{12}H_{19}OS$ (MH^+) 211.1157, found 211.1161.

Cyclopropane Alcohol 71. A solution of lithium diisopropylamide in tetrahydrofuran (1.0 M, 3.0 mL, 1.4 equiv) was added via cannula to a solution of the thiol ester **70** (0.43 g, 2.18 mmol, 1.1 equiv) in tetrahydrofuran (20 mL) at −78 °C. After the mixture was stirred at −78 °C for 10 min, anhydrous cerium(III) chloride (0.82 g, 3.31 mmol, 1.6 equiv) was added, and the resulting orange suspension was stirred at −78 °C for 30 min. A solution of the aldehyde **45** (0.87 g, 2.07 mmol, 1 equiv) in tetrahydrofuran (8 mL) was then added via cannula over 2 min, and the reaction mixture was maintained at −78 °C for 40 min. The reaction was quenched with water (3 mL) at −78 °C, and sodium tartrate (0.5 g) was added. The reaction mixture was partitioned between water (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 100 mL), and the combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 3 → 10%) to give the cyclopropane alcohol **71** (0.82 g, 63%) as a pale yellow oil: R_f = 0.23 (10% ethyl acetate in hexanes); IR (neat) 3497 (br, OH), 3078 (w), 2964 (m), 2133 (w), 1677 (s, C=O), 1428 (m), 1250 (m), 1111 (s), 955 (m), 853 (s), 703 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.64–7.69 (m, 4 H, *Ph*Si), 7.37–7.44 (m, 6 H, *Ph*Si), 5.81 (s, 1 H, C=CH), 5.53 (d, 1 H, J = 6.6 Hz, CHOH), 4.58 (dd, 1 H, J = 15.1, 2.0 Hz, SiOCH_AH$_B$), 4.32 (dd, 1 H, J = 15.1, 1.7 Hz, SiOCH$_A$$H_B$), 2.90–2.94 (m, 2 H, SC$H_2CH_2$Cy), 1.47–1.51 (m, 2 H, SCH$_2$CH_2Cy), 1.20 (s, 9 H, C(CH_3)$_3$), 1.06 (s, 9 H, SiC(CH_3)$_3$), 0.81 (m, 2 H, two of *Cy*), 0.63 (m, 2 H, two of *Cy*), 0.22 (s, 9 H, Si(CH_3)$_3$); HRMS calcd for $C_{37}H_{49}O_3SSi_2$ ($M - H^+$) 629.2941, found 629.2906.

Cyclopropane Disulfide 72. Sodium hydroxide (50% aqueous, 0.5 mL) was added via pipette to an ice-cooled solution of the cyclopropane alcohol **71** (1.20 g, 1.90 mmol) in a mixture of tetrahydrofuran, methanol, and propyl disulfide (4:1:1, respectively, 18 mL). The yellow reaction mixture was stirred at 0 °C for 4 h and then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: toluene in hexanes, 60 → 90%) provided the cyclopropane disulfide **72** (0.66 g, 64%) as a pale yellow oil: R_f = 0.16 (10% ethyl acetate in hexanes); IR (neat) 3444 (br, OH), 3287 (m, C≡CH), 3071 (w), 2960 (s), 2237 (m), 1472 (m), 1428 (s), 1113 (s), 823 (s), 702 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.66–7.74 (m, 4 H, *Ph*Si), 7.38–7.46 (m, 6 H, *Ph*Si), 5.77 (d, 1 H, J = 2.0 Hz, C=CH), 5.57 (d, 1 H, J = 6.1 Hz, CHOH), 4.60 (d, 1 H, J = 15.1 Hz, SiOCH_AH$_B$), 4.34 (d, 1 H, J = 15.1 Hz, SiOCH$_A$$H_B$), 3.23 (d, 1 H, J = 2.4 Hz, C≡CH), 2.77–2.82 (m, 2 H, SSCH_2CH$_2$Cy), 2.63 (t, 2 H, J = 7.3 Hz, SSCH_2CH$_2$CH$_3$), 1.65–1.72 (m, 4 H, SSCH$_2$CH_2Cy and SSCH$_2$CH_2CH$_3$), 1.09 (s, 9 H, SiC(CH_3)$_3$), 0.98 (t, 3 H, J = 7.3 Hz, SSCH$_2$CH$_2$CH_3), 0.82–0.84 (m, 2 H, two of *Cy*), 0.62–0.63 (m, 2 H, two of *Cy*); HRMS calcd for $C_{32}H_{40}O_2S_2Si$ (M^+) 548.2239, found 548.2228.

