Base-Catalyzed Isomerization of Alkynyloxiranes. A General Synthesis of Furans

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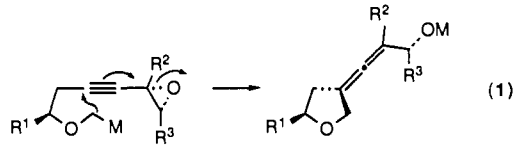
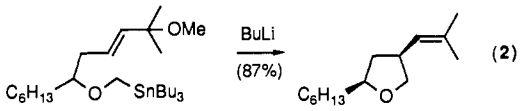
Abstract: Alkynyloxiranes **5**, available through coupling of vinylic halides with terminal alkynes followed by epoxidation with MCPBA, are isomerized to furans **6** upon treatment with KO-*t*-Bu in *t*-BuOH–18-crown-6. The reaction has been employed for the synthesis of furans with substituents at the 2,2,4, 2,5, and 2,3,5 positions. A pathway involving initial 1,4-elimination to a cumulenyl alkoxide B, which then cyclizes to a vinylic anion C, is proposed. Support for the proposed pathway includes deuterium incorporation when *t*-BuOD is employed as the solvent and isolation of vinylacetylene products when furan formation is structurally prevented.

In connection with studies on intramolecular S_N2' additions of organometallics to alkynyloxiranes we were interested in testing the feasibility of the cyclization shown in eq 1 as a route to allenylidenehydrofurans. A precedent for such a cyclization can be found in the work of Broka, who reported the formation of tetrahydrofuran V upon treatment of allylic ether IV with BuLi (eq 2).[1] A suitable model alkynyloxirane **5a** was prepared through



(1)

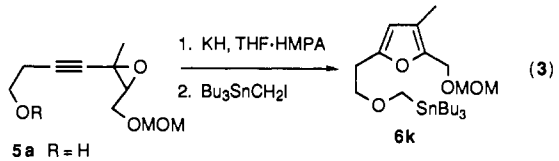
I M = $SnBu_3$
II M = Li



(2)

coupling of alkyne **2f** with vinylic iodide **1**[2] as described by Sonogashiro.[3] Subsequent epoxidation of the double bond with MCPBA and then protection as the MOM derivative led to epoxy ether **5f**. Cleavage of the TBS ether afforded the corresponding alcohol **5a** (Scheme I).

Treatment of alcohol **5a** with KH in THF–HMPA and then addition of Bu_3SnCH_2I led not to the expected ether **5k**, but gave the furan **6k** instead (eq 3). When the Bu_3SnCH_2I was omitted, alkynyloxirane **5a** cyclized to furan **6a** in 60% yield (Table I, entry 1).[4]

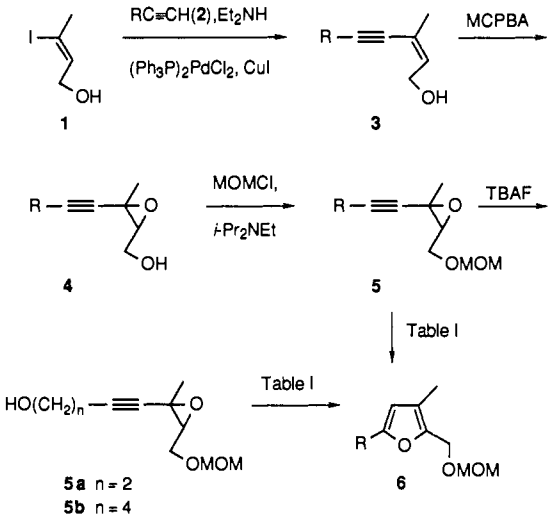


(3)

5a R = H
5k R = CH_2SnBu_3

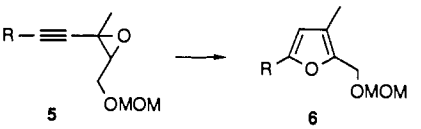
In order to explore the scope of this novel cyclization, we synthesized the alkynyloxiranes **5b–e** by the sequence shown in Scheme I. Oxirane **5b**, a homologue of **5a**, cyclized to furan **6b** in 55% yield upon stirring with KH in THF–HMPA (Table I, entry 2). However **5c**, lacking an OH substituent, was recovered unchanged under these conditions (Table I, entry 3). Evidently an alkoxide base is required for furan formation. In fact, when

Scheme I[a]



[a] **a**, R = $(CH_2)_2OH$; **b**, R = $(CH_2)_4OH$; **c**, R = n-C_6H_{13}; **d**, R = n-C_4H_9; **e**, R = CH_2OBn; **f**, R = $(CH_2)_2OTBS$; **g**, R = $(CH_2)_4OTBS$; **h**, R = CH_2OTBS; **i**, R = CH_2OH; **j**, R = $CH{=}CH_2$.

Table I. Cyclization of Alkynyloxiranes **5** to Furans **6**



entry	series	R	conditions[a]	yield, %
1	**a**	$(CH_2)_2OH$	A	60
2	**b**	$(CH_2)_4OH$	A	55
3	**c**	n-C_6H_{13}	A	0[b]
4	**c**	n-C_6H_{13}	B	70
5	**d**	n-C_4H_9	B	57
6	**e**	CH_2OBn	B	70
7	**a**	$(CH_2)_2OH$	B	86[c]
8	**b**	$(CH_2)_4OH$	B	75

[a] A = KH, THF–HMPA; B = KO-*t*-Bu, *t*-BuOH, 18-crown-6. [b] Recovered starting material. [c] A 3:1 mixture of R = CH_2CH_2OH and $CH{=}CH_2$.

alkynyloxirane **5c** was treated with KO-*t*-Bu, cyclization to **6c** took place but the reaction was slow. Addition of 18-crown-6 to the mixture increased the efficiency, and furan **6c** could thus be obtained in 70% yield (Table I, entry 4). The butyl- and [(benzyloxy)methyl]furan **6d** and **6e** were likewise prepared (Table I, entries 5 and 6). In all cases, the yields of products were higher with KO-*t*-Bu–18-crown-6 than with KH–HMPA. Interestingly, the 2-hydroxyethyl alkyne **5a** afforded a 3:1 mixture of (2-

(1) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336.
(2) Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863.
(3) Sonogashiro, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(4) For leading references to furan synthesis and furan natural products, see: Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

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Scheme II

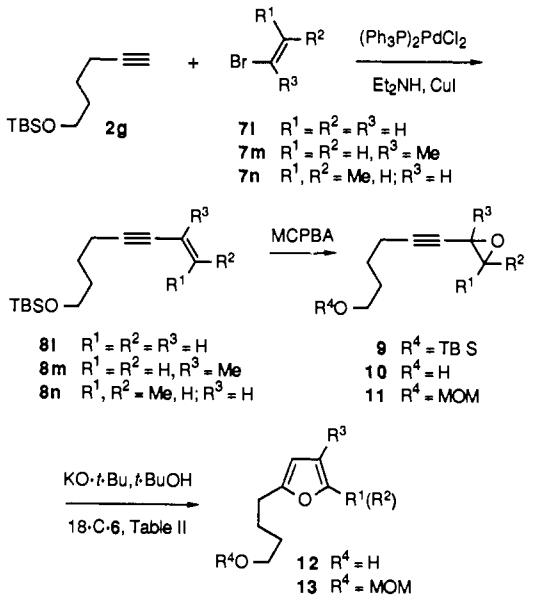


Table II. Cyclization of Alkynyloxiranes **10** and **11** to Furans **12** and **13**

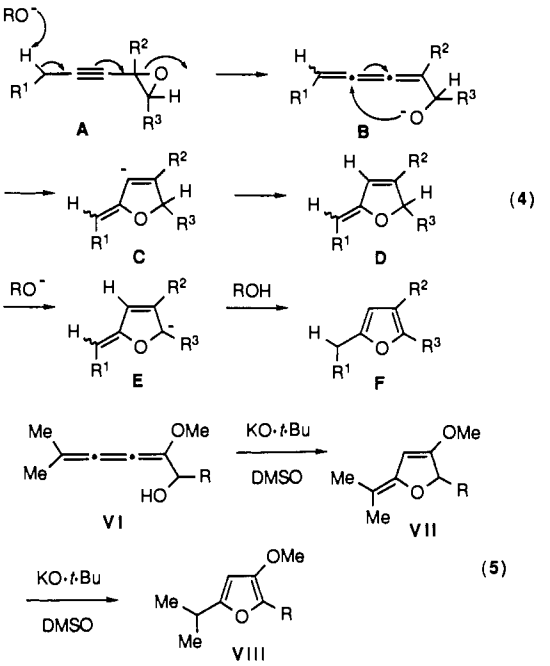
entry	epoxide	R^1, R^2	R^3	R^4	conditions[a]	yield, %
1	**10l**	H, H	H	H	A	trace[b]
2	**10m**	H, H	Me	H	A	33
3	**10n**	H, Me	H	H	B	20
4	**11l**	H, H	H	MOM	B	75
5	**11m**	H, H	Me	MOM	B	85
6	**11n**	H, Me	H	MOM	B	73

[a] A = KO-*t*-Bu, *t*-BuOH, 18-crown-6; B = K, *t*-BuOH then 18-crown-6. [b] No starting material was recovered.

hydroxyethyl)furan **6a** and the elimination product vinylfuran **6j** under these conditions. The latter product was not observed in reactions employing KH as the base (Table I, entries 1 vs 7).

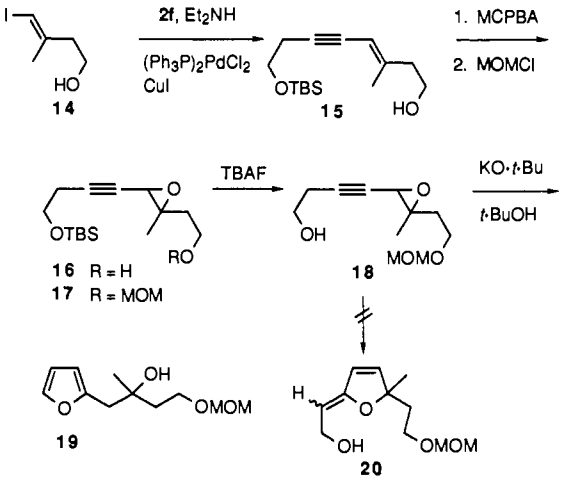
To further examine the scope of the furan cyclization, we prepared some additional alkynyloxiranes, as outlined in Scheme II, starting from alkyne **2g**. Coupling with vinyl bromide (**7l**), 2-bromopropene (**7m**), and 1-bromopropene (**7n**, *E*–*Z* mixture) afforded the vinylacetylenes **8l**–n in high yield. Epoxidation with MCPBA gave the TBS epoxy ethers **9**. The derived alcohols **10** were converted to the furans **12** upon treatment with KO-*t*-Bu–18-crown-6 but only in low yield (Table II, entries 1–3). We suspected that the alkoxide derived from the alcohol **10** was reacting with the epoxide moiety, leading to dimeric and polymeric ethers. Treatment of the TBS ethers **9** with KO-*t*-Bu led to mixtures of products arising from partial desilylation. Protection of the alcohols as the MOM ethers **11** solved the problem. These derivatives were efficiently converted to the furans **13** upon treatment with KO-*t*-Bu (Table II, entries 4–6). It was found that KO-*t*-Bu prepared in situ was more effective than material obtained commercially.

As a working hypothesis for these unusual cyclization reactions, we formulated a pathway involving an initial 1,4-elimination leading to the cumulene B, which then undergoes cyclization to C, proton transfer via D and E, and then protonation (eq 4). Precedent for the cyclization of cumulenes such as B can be found in the studies of Arens and co-workers, who showed that alcohols, prepared by the addition of lithiated methoxycumulenes to aldehydes, were converted to furans upon treatment with KO-*t*-Bu in DMSO (eq 5).[5] With systems such as VI, the intermediate isopropylidene product VII could be isolated. On heating with



base, VII was slowly converted to furan VIII. Allenyloxiranes were also shown to yield furans upon base treatment, whereas allenylcarbinols were converted to 2,5-dihydrofurans. However, in all of the foregoing examples, a methoxy substituent was present at the vinylic center adjacent to the OH. Such a substituent might be expected to facilitate cyclization by stabilizing the proposed vinylic anion C (R^2 = OMe).[6]

Hoping to isolate a cumulene or dihydrofuran, we prepared the alkynyloxirane **18** through coupling of vinyl iodide **14**[7] with alkyne **2f** followed by epoxidation, protection, and desilylation, as for **5a**. On treatment with base, epoxide **18** was converted to the furan **19**. None of the cumulene or the related alkylidenefuran (cf. **20**) could be detected. Evidently the initially formed cumulenyl



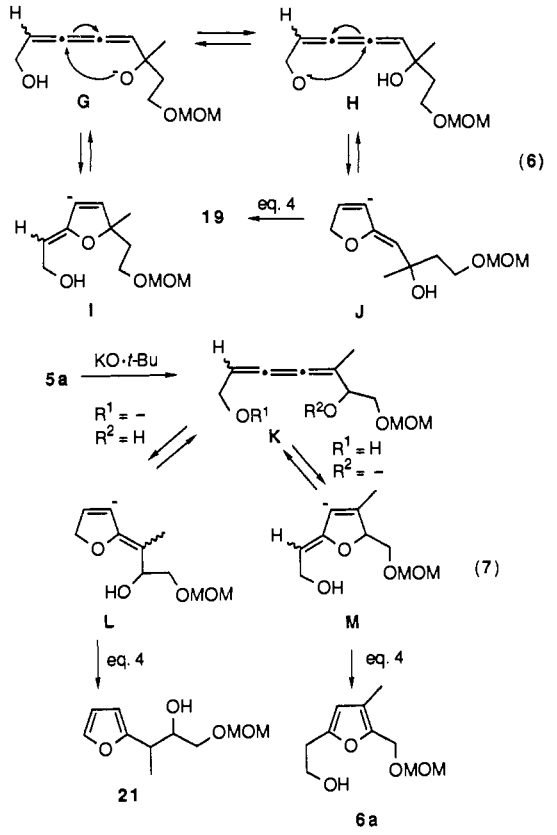
alkoxide G undergoes proton transfer to the isomeric alkoxide H, which then cyclizes to J and isomerizes to **19** along the pathway described in eq 4. This finding suggests that the alkoxide cyclizations could be reversible, with aromatic stabilization providing the driving force for eventual furan formation. It also raises the question as to why the presumed cumulene alkoxide intermediate K from alkynyloxirane **5a** shows no tendency to undergo proton

(5) Rompes, J. A.; Hoff, S.; Montijn, P. P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 1445. Schreurs, P. H. M.; Meyer, J.; Vermeer, P.; Brandsma, L. *Tetrahedron Lett.* **1976**, 2387. Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609. Grange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746.

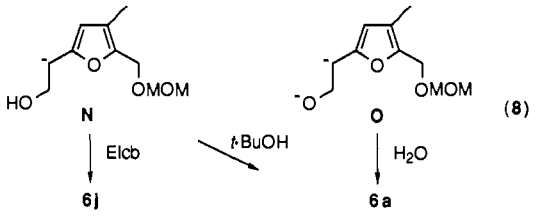
(6) The (*Z*)-2-methoxyvinyl anion has been calculated to be some 3 kcal lower in energy than the vinyl anion. Harris, N. J.; Sebastian, J. F. 201st National Meeting of the American Chemical Society, Atlanta, GA, April 14–19, 1991; American Chemical Society: Washington, DC, 1991; Division of Organic Chemistry Abstract 16.

(7) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

transfer leading to a mixture of furan products **6a** and **21**. Possibly cyclization to L is kinetically less favored than cyclization to M for steric reasons.

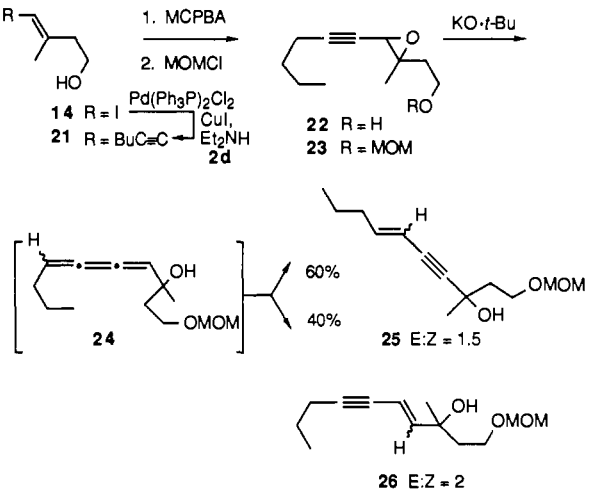


Another point worth noting in connection with the cyclization of alkynyloxirane **5a** is the formation of vinylfuran **6j** in *t*-BuOH but not in THF (Table I, entries 7 vs 1). Control experiments showed that the furan product **6a** does not eliminate to **6j** with KO-*t*-Bu in *t*-BuOH under the cyclization conditions. Thus, **6j** must be a primary product of the furan-producing sequence in *t*-BuOH but not in THF. According to eq 4, the proposed furan precursor E is a stabilized benzylic type anion. In the case of **6a**, this can be represented by the principal resonance contributor N. However, with KH as the base the dianion O would be present. In *t*-BuOH the formation of furans **6a** and **6j** can be viewed as a competition between E1cB elimination and protonolysis of N. The dianion O would expectedly undergo rapid preferential C–protonation on quenching, thereby precluding E1cB elimination.