Cyclopropane Dinitrobenzoate 73. 3,5-Dinitrobenzoic acid (0.19 g, 0.89 mmol, 10.0 equiv), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (0.171 g, 0.89 mmol, 10.0 equiv), and 4-(dimethylamino)pyridine (0.054 g, 0.44 mmol, 5.0 equiv) were added sequentially to a solution of the cyclopropane disulfide **72** (0.049 g, 0.089 mmol, 1 equiv) in dichloromethane (5 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 30 min and then was partitioned between water (20 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (3% ethyl acetate in hexanes) to give the cyclopropane dinitrobenzoate **73** (0.054 g, 82%) as a colorless oil: R_f = 0.25 (10% ethyl acetate in hexanes); IR (neat) 3289 (m), 3072 (w), 2959 (m), 2241 (m), 1738 (s, C=O), 1629 (m), 1547 (s, NO_2), 1428 (m), 1344 (s, NO_2), 1266 (s), 1113 (m), 703 (m); ^{1}H NMR (400 MHz, $CDCl_3$), 9.20 (t, 1 H, J = 2.2 Hz, Ph(NO$_2$)$_2$$H_p$), 9.01 (d, 2 H, J = 2.2 Hz, Ph(NO$_2$)$_2$$H_o$), 7.64–7.70 (m, 4 H, *Ph*Si), 7.35–7.45 (m, 6 H, *Ph*Si), 6.78 (s, 1 H, C≡CCH(OR)Cy), 6.18 (d, 1 H, J = 2.2 Hz, C≡CH), 4.60 (d, 1 H, J = 17.6 Hz, SiOCH_AH$_B$), 4.48 (d, 1 H, J = 17.6 Hz, SiOCH$_A$$H_B$), 3.36 (d, 1 H, J = 1.7 Hz, C≡CH), 2.72 (t, 2 H, J = 7.8 Hz, SSCH_2CH$_2$Cy), 2.60 (t, 2 H, J = 7.2 Hz, SSCH_2CH$_2$CH$_3$), 1.62–1.69 (m, 4 H, SSCH$_2$CH_2Cy and SSCH$_2$CH_2CH$_3$), 1.08 (s, 9 H, SiC(CH_3)$_3$), 0.96 (t, 3 H, J = 7.3 hz, SSCH$_2$CH$_2$CH_3), 0.79–0.81 (m, 2 H, two of *Cy*), 0.62–0.63 (m, 2 H, two of *Cy*); HRMS calcd for $C_{39}H_{42}N_2O_7S_2Si$ (M^+) 742.2203, found 742.2246. Anal. Calcd for $C_{39}H_{42}N_2O_7S_2Si$: C, 63.05; H, 5.70; N, 3.77. Found: C, 63.20; H, 5.91; N, 3.63.