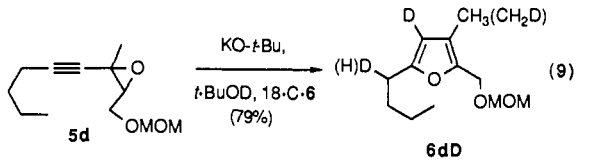


Returning now to the search for a cumulene intermediate, we prepared the butyl-substituted alkynyloxirane **23** from iodide **14** and 1-hexyne (**2d**) in order to bypass the alternative cyclization pathway. Basic treatment of oxirane **23** gave rise to a 60:40 mixture of enynes **25** and **26**, each a mixture of *E* and *Z* isomers favoring the former, in addition to other unidentified products. Enynes **25** and **26** could reasonably arise from cumulene **24**.[8] Neither **24** nor the related alkylidenefuran cyclization product could be detected in this reaction. These findings lend support to the pathway proposed in eq 4 and suggest that the cyclizations observed by Arens at al.[5] are facilitated by the OMe substituent.

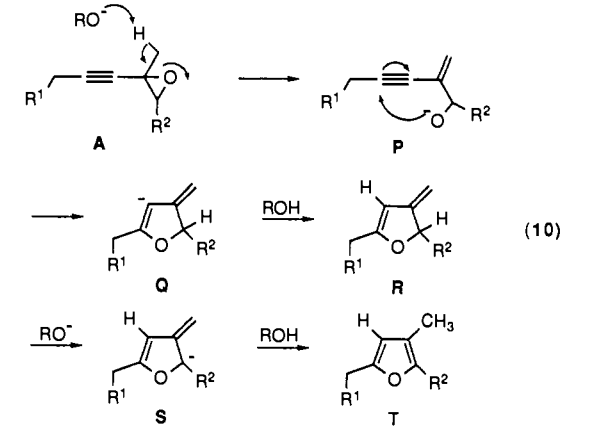
(8) Sargsyan, M. C.; Badanyan, Sh. O. *Arm. Khim. Zh.* **1977**, *30*, 1000.



Direct evidence for the vinylic anion intermediate C came from cyclizations of alkynyloxirane **5d** in *t*-BuOD. The mass spectrum of the furan product (**6dD**) showed 4% d_0, 48% d_1, 40% d_2, and 7% d_3. The ^{1}H NMR spectrum was devoid of the vinylic furan



proton. Furthermore, the α-CH_2 signals were diminished by nearly 20%, and the vinyl CH_3 signal was decreased roughly 10%. Furan **6d** was not significantly deuterated at any of these positions under the cyclization conditions in *t*-BuOD. The incorporation of deuterium in the vinylic CH_3 substituent implicates a second pathway for furan formation involving an initial 1,2-elimination and subsequent cyclization of the resulting α-methylene homopropargylic alkoxide P (eq 10).[9] The vinylic anion Q would



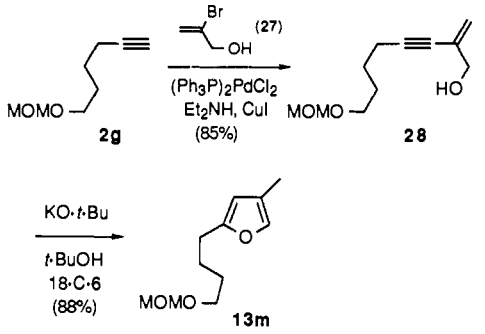
undergo protonation (or deuteration) by the alcohol solvent. Subsequent proton abstraction from R by the alkoxide base would lead to the allylic anion S, whose protonation (or deuteration) results in the observed furan product. That deuterium incorporation is more efficient at the initial vinylic anions C and Q as opposed to the subsequent allylic anions E and S may be the consequence of a conducted tour mechanism for the allylic isomerizations D → F and R → T.[10]

Verification of the foregoing alternative pathway was secured through synthesis of the α-methylene homopropargylic alcohol **28**. Treatment with KO-*t*-Bu in *t*-BuOH–18-crown-6 under the

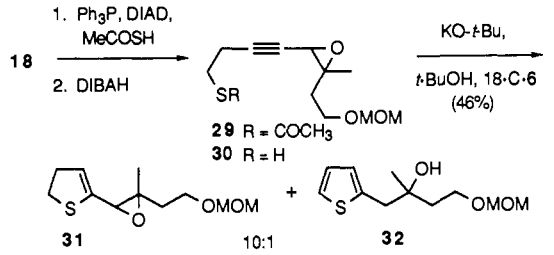
(9) Brandsma and de Jong have shown that homopropargylic thiols cyclize to dihydrothiophenes in the presence of strong base. de Jong, R. L. P.; Brandsma, L. *Synth. Commun.* **1990**, *20*, 3427.

(10) Almy, J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 4459.

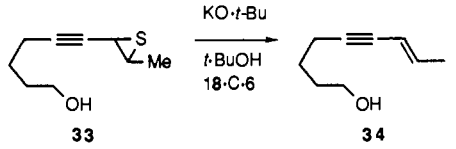
standard reaction conditions afforded furan **13m** in 88% yield. This sequence, which represents a remarkably direct and potentially general new route to furans and related heterocycles, is currently under investigation.



In an effort to extend the present methodology to thiophenes, we prepared the sulfhydryl analogue **30** of alkynyloxirane **18**. Upon treatment with KO-*t*-Bu in *t*-BuOH, thiol **30** was converted to a 10:1 mixture of 2,3-dihydrothiophene **31** and thiophene **32** in 46% yield. Evidently, cyclization of the thiolate anion is faster



than 1,4-elimination in this system.[9] Attempts to convert the alkynylthiirane **33** to the thiophene product with base led to the vinylacetylene **34** as the only isolable product. Thus, the methodology does not appear to be applicable to thiophenes.[11]



Experimental Section

(*Z*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2-hepten-4-yn-1-ol (3f). To a solution of 2.82 g (14.3 mmol) of vinyl iodide **1** in 75 mL of diethylamine were added 0.30 g (0.42 mmol) of bis(triphenylphosphine)palladium(II) chloride and 0.27 g (1.42 mmol) of copper iodide to yield a dark green solution. A solution of 3.42 g (18.5 mmol) of alkyne **2f** in 20 mL of diethylamine was added to the reaction mixture at room temperature. The solution turned yellow within 15 min. The reaction mixture was stirred at room temperature for 2 h, and then the mixture was diluted with ether, quenched with saturated aqueous ammonium chloride, and allowed to stir for 30 min. The reaction mixture was separated, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 3.10 g (91%) of enyne **3f** as a clear and colorless oil: IR (cm^{-1}, film) 3346, 2932, 1632, 1256, 1006; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (t, 1 H, J = 5.3 Hz, vinyl H), 4.27 (t, 2 H, J = 6.0 Hz, CH_2OH), 3.73 (t, 2 H, J = 7.0 Hz, CH_2OTBS), 2.54 (t, 2 H, J = 7.0 Hz, CH_2CC), 1.84 (q, 3 H, J = 1.1 Hz, CCH_3), 1.47 (t, 1 H, J = 6.0 Hz, OH), 0.88 (s, 9 H, $C(CH_3)_3$), 0.06 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{13}H_{23}O_2Si$ ($M^+ - CH_3$) 239.1467, found 239.1472. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.30. Found: C, 65.99; H, 10.28.

***cis*-7-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-3-methyl-4-heptyn-1-ol (4f).** To a stirred solution of 2.75 g (11.5 mmol) of enyne **3f** and 4.00 g of Na_2HPO_4 in 45 mL of THF at 0 °C was added 3.98 g (23.1 mmol) of 85% *m*-CPBA all at once. The reaction mixture was allowed to stir at 0 °C for 4 h, and then it was warmed to room temperature, diluted with ether, and quenched with aqueous saturated $NaHCO_3$. The layers were separated, and the organic layer was washed with 10% NaOH and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (30% EtOAc–hexane) afforded 2.43 g (83%) of epoxide **4f** as a clear and colorless oil: IR (film, cm^{-1}) 3422, 2932, 2365, 1474, 1060, 1006; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81–3.88 (m, 2 H, CH_2OH), 3.69 (t, 2 H, J = 6.9 Hz, CH_2OTBS), 3.05 (t, 1 H, J = 5.9 Hz, epoxide H), 2.40 (t, 2 H, J = 6.9 Hz, CH_2CC), 1.71 (t, 1 H, J = 5.8 Hz, OH), 1.53 (s, 3 H, CH_3), 0.88 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{14}H_{25}O_2Si$ (M^+ – OH) 253.1624, found 253.1623. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.17; H, 9.69. Found: C, 62.00; H, 9.70.

***cis*-5,6-Epoxy-7-(methoxymethoxy)-5-methyl-3-heptyn-1-ol (5a).** To a stirred solution of 1.08 g (3.60 mmol) of TBS ether **5f** and 0.62 mL (10.9 mmol) of glacial acetic acid in 15 mL of THF at 0 °C was added 10.9 mL (10.9 mmol) of 1.0 M TBAF in THF. The mixture was brought to room temperature and stirred for 12 h. The reaction mixture was diluted with ether and quenched with water, and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 0.55 g (83%) of alcohol **5a** as a clear light yellow oil: IR (film, cm^{-1}) 3422, 2932, 2889, 1447, 1109, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2 H, OCH_2O), 4.29 (bs, 2 H, CH_2OH), 3.60 (X of ABX, 2 H, J_{AX} = 6.0, J_{BX} = 6.7 Hz, CH_2OMOM), 3.34 (s, 3 H, OCH_3), 1.93, 1.78 (ABX, 2 H, J_{AB} = 14.4, J_{AX} = 6.0, J_{BX} = 6.7 Hz, CH_2CH$_2$OMOM), 1.65 (bs, 1 H, OH), 1.44 (s, 3 H, CCH_3); HRMS calcd for $C_9H_{13}O_4$ (M^+ – OMe) 169.0865, found 169.0867. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.22; H, 8.18.

***cis*-6-(Benzyloxy)-2,3-epoxy-1-(methoxymethoxy)-3-methyl-4-hexyne (5e).** A dispersion of 0.03 g (1.18 mmol) of NaH in 10 mL of THF was added to 0.22 g (1.18 mmol) of alcohol **5l** and 0.14 mL (1.18 mmol) of benzyl bromide, and the mixture was allowed to stir at reflux. The reaction mixture was cooled to room temperature after 2 h, diluted with ether, quenched with water, and separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (25% EtOAc–hexane) afforded 0.27 g (82%) of benzyl ether **5e** as a clear light yellow oil: IR (cm^{-1}, film) 3030, 2987, 2889, 1453, 1213, 1104, 1077, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.35 (m, 5 H, Ph), 4.67 (dd, 2 H, J = 6.6, 7.9 Hz, CH_2OMe), 4.56 (s, 2 H, CH_2Ph), 4.18 (s, 2 H, CH_2OBn), 3.72, 3.83 (ABX, 2 H, J_{AX} = 4.9, J_{BX} = 5.8, J_{AB} = 11.5 Hz, CH_2OMOM), 3.37 (s, 3 H, OCH_3), 3.12 (X of ABX, 1 H, J_{AX} = 4.9, J_{BX} = 5.8 Hz, epoxide H), 1.58 (s, 3 H, CH_3); HRMS calcd for $C_{14}H_{15}O_3$ (M^+ – OMOM) 231.1021, found 231.1021. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.43; H, 7.33.

***cis*-7-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-1-(methoxymethoxy)-3-methyl-4-heptyne (5f).** To a stirred solution of 2.05 g (8.06 mmol) of alcohol **4f** in 10 mL of CH_2Cl_2 at 0 °C was added 4.21 mL (24.2 mmol) of diisopropylethylamine, followed by 0.92 mL (12.1 mmol) of MOMCl. The reaction mixture was allowed to stir at 0 °C to room temperature for 12 h, was then diluted with ether, and quenched with water, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 2.45 g (97%) of the methoxymethyl ether **5f** as a clear and colorless oil: IR (cm^{-1}, film) 2954, 2856, 2246, 1736, 1474, 1256, 1109, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (s, 2 H, CH_2OMe), 3.81, 3.67 (ABX, 2 H, J_{AB} = 11.4, J_{AX} = 5.1, J_{BX} = 5.6 Hz, CH_2OMOM), 3.68 (t, 2 H, J = 7.1 Hz, CH_2OTBS), 3.38 (s, 3 H, OCH_3), 3.06 (X of ABX, J_{AX} = 5.1, J_{BX} = 5.6 Hz, epoxide H), 2.40 (t, 2 H, J = 7.1 Hz, CH_2CH$_2$OTBS), 1.53 (s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{14}H_{25}O_2Si$ (M^+ – OMOM) 253.1624, found 253.1625. Anal. Calcd for $C_{16}H_{30}O_4Si$: C, 61.10; H, 9.62. Found: C, 61.13; H, 9.62.

2-[(Methoxymethoxy)methyl]-3-methyl-5-(2-hydroxyethyl)furan (6a). A. Cyclization with KO-*t*-Bu. To a solution of 0.10 g (0.50 mmol) of epoxy alkyne **5a** in 2 mL of *tert*-butyl alcohol were added 0.29 g (1.10 mmol) of 18-crown-6 and 0.12 g (1.10 mmol) of potassium *tert*-butoxide. The yellow solution was allowed to stir at ~60 °C for 20 h, and then it was cooled to room temperature. The reaction mixture was diluted with ether and quenched with water. The aqueous layer was extracted with ether, and the combined organic layers were washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 86 mg (86%) of a 3:1 mixture of furans **6a** and **6j** as a clear faint yellow oil: IR (cm^{-1}, film) 3412, 2932, 2889, 1147, 1098, 1033, 924; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H, furan H), 4.64 (s, 2 H, CH_2OMe), 4.45 (s, 2 H, CH_2OMOM), 3.84 (dt, 2 H, J = 6.1, 6.1 Hz, CH_2OH), 3.37 (s, 3 H, OCH_3), 2.82 (t, 2 H, J = 6.1 Hz, CH_2CH$_2$OH), 2.00 (s, 3 H, CH_3), 1.66 (t, 1 H, J = 6.1 Hz, OH); HRMS calcd for

(11) A preliminary disclosure of a portion of these studies has appeared. Marshall J. A.; DuBay, W. J. *J. Org. Chem.* **1991**, *56*, 1685.

$C_{10}H_{16}O_4$ (M^+) 200.1049, found 200.1048. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06. Found: C, 59.93; H, 8.10.

B. Cyclization with KH. To a dispersion of 0.05 g (1.20 mmol) of KH in 2.0 mL of THF–HMPA (20:1) was added 0.10 g (0.54 mmol) of the epoxy alkyne **5a** in 2.0 mL of THF. Hydrogen gas was evolved. The reaction mixture was allowed to stir at room temperature for 5 h, and then it was diluted with ether and quenched with water. The aqueous layer was extracted with ether, and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 60 mg (60%) of furan **6a** as a clear faint yellow oil.

5-(4-Hydroxybutyl)-2-[(methoxymethoxy)methyl]-3-methylfuran (6b). A. Cyclization with KO-*t*-Bu. The procedure described for **6a** was followed using 0.10 g (0.44 mmol) of alcohol **5b**, 0.25 g (0.96 mmol) of 18-crown-6, and 0.11 g (0.96 mmol) of KO-*t*-Bu in 2 mL of *t*-BuOH. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 75 mg (75%) of furan **6b** as a clear faint yellow oil: IR (cm^{-1}, film) 3412, 2932, 2878, 1567, 1147, 1098, 1033; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (s, 1 H, furan H), 4.63 (s, 2 H, CH_2OMe), 4.44 (s, 2 H, CH_2OMOM), 3.64 (dt, 2 H, J = 5.4, 6.3 Hz, 3.38 (s, 3 H, OCH_3), 2.59 (t, 2 H, J = 7.0 Hz, CH_2CC), 1.99 (s, 3 H, CH_3), 1.56–1.72 (m, 4 H, $CH_2CH_2CH_2OH$), 1.25 (t, 1 H, J = 5.4 Hz, OH); HRMS calcd for $C_{12}H_{20}O_4$ (M^+) 228.1362, found 228.1364. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.89; H, 8.85.

B. Cyclization with KH. The procedure described for **6a** was followed with 0.10 g (0.44 mmol) of alcohol **5b** and 0.11 g (0.96 mmol) of KH in 2 mL of THF–HMPA (20:1). Flash chromatography on silica gel (50% EtOAc–hexane) afforded 55 mg (55%) of furan **6b** as a clear faint yellow oil.