Cyclopropane Thiol 56. Tributylphosphine (0.167 mL, 0.67 mmol, 10.0 equiv) was added via syringe to a deoxygenated, ice-cooled solution of the cyclopropane dinitrobenzoate **73** (0.050 g, 0.67 mmol, 1 equiv) in a 4:1 mixture of 1,2-dimethoxyethane and water (5 mL). The resulting purple solution was stirred at 0 °C for 30 min and then was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the cyclopropane thiol **56** (0.031 g, 68%) as a colorless oil: R_f = 0.56 (toluene); IR (neat) 3289 (w, C≡CH), 3097 (w), 2931 (m), 2236 (w), 1739 (m), 1547 (s), 1428 (m), 1344 (s), 1265 (m), 1157 (m), 1113 (m), 703 (m); ^{1}H NMR (400 MHz, $CDCl_3$) 9.20 (t, 1 H, J = 2.2 Hz, Ph(NO$_2$)$_2$$H_p$), 9.02 (d, 2 H, J = 2.2 Hz, Ph(NO$_2$)$_2$$H_o$), 7.64–7.70 (m, 4 H, *Ph*Si), 7.34–7.45 (m, 6 H, *Ph*Si), 6.78 (s, 1 H, C≡CCH(OR)Cy), 6.18 (d, 1 H, J = 2.2 Hz, C≡CH), 4.59 (d, 1 H, J = 16.7 Hz, SiOCH_AH$_B$), 4.48 (d, 1 H, J = 16.7 Hz, SiOCH$_A$$H_B$), 3.36 (d, 1 H, J = 2.2 Hz, C≡CH), 2.54–2.60 (m, 2 H, HSCH_2CH$_2$Cy), 1.52–1.57 (m, 2 H, HSCH$_2$CH_2Cy), 1.33 (t, 1 H, J = 7.9 Hz, SH), 1.08 (s, 9 H, SiC(CH_3)$_3$), 0.79–0.81 (m, 2 H, two of *Cy*), 0.62–0.63 (m, 2 H, two of *Cy*); HRMS calcd for $C_{36}H_{37}N_2O_7SSi$ (MH^-) 669.2091, found 669.2073.

General Cyclization Procedure (Cyclopropane Thiol 56). Triethylamine (5 equiv) was added to a deoxygenated solution of the cyclopropane thiol **56** (0.010 M) and trapping agent (1,4-cyclohexadiene or methanol, each 4.0 M) in dimethyl sulfoxide at 23 °C. After being stirred at 23 °C for 10 h, each reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 × 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (3–5% ethyl acetate in hexanes, 2 elutions). Product yields were determined prior to chromatography by addition of (*Z*)-1,2-dichloroethylene as an internal standard and ^{1}H NMR analysis.

Spirocyclopropanetetrahydrothiophene derivative 74: R_f = 0.70 (3% ethyl acetate in hexanes); IR (neat) 3070 (w), 3000 (w), 2928 (m), 1427 (m), 1110 (s), 1073 (m), 859 (m), 740 (m), 701 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.69–7.70 (m, 4 H, *Ph*Si), 7.35–7.68 (m, 10 H, *Ph*Si, *Ar*-2, *Ar*-4, *Ar*-5, and *Ar*-6), 4.77 (s, 2 H, SiOCH_2), 4.15 (s, 1 H, SCHCy), 3.02–3.15 (m, 2 H, SCH_2CH$_2$), 2.15–2.21 (m, 1 H, one of SCH$_2$CH_2), 1.86–1.93 (m, 1 H, one of SCH$_2$CH_2), 1.09 (s, 9 H, SiC(CH_3)$_3$), 0.58–0.64 (m, 1 H, one of *Cy*), 0.41–0.52 (m, 3 H, three of *Cy*); HRMS calcd for $C_{29}H_{34}OSSi$ (M^+) 458.2100, found 458.2106.

Ring-opened sulfide 75: R_f = 0.77 (3% ethyl acetate in hexanes); IR (neat) 3067 (w), 2964 (m), 2933 (m), 1426 (m), 1108 (s), 1077 (m), 821 (m), 703 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.68–7.71 (m, 4 H, *Ph*Si), 7.24–7.43 (m, 10 H, *Ph*Si, *Ar*-2, *Ar*-4, *Ar*-5, and *Ar*-6), 4.76 (s, 2 H, SiOCH_2), 3.23 (t, 2 H, J = 8.6 Hz, SCH_2CH$_2$), 2.96 (t, 2 H, J = 8.6 Hz, SCH$_2$CH_2), 2.22 (q, 2 H, J = 7.6 Hz, CH_2CH$_3$), 1.09 (s, 9 H, SiC(CH_3)$_3$), 1.03 (t, 3 H, J = 7.6 Hz, CH$_2$CH_3); HRMS calcd for $C_{29}H_{34}OSSi$ (M^+) 458.2100, found 458.2101.