5-Butyl-2-[(methoxymethoxy)methyl]-3-methylfuran (6d). A solution of 40 mg (1.04 mmol) of potassium in 4 mL of *t*-BuOH was heated to ~65 °C with stirring until all of the potassium had reacted. A solution of 0.10 g (0.47 mmol) of epoxide **5d** in 1 mL of *t*-BuOH was added to the preformed KO-*t*-Bu, and the mixture was allowed to stir for 1 h. The reaction mixture was diluted with ether and quenched with water, and the layers were separated. The aqueous layer was extracted with ether, and the layers were combined, washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 57 mg (57%) of furan **6d** as a clear and colorless oil: IR (cm^{-1}, film) 2932, 1567, 1098, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 1 H, furan H), 4.64 (s, 2 H, CH_2OCH_3), 4.44 (s, 2 H, CH_2OMOM), 3.38 (s, 3 H, OCH_3), 2.54 (t, 2 H, J = 7.8 Hz, $CH_2CH_2CH_2CH_3$), 1.99 (s, 3 H, CCH_3), 1.63–1.52 (m, 2 H, $CH_2CH_2CH_3$), 1.40–1.24 (m, 2 H, CH_2CH_3), 0.90 (t, 3 H, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) 156.2, 144.7, 120.0, 108.1, 95.0, 58.7, 55.2, 30.1, 27.7, 22.3, 13.8, 9.8; HRMS calcd for $C_{12}H_{20}O_3$ (M^+) 212.1412, found 212.1410. Anal. Calcd for $C_{12}H_{21}O_3$: C, 67.57; H, 9.45. Found: C, 67.84; H, 9.35.

5-Butyl-2-[(methoxymethoxy)methyl]-3-methyl-4-deuteriofuran (6dD). A solution of 0.13 g (3.28 mmol) of potassium in 7 mL of *t*-BuOD was heated to ~65 °C with stirring until all of the potassium had reacted. A solution of 0.14 g (0.66 mmol) of epoxide **5d** in 1 mL of *t*-BuOD was added to the preformed KO-*t*-Bu and allowed to stir for 1 h. The reaction mixture was diluted with ether and quenched with water, and the layers were separated. The aqueous layer was extracted with ether and the layers were combined, washed with 10% aqueous K_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 90 mg (64%) of furan **6dD** as a clear and colorless oil: IR (cm^{-1}, film) 2954, 1627, 1153, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2 H, CH_2OCH_3), 4.44 (s, 2 H, CH_2OMOM), 3.37 (s, 3 H, OCH_3), 2.54 (t, 2 H, J = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.98 (s, 3 H, CCH_3), 1.60–1.54 (m, 2 H, $CH_2CH_2CH_3$), 1.37–1.30 (m, 2 H, CH_2CH_3), 0.89 (t, 3 H, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) 156.4, 145.1, 120.2, 95.4, 59.1, 55.6, 30.4, 30.3, 28.1, 22.7, 14.2, 10.2; MS 212.16 $C_{12}H_{20}O_3$ (4%), 213.18 $C_{12}H_{19}O_3D$ (48%), 214.18 $C_{12}H_{18}O_3D_2$ (40%), 215.18 $C_{12}H_{17}O_3D_3$ (8%).

8-[(*tert*-Butyldimethylsilyl)oxy]-1-octen-3-yne (8l). The procedure described for **3f** was followed using 2.50 g (23.4 mmol) of vinyl bromide **7l** in 130 mL of diethylamine, 0.41 g (0.59 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.45 g (2.34 mmol) of CuI, and 5.47 g (25.7 mmol) of alkyne **2g** in 20 mL of diethylamine. Flash chromatography on silica gel (100% hexane) afforded 5.55 g (99%) of enyne **8l** as a clear and colorless liquid: IR (cm^{-1}, film) 2954, 2856, 2224, 1611, 1256, 1109; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddt, 1 H, J = 10.9, 17.5, 2.1 Hz, $CHCH_2$), 5.53 (dd, 1 H, J = 17.5, 2.4 Hz, CHCH*H*), 5.36 (dd, 1 H, J = 10.9, 2.4 Hz, CHCH*H*), 3.62 (t, 2 H, J = 6.1 Hz, CH_2OTBS), 2.31 (dt, 2 H, J = 6.9, 2.1 Hz, CH_2CC), 1.62–1.54 (m, 4 H, $CH_2CH_2CH_2OTBS$), 0.87 (s, 9 H, $C(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{14}H_{25}OSi$ (M^+ – H) 237.1675, found 237.1678. Anal. Calcd for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99. Found: C, 70.62; H, 11.03.

8-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxy-3-octyne (9l). The procedure described for **4f** was followed using 4.00 g of (16.8 mmol) of enyne **8l**, 5.79 g (33.5 mmol) of 85% *m*-CPBA, and 5.79 g of Na_2HPO_4 in 65 mL, of CH_2Cl_2. Flash chromatography on silica gel (5% EtOAc–hexane) afforded 3.95 g (93%) of epoxide **9l** as a clear and colorless oil: IR (cm^{-1}, film) 2954, 2856, 2246, 1376, 1251, 1104; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (t, 2 H, J = 6.0 Hz, CH_2OTBS), 3.32 (dd, 1 H, J = 2.6, 4.1 Hz, $CHCH_2$), 2.84 (ddd, 2 H, J = 2.6, 4.1, 18.7 Hz, $CHCH_2$), 2.21 (t, 2 H, J = 7.0 Hz, CH_2CC), 1.59–1.54 (m, 4 H, $CH_2CH_2CH_2OTBS$), 0.87 (s, 9 H, $C(CH_3)_3$), 0.03 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{10}H_{27}O_2Si$ (M^+ – $C(CH_3)_3$) 197.0998, found 197.0995. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.08; H, 10.30. Found: C, 65.94; H, 10.26.

1,2-Epoxy-3-octyn-8-ol (10l). The procedure described for **5a** was followed using 2.70 g (10.6 mmol) of TBS ether **9l** in 10 mL of THF, 1.8 mL (31.8 mmol) of glacial acetic acid, and 31.8 mL (31.8 mmol) of 1.0 M TBAF in THF. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 1.15 g (78%) of alcohol **10l** as a clear and colorless oil: IR (cm^{-1}, film) 3390, 2943, 2867, 2246, 1376, 1055; ^1H NMR (500 MHz, $CDCl_3$) δ 3.64 (t, 2 H, J = 5.2 Hz, CH_2OH), 3.32 (dt, 1 H, J = 1.6, 4.1 Hz, $CHCH_2$), 2.84 (ddd, 2 H, J = 4.1, 5.9, 19.6 Hz, $CHCH_2$), 2.23 (dt, 2 H, J = 1.6, 7.0 Hz, $CCCH_2$), 1.68–1.55 (m, 4 H, $CH_2CH_2CH_2OH$), 1.32 (bs, 1 H, OH); ^{13}C NMR (500 MHz, $CDCl_3$) 84.7, 77.4, 62.2, 49.1, 40.4, 32.0, 25.0, 18.8.

1,2-Epoxy-8-(methoxymethoxy)-3-octyne (11l). The procedure described for **5f** was followed using 0.50 g (3.59 mmol) of alcohol **10l**, 0.41 mL (5.39 mmol) of MOMCl, and 1.90 mL (10.8 mmol) of diisopropylethylamine in 5 mL of CH_2Cl_2. Flash chromatography on silica gel (5% EtOAc–hexane) afforded 0.50 g (76%) of methoxymethyl ether **11l** as a clear and colorless oil: IR (cm^{-1}, film) 2943, 2246, 1371, 1109, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2 H, OCH_2O), 3.51 (t, 2 H, J = 6.1 Hz, CH_2OMOM), 3.34 (s, 3 H, OCH_3), 3.32 (dt, 1 H, J = 1.5, 2.7 Hz, $CHCH_2$), 2.83 (ddd, 2 H, J = 5.8, 2.7, 13.3 Hz, $CHCH_2$), 2.23 (dt, 2 H, J = 1.5, 6.9 Hz, $CCCH_2$), 1.72–1.53 (m, 4 H, $CH_2CH_2CH_2OMOM$); ^{13}C NMR (300 MHz, $CDCl_3$) 96.3, 84.0, 77.1, 67.0, 55.0, 48.6, 39.9, 28.8, 25.0, 18.4; HRMS calcd for $C_9H_{13}O_3$ (M^+ – CH_3) 169.0865, found 169.0863.

2-(4-Hydroxybutyl)-4-methylfuran (12m). The procedure described for **6a** was followed using 0.10 g (0.65 mmol) of alcohol **10m**, 0.86 g (3.24 mmol) of 18-crown-6, and 0.36 g (3.24 mmol) of KO-*t*-Bu in 7 mL of *t*-BuOH. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 33 mg (33%) of furan **12m** as a clear and colorless oil: IR (cm^{-1}, film) 3335, 2932, 2867, 1616, 1115, 1060; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 1 H, C(5) H), 5.83 (s, 1 H, C(3) H), 3.52 (bs, 2 H, CH_2OH), 2.58 (t, 2 H, J = 7.0 Hz, $CH_2(CH_2)_3OH$), 1.96 (s, 3 H, CCH_3), 1.76–1.53 (m, 4 H, $CH_2CH_2CH_2OH$), 1.37 (bs, 1 H, OH); ^{13}C NMR (300 MHz, $CDCl_3$) 156.0, 137.3, 120.4, 107.8, 62.7, 32.2, 27.8, 24.3, 9.8; HRMS calcd for $C_9H_{14}O_2$ (M^+) 154.0994, found 154.0996.

2-[4-(Methoxymethoxy)butyl]furan (13l). The procedure described for **6a** was followed using 0.20 g (1.09 mmol) of ether **11l**, 1.44 g (5.46 mmol) of 18-crown-6, and 0.61 g (5.46 mmol) of KO-*t*-Bu in 11 mL of *t*-BuOH. Flash chromatography on silica gel (10% EtOAc–hexane) afforded 150 mg (75%) of furan **13l** as a clear and colorless oil: IR (cm^{-1}, film) 2943, 1507, 1147, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, 1 H, J = 1.9, 0.9 Hz, C-5 furan H), 6.26 (dd, 1 H, J = 1.9, 3.1 Hz, C-4 furan H), 5.97 (dd, 1 H, J = 3.1, 0.9 Hz, C-3 furan H), 4.60 (s, 2 H, OCH_2O), 3.52 (t, 2 H, J = 6.3 Hz, CH_2OMOM), 3.34 (s, 3 H, OCH_3), 2.64 (t, 2 H, J = 6.4 Hz, $CH_2(CH_2)_3OMOM$), 1.77–1.63 (m, 4 H, $CH_2CH_2CH_2OMOM$); ^{13}C NMR (300 MHz, $CDCl_3$) 156.0, 140.8, 110.0, 104.8, 96.4, 67.4, 55.1, 29.2, 27.7, 24.8; HRMS calcd for $C_{10}H_{16}O_3$ (M^+) 184.1099, found 184.1093.

(*E*)-8-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-3-octen-5-yn-1-ol (15). The procedure described for **3f** was followed using 1.80 g (8.49 mmol) of vinyl iodide **14** in 45 mL of diethylamine, 0.30 g (0.42 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.16 g (0.85 mmol) of CuI, and 2.03 g (11.0 mmol) of alkyne **2f** in 10 mL of diethylamine. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 1.76 g (74%) of enyne **15** as a clear and colorless liquid: IR (cm^{-1}, film) 3357, 2954, 2856, 1474, 1104, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (bs, 1 H, vinyl H), 3.66–3.75 (m, 4 H, CH_2OH, CH_2OTBS), 2.54 (dt, 2 H, J = 7.2, 2.0 Hz, CH_2CC), 2.31 (t, 2 H, J = 6.3 Hz, CH_2CH_2OH), 1.88 (s, 3 H, CH_3), 1.31 (t, 1 H, J = 5.8 Hz, OH), 0.88 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{15}H_{28}O_2Si$ (M^+ – $C(CH_3)_3$) 211.1154, found 211.1156. Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.10; H, 10.51. Found: C, 67.16; H, 10.57.

***trans*-8-[(*tert*-Butyldimethylsilyl)oxy]-3,4-epoxy-3-methyl-5-octyn-1-ol (16).** The procedure described for **4f** was followed with 1.50 g (5.34 mmol) of enyne **15**, 1.85 g (10.7 mmol) of 85% *m*-CPBA, and 1.85 g of Na_2HPO_4 in 20 mL of CH_2Cl_2. Flash chromatography on silica gel (30% EtOAc–hexane) afforded 1.18 g (75%) of epoxide **16** as a clear and

colorless oil: IR (cm^{-1}, film) 3433, 2954, 2856, 1474, 1109, 1055, 1006; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68–3.78 (m, 4 H, CH_2OTBS and CH_2OH), 3.37 (t, 1 H, J = 1.6 Hz, epoxide H), 2.43 (dt, 2 H, J = 1.6, 7.1 Hz, CH_2CC), 1.80–1.90 (m, 3 H, CH_2CH_2OH), 1.44 (s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.05 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{15}H_{27}O_2Si$ (M^+ – OH) 267.1780, found 267.1787. Anal. Calcd for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.17; H, 9.93.

***trans*-8-[(*tert*-Butyldimethylsilyl)oxy]-3,4-epoxy-1-(methoxymethoxy)-3-methyl-5-octyne (17).** The procedure described for **5f** was followed using 1.07 g (3.61 mmol) of alcohol **16**, 0.41 mL (5.41 mmol) of MOMCl, and 1.89 mL (10.8 mmol) of diisopropylethylamine in 5 mL of CH_2Cl_2. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 1.16 g (97%) of methoxymethyl ether **17** as a clear and colorless oil: IR (cm^{-1}, film) 2954, 2856, 1469, 1109, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (s, 2 H, CH_2OMe), 3.70 (t, 2 H, J = 7.1 Hz, CH_2OTBS), 3.59 (dt, 2 H, J = 1.3, 6.2 Hz, CH_2OMOM), 3.34 (s, 3 H, OCH_3), 3.28 (t, 1 H, J = 1.6 Hz, epoxide H), 2.42 (dt, 2 H, J = 1.6, 7.1 Hz, CH_2CC), 1.72–1.95 (m, 2 H, CH_2CH_2OMOM), 1.42 (s, 3 H, CH_3), 0.87 (s, 9 H, $C(CH_3)_3$), 0.04 (s, 6 H, $Si(CH_3)_2$); HRMS calcd for $C_{17}H_{32}O_4Si$ (M^+) 328.2070, found 328.2068. Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.00; H, 9.75.

***trans*-5,6-Epoxy-8-(methoxymethoxy)-6-methyl-3-octyn-1-ol (18).** The procedure described for **5a** was followed using 0.95 g (2.89 mmol) of TBS ether **17** in 12.0 mL of THF, 0.50 mL (8.70 mmol) of glacial acetic acid, and 8.70 mL (8.70 mmol) of 1.0 M TBAF in THF. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 0.44 g (71%) of alcohol **18** as a clear faint yellow oil: IR (cm^{-1}, film) 3422, 2932, 2889, 1447, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2 H, CH_2OMe), 3.71 (dt, 2 H, J = 6.3, 6.3 Hz, CH_2OH), 3.60 (dt, 2 H, J = 1.8, 6.0 Hz, CH_2OMOM), 3.35 (s, 3 H, OCH_3), 3.31 (t, 1 H, J = 1.6 Hz, epoxide H), 2.49 (dt, 2 H, J = 1.6, 6.3 Hz, CH_2CC), 1.95–1.78 (m, 2 H, CH_2CH_2OMOM), 1.73 (t, 1 H, J = 6.3 Hz, OH), 1.43 (s, 3 H, CH_3); HRMS calcd for $C_9H_{13}O_3$ (M^+ – CH_2OCH_3) 169.0865, found 169.0869.

2-[4-(Methoxymethoxy)-2-methyl-2-hydroxybutyl]furan (19). The procedure described for **6a** was followed using 0.10 g (0.47 mmol) of alcohol **18**, 0.27 g (1.03 mmol) of 18-crown-6, and 0.12 g (1.03 mmol) of KO-*t*-Bu in 2 mL of *t*-BuOH. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 55 mg (55%) of furan **19** as a clear and colorless oil: IR (film, cm^{-1}) 3444, 2932, 2889, 1796, 1736, 1109, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, 1 H, J = 1.8 Hz, C-5 H), 6.29 (dd, 1 H, J = 1.8, 3.1 Hz, C-4 H), 6.09 (d, 1 H, J = 3.1 Hz, C-3 H), 4.61 (s, 2 H, OCH_2O), 3.72–3.84 (m, 2 H, CH_2OMOM), 3.36 (s, 3 H, OCH_3), 3.02 (s, 1 H, OH), 2.84 (s, 2 H, CH_2-C(2)), 1.76–1.87 (m, 2 H, CH_2CH_2OMOM), 1.21 (s, 3 H, CCH_3); HRMS calcd for $C_{11}H_{19}O_4$ (M + H) 215.1283, found 215.1287. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.63; H, 8.43.