Spirocyclopropanetetrahydrothiophene derivative 78: R_f = 0.41 (5% ethyl acetate in hexanes); IR (neat) 3071 (w), 2999 (m), 2930 (m), 2857 (m), 1428 (m), 1112 (s), 1076 (s), 824 (m), 701 (s); ^{1}H NMR (400 MHz, $CDCl_3$) 7.68–7.70 (m, 4 H, *Ph*Si), 7.57 (s, 1 H, *Ar*-2), 7.35–7.43 (m, 9 H, *Ph*Si, *Ar*-4, *Ar*-5, and *Ar*-6), 4.77 (s, 2 H, SiOCH_2), 3.26 (s, 3 H, CH_3O), 3.16–3.23 (m, 1 H, one of SCH_2CH$_2$), 2.97–3.01 (m, 1 H, one of SCH_2CH$_2$), 2.76–2.84 (m, 1 H, one of SCH$_2$CH_2), 1.67–1.71 (m, 1 H, one of SCH$_2$CH_2), 1.10 (s, 9 H, SiC(CH_3)$_3$), 0.60–0.69 (m, 2 H, two of *Cy*), 0.19–0.24 (m, 1 H, one of *Cy*), −0.12 to −0.17 (m, 1 H, one of *Cy*); HRMS calcd for $C_{30}H_{36}O_2SSi$ (M^+) 488.2210, found 488.2235.

Desilylation of the spirocyclopropanetetrahydrothiophene derivatives **74** and **78** was performed according to the general procedure to provide the cyclopropane alcohols **79** and **80**, respectively.

Cyclopropane alcohol 79 (d_1): R_f = 0.17 (20% ethyl acetate in hexanes); IR (neat) 3360 (br, OH), 3079 (w), 2931 (m), 1428 (m), 1153 (w), 1020 (m), 860 (s), 677 (m); ^{1}H NMR (500 MHz, CD_2Cl_2) 7.55 (s, 1 H, *Ar*-2), 7.45 (s, 1 H, *Ar*-4 or *Ar*-6), 7.27 (s, 1 H, *Ar*-4 or *Ar*-6), 4.67 (d, 2 H, J = 5.8 Hz, HOCH_2), 4.15 (s, 1 H, SCHCy), 3.17–3.23 (m, 1

H, one of SCH_2CH_2), 2.96–3.00 (m, 1 H, one of SCH_2CH_2), 2.72–2.78 (m, 1 H, one of SCH_2CH_2), 1.75 (t, 1 H, J = 5.8 Hz, OH), 1.67–1.72 (m, 1 H, one of SCH_2CH_2), 0.56–0.64 (m, 2 H, two of Cy), 0.21–0.25 (m, 1 H, one of Cy), −0.17 to −0.21 (m, 1 H, one of Cy); HRMS calcd for $C_{13}H_{15}DOS$ (M^+) 220.1032, found 220.1055.

Cyclopropane alcohol 80 (d_1): R_f = 0.20 (20% ethyl acetate in hexanes); IR (neat) 3369 (br, OH), 3079 (w), 2931 (m), 1426 (m), 1151 (w), 1075 (s), 1020 (m), 888 (s), 677 (m); ^1H NMR (500 MHz, CD_2Cl_2) 7.55 (s, 1 H, Ar-2), 7.45 (s, 1 H, Ar-4 or Ar-6), 7.27 (s, 1 H, Ar-4 or Ar-6), 4.66 (d, 2 H, J = 5.7 Hz, $HOCH_2$), 3.17–3.23 (m, 1 H, one of SCH_2CH_2), 3.22 (s, 3 H, CH_3O), 2.96–3.00 (m, 1 H, one of SCH_2CH_2), 2.72–2.78 (m, 1 H, one of SCH_2CH_2), 1.75 (t, 1 H, J = 5.8 Hz, OH), 1.67–1.72 (m, 1 H, one of SCH_2CH_2), 0.56–0.64 (m, 2 H, two of Cy), 0.21–0.25 (m, 1 H, one of Cy), −0.17 to −0.21 (m, 1 H, one of Cy); HRMS calcd for $C_{14}H_{17}D_1O_2S$ 253.1327, found 253.1320.