(*Z*)-3-Methyl-3-decen-5-yn-1-ol (21). The procedure described for **3f** was followed using 2.00 g (9.40 mmol) of vinyl iodide **14** in 45 mL of diethylamine, 0.33 g (0.47 mmol) of bis(triphenylphosphine)palladium(II) chloride, 0.18 g (0.94 mmol) of CuI, and 1.41 mL (12.3 mmol) of alkyne **2d** in 15 mL of diethylamine. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 1.15 g (74%) of enyne **21** as a clear faint yellow oil: IR (cm^{-1}, film) 3335, 2954, 2867, 1632, 1049, 1000; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (bs, 1 H, vinyl H), 3.69 (dt, 2 H, J = 6.2, 6.2 Hz, CH_2OH), 2.30–2.39 (m, 4 H, CH_2CC and CH_2CH_2OH), 1.88 (s, 3 H, CCH_3), 1.24–1.56 (m, 5 H, $CH_2CH_2CH_3$ and OH), 0.90 (t, 3 H, J = 7.2 Hz, CH_2CH_3); HRMS calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1355. Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.58; H, 10.95.

***cis*-3,4-Epoxy-3-methyl-5-decyn-1-ol (22).** The procedure described for **4f** was followed using 1.00 g (6.02 mmol) of enyne **21**, 2.08 g (12.0 mmol) of 85% *m*-CPBA, and 2.08 g of Na_2HPO_4 in 25 mL of CH_2Cl_2. Flash chromatography of silica gel (25% EtOAc–hexane) afforded 0.80 g (73%) of epoxide **22** as a clear and colorless oil: IR (cm^{-1}, film) 3422, 2932, 2878, 2365, 2235, 1458, 1082, 1055; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66–3.78 (m, 2 H, CH_2OH), 3.38 (t, 1 H, J = 1.6 Hz, epoxide H), 2.21 (dt, 2 H, J = 1.6, 7.0 Hz, CH_2CC), 1.78–1.95 (m, 2 H, CH_2CH_2OH), 1.44 (s, 3 H, CH_3), 1.32–1.57 (m, 5 H, $CH_2CH_2CH_3$ and OH), 0.89 (t, 3 H, J = 7.2 Hz, CH_2CH_3); HRMS calcd for $C_{11}H_{18}O_2$ (M^+) 182.1307, found 182.1309.

***cis*-3,4-Epoxy-1-(methoxymethoxy)-3-methyl-5-decyne (23).** The procedure described for **5f** was followed using 0.72 g (3.95 mmol) of alcohol **22**, 0.45 mL (5.93 mmol) of MOMCl, and 2.07 mL (11.9 mmol) of diisopropylethylamine in 5 mL of CH_2Cl_2. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 0.75 g (84%) of methoxymethyl ether **23** as a clear and colorless oil: IR (cm^{-1}, film) 2954, 2878, 2235, 1464, 1147, 1109, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2 H, CH_2OMe), 3.45–3.66 (m, 2 H, CH_2OMOM), 3.35 (s, 3 H, OCH_3), 3.29 (t, 1 H, J = 1.7 Hz, epoxide H), 2.21 (dt, 2 H, J = 1.7, 6.9 Hz, CH_2CC), 1.72–1.95 (m, 2 H, CH_2CH_2OH), 1.42 (s, 3 H, CCH_3), 1.55–1.31 (m, 5 H, $CH_2CH_2CH_3$ and OH), 0.88 (t, 3 H, J = 7.2 Hz, CH_2CH_3); HRMS calcd for $C_{13}H_{22}O_3$ (M^+) 226.1569, found 226.1561. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.92; H, 9.79.

1-(Methoxymethoxy)-3-methyl-6-decen-4-yn-3-ol (25E and 25Z) and **1-(Methoxymethoxy)-3-methyl-4-decen-6-yn-3-ol (26E and 26Z).** The procedure described for **6a** was followed using 0.10 g (0.44 mmol) of ether **23**, 0.26 g (0.97 mmol) of 18-crown-6, and 0.11 g (0.97 mmol) of KO-*t*-Bu in 2 mL of *t*-BuOH. Flash chromatography on silica gel (50% EtOAc–hexane) afforded 70 mg (70%) of enynes **25E**, **25Z**, **26E**, **26Z**, of which 28 mg is a mixture of **25E** and **25Z** and 42 mg is a mixture of the regioisomers **26E** and **26Z**.

8-(Methoxymethoxy)-2-methylene-3-octyn-1-ol (28). The procedure described for **3f** was followed using 3.47 g (25.3 mmol) of vinyl bromide **27** in 75 mL of diethylamine, 0.37 g (0.53 mmol) of bis(triphenylphosphine)palladium(II) chloride, 40 mg (2.11 mmol) of CuI, and 3.00 g (21.1 mmol) of alkyne **2g** in 10 mL of diethylamine. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 3.54 g (85%) of enyne **28** as a clear light yellow oil: IR (cm^{-1}, film) 3433, 2932, 2224, 1622, 1453, 1218, 1044; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 1 H, methylene H), 5.36 (s, 1 H, methylene H), 4.60 (s, 2 H, OCH_2O), 4.08 (d, 2 H, J = 6.5 Hz, CH_2OH), 3.54 (t, 2 H, J = 6.2 Hz, CH_2OMOM), 3.34 (s, 3 H, OCH_3), 2.35 (t, 2 H, J = 6.9 Hz, CH_2CC), 1.76–1.58 (m, 5 H, $CH_2CH_2CH_2OMOM$ and OH); ^{13}C NMR (300 MHz, $CDCl_3$) 131.6, 118.8, 96.3, 91.5, 78.8, 67.2, 67.0, 65.4, 55.1, 28.8, 25.3, 19.1.

***S*-*trans*-5,6-Epoxy-8-(methoxymethoxy)-6-methyl-3-octynyl Thioacetate (29).** To a solution of 2.06 g (7.86 mmol) of PPh_3 in 25 mL THF was added 1.58 mL (8.01 mmol) of DIAD with stirring at 0 °C. After 30 min, 0.78 mL (10.9 mmol) of HSAc, followed by 0.33 g (1.54 mmol) of alcohol **18** in 5 mL of the THF was added, and the mixture was stirred for 1 h. The reaction mixture was poured into saturated $NaHCO_3$, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (20% EtOAc–hexane) afforded 0.27 g (64%) of thioacetate **29** as clear yellow oil: IR (film, cm^{-1}), 2987, 2932, 2889, 2823, 2246, 1747, 1692, 1245, 1109, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2 H, OCH_2O), 3.60 (dt, 2 H, J = 6.0, 2.1 Hz, OCH_2OMOM), 3.35 (s, 3 H, OCH_3), 3.29 (t, 1 H, J = 1.6 Hz, epoxide H), 3.00 (t, 2 H, J = 7.0 Hz, CH_2S), 2.50 (dt, 2 H, J = 7.0, 1.6 Hz, CH_2CC), 2.32 (s, 3 H, $CH_3C(O)$), 2.03–1.75 (m, 2 H, CH_2CH_2OMOM), 1.43 (s, 3 H, CCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) 195.5, 96.7, 84.3, 77.5, 64.0, 61.4, 55.6, 51.5, 37.3, 30.9, 28.4, 20.1, 18.8.

***trans*-5,6-Epoxy-6-methyl-8-(methoxymethoxy)-3-octyne-1-thiol (30).** To a solution of 0.27 g (1.0 mmol) of thioacetate **29** in 4.0 mL of CH_2Cl_2 at –78 °C was added 2.2 mL (2.2 mmol) of a 1.0 M solution of DIBALH in hexanes. The reaction mixture was allowed to stir at –78 °C for 2 h, and then the reaction mixture was quenched with saturated aqueous Rochelle's salt, allowed to warm to room temperature, and stirred for 1 h. The reaction mixture was then separated. The organic layer was washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 125 mg (54%) of thiol **30** as a clear and colorless oil: IR (film, cm^{-1}) 2932, 2889, 2832, 2562, 2235; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2 H, OCH_2O), 3.57–3.62 (m, 2 H, CH_2OMOM), 3.35 (s, 3 H, OCH_3), 3.30 (t, 1 H, J = 1.7 Hz, epoxide H), 2.61–2.69 (m, 2 H, CH_2S), 2.52–2.57 (m, 2 H, CH_2CC), 1.73–1.96 (m, 2 H, CH_2CH_2OMOM), 1.65 (t, 1 H, J = 1.8 Hz, SH), 1.44 (s, 3 H, CCH_3); ^{13}C NMR (500 $CDCl_3$) 96.8, 84.2, 78.0, 64.0, 61.5, 55.7, 51.5, 37.3, 24.5, 24.0, 18.9; HRMS calcd for $C_{11}H_{18}O_3S$ (M^+) 230.0977, found 230.0974.