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Stereochemical Dissection of a Carbene Fragmentation Reaction†

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Abstract: The fragmentation of (*S*)-3-(2-butoxy)-3-chlorodiazirine (**9**) in acetonitrile proceeds via N_2 loss to (*S*)-2-butoxychlorocarbene (**10**) and thence via CO scission to a 2-butyl cation/chloride anion pair (**11**) that collapses to (*S*)-2-chlorobutane (**12**) with ~56% net retention. In 1-butanol, ion pair **11** affords 55% chloride **12** by ion pair return with 82% net retention and 45% of (*R*)-2-butyl 1-butyl ether (**13**) by ion pair solvolysis with ~71% net inversion.

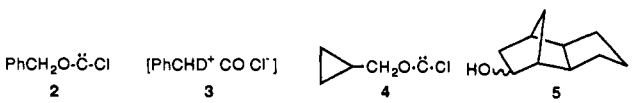
In the 1950's Hine[2] and Skell[3] demonstrated that alkoxyhalocarbenes (**1**) formed when dihalocarbenes reacted with alkoxide ions, and Skell found that these derived carbenes fragmented to alkyl cations upon loss of halide and carbon monoxide,[3] eq 1.

$$RO^- + :CX_2 \rightarrow ROCX_2 \xrightarrow{-X^-} RO\text{–}\ddot{C}\text{–}X \rightarrow R^+ + CO + X^- \quad (1)$$

1

The latter process was termed "deoxideation". Carbon monoxide is isoelectronic to N_2, so that deoxideation resembles the generation of alkyl cations by deaminative reactions,[4] particularly the hydrolysis of alkanediazotates (see below), which also occurs in the presence of strong base.[5] Although the utility of the original deoxideation reaction as a means of generating cations was offset by the accompanying strongly basic conditions, Smith and Stevens subsequently showed that 3-methoxy- and 3-isobutoxy-3-chlorodiazirines gave the corresponding alkoxychlorocarbenes upon thermolysis. Fragmentation of the carbenes could then be studied under neutral conditions.[6]

Exploiting this methodology, we found that the thermolysis of (benzyloxy)chlorodiazirine in acetonitrile at 25 °C gave (benzyloxy)chlorocarbene (**2**), which fragmented to benzyl chloride

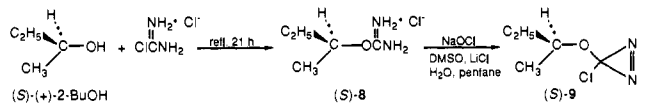


2 **3** **4** **5**

and CO.[7] When this reaction was repeated with (*S*)-[(α-deuteriobenzyl)oxy]chlorodiazirine, leading to the chiral, labeled carbene, (*S*)-**2**-α-d_1, the product benzyl-α-d_1 chloride was obtained with 60–80% net retention, consistent with front-side chloride return in the intermediate ion pair **3**, formed upon fragmentation of **2**-α-d_1.[8]

Importantly, not all examples of carbene **1** fragment readily; the C–X bond must be sufficiently weak to permit fragmentation to compete with the more usual intermolecular reactions that lead to carbene capture. For example, (benzyloxy)bromocarbene fragments easily to benzyl bromide and CO, but (benzyloxy)fluorocarbene resists fragmentation, giving instead typical carbene capture products.[9] (Benzyloxy)cyanocarbene similarly eschews fragmentation in favor of intermolecular reactions.[10]

Scheme I



Within the alkoxychlorocarbene family, however, the carbene fragmentation reaction appears to be rather general. Thus, diazirine-generated (cyclopropylmethoxy)chlorocarbene (**4**) fragmented efficiently, affording a mixture of C_4-alkyl chlorides consistent with the intermediacy of cyclopropylcarbinyl cation/chloride anion pairs.[11] Similarly, the formation of epimeric chlorides (with 70–80% of the exo isomer) upon the CCl_2-mediated deoxideation of either epimer of the 2-norbornyl-type alcohols **5**

† In memoriam: Professor Gerhard Ludwig Closs, 1928–1992.

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