2-[*trans*-1,2-Epoxy-4-(methoxymethoxy)-2-methylbutyl]-4,5-dihydrothiophene (31). A solution of 0.10 g (2.61 mmol) of potassium in 5 mL of *t*-BuOH was heated to ~65 °C with stirring until all of the potassium had reacted. A solution of 0.12 g (0.52 mmol) of thiol **30** in 1 mL of *t*-BuOH was added. After 15 min, the reaction mixture was diluted with ether and quenched with water, and the layers were separated. The aqueous layer was extracted with ether, and the layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography on silica gel (25% EtOAc–hexane) afforded 60 mg (50%) of dihydrothiophene **31** as a clear yellow oil and 6 mg (5%) of thiophene **32** as a clear yellow oil: IR (cm^{-1}, film) 3472, 2923, 2889, 2823, 2769, 1714, 1605, 1442, 1388, 1213, 1147, 1109, 1039, 919; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (m, 1 H, vinyl H), 4.59 (s, 2 H, OCH_2O), 3.61 (t, 2 H, J = 6.4 Hz, CH_2OMOM), 3.40 (s, 1 H, epoxide H), 3.34 (s, 3 H, OCH_3), 3.22–3.32 (m, 2 H, CH_2S), 2.73–2.79 (m, 2 H, CH_2CH_2S), 1.76–1.96 (m, 2 H, CH_2CH_2OMOM), 1.25 (s, 3 H, CCH_3); ^{13}C NMR (300 MHz, $CDCl_3$) 138.0, 119.6, 96.5, 64.0, 61.6, 60.3, 55.3, 37.8, 35.4, 33.3, 16.3; HRMS calcd for $C_{11}H_{18}O_3S$ (M^+) 230.0977, found 230.0981.

2-[2-Hydroxy-4-(methoxymethoxy)-2-methylbutyl]thiophene (32): IR (cm^{-1}, film) 3455, 2932, 2823, 1376, 1147, 1104, 1039; ^1H NMR (500

MHz, $CDCl_3$) δ 7.15 (dd, 1 H, J = 5.2, 1.2 Hz, C-5 thiophene H), 6.93 (dd, 1 H, J = 3.4, 5.2 Hz, C-4 thiophene H), 6.84 (ddd, 1 H, J = 3.4, 1.2, 1.9 Hz, C-3 thiophene H), 4.61, 4.60 (AB, 2 H, J = 6.6 Hz, OCH_2O), 3.81-3.74 (m, 2 H, CH_2OMOM), 3.36 (s, 3 H, OCH_3), 3.02, 2.98 (AB, 2 H, J = 14.6 Hz, $CH_2C(2)$), 2.94 (s, 1 H, OH), 1.98-1.73 (m, 2 H, CH_2CH_2OMOM), 1.23 (s, 3 H, CCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) 139.7, 127.4, 127.0, 124.8, 97.0, 72.4, 65.1, 55.9, 43.3, 39.8, 26.9.

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Registry No. **1**, 35761-83-2; **2d**, 693-02-7; **2f**, 78592-82-2; **2g**, 73448-13-2; **3f**, 132462-00-1; **4f**, 132462-01-2; **5a**, 132461-84-8; **5b**, 132461-85-9; **5c**, 132461-86-0; **5d**, 138659-72-0; **5e**, 132461-87-1; **5f**, 132462-02-3; **5i**, 138059-73-1; **6a**, 132461-88-2; **6b**, 132461-89-3; **6c**, 132461-91-7; **6d**, 138659-74-2; **6dD**, 138059-75-3; **6e**, 132491-02-2; **6j**, 132461-92-8; **7l**, 593-60-2; **8l**, 138059-76-4; **9l**, 138059-77-5; **10l**, 138059-78-6; **10m**, 138059-79-7; **10n**, 138059-80-0; **11l**, 138059-81-1; **11m**, 138059-82-2; **11n**, 138059-83-3; **12m**, 138059-84-4; **12n**, 116118-62-8; **13l**, 138059-85-5; **13m**, 138059-86-6; **13n**, 138059-87-7; **14**, 78592-73-1; **15**, 138059-88-8; **16**, 138059-89-9; **17**, 138059-90-2; **18**, 132461-98-4; **19**, 132461-99-5; **21**, 138059-91-3; **22**, 138059-92-4; **23**, 138059-93-5; (*Z*)-**25**, 132461-95-1; (*E*)-**25**, 132461-94-0; (*E*)-**26**, 132461-96-2; (*Z*)-**26**, 132461-97-3; **27**, 598-19-6; **28**, 138059-94-6; **29**, 138089-50-6; **30**, 138059-95-7; **31**, 138059-96-8; **32**, 138059-97-9.

Supplementary Material Available: Experimental procedures for **3c**, **3d**, **3g**, **3h**, **4c**, **4d**, **4g**, **4h**, **5b-d**, **5g-i**, **6c**, **6e**, **8m**, **8n**, **9m**, **9n**, **10m**, **10n**, **11m**, **11n**, **12n**, **13m**, and **13n** (9 pages). Ordering information is given on any current masthead page.

Does Diatomic Sulfur (S_2) React as a Free Species?

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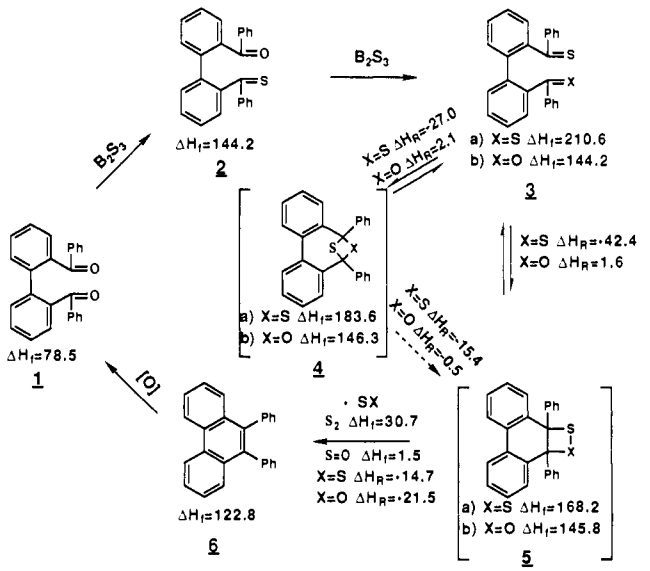
Abstract: A detailed study into the design and synthesis of stable 1,2-dithietane derivatives for the generation of diatomic sulfur (S_2) was undertaken. Computer-aided evaluation of enthalpic differences was used to direct the synthesis of target compounds and, although all of the compounds calculated to afford S_2 that were prepared did yield diatomic sulfur, an isolable 1,2-dithietane other than dithiatopazine failed to materialize. The results of this study provide convincing evidence that the computational procedure outlined can be successfully used to predict the course of S_2 extrusion pathways from potential dithionocarbonylated derivatives. To determine if the disulfide moiety found in the Diels-Alder adduct derived from the addition of diatomic sulfur to conjugated 1,3-dienes is due to a transference mechanism involving the transient 1,2-dithietane intermediate, a chiral nonracemic binaphthyl source of S_2 was prepared. Reactions of S_2 from this source with chiral nonracemic and prochiral conjugated 1,3-dienes indicate that the added disulfide moiety would be inconsistent with a transference mechanism and that a "free" acting S_2 unit is more likely to be involved.

Recently we described a synthetically useful method[1] based on favorable enthalpic considerations (Scheme I) for generating diatomic sulfur (S_2). Although the proposed pathway for the S_2 extrusion implicated a transient 1,2-dithietane intermediate **5a** derived from the labile 2,2'-bis(thiobenzoyl)biphenyl (**3a**), evidence for the formation of the 4-membered cyclic disulfide (an unknown class of compounds) was by inference only.[1] Nicolaou and co-workers,[2] however, were subsequently able to prepare and isolate the first example of a stable 1,2-dithietane (Scheme II), dithiatopazine (**7**), and show by trapping experiments using 2,3-diphenylbutadiene that it also extrudes the S_2 fragment. Unfortunately, other sulfurated products (**10**) which are not produced using the biphenyl route and which may be construed as having been derived from the addition of activated elemental sulfur,[1,3] an alternate mode of sulfur extrusion,[4] are also formed in significant yield.

In both the biphenyl route[1] and the Nicolaou[2] approach, it is possible that the S_2 fragment added to 1,3-dienes might be entirely due to a transference process that directly involves the 1,2-dithietane intermediate as opposed to a "free" acting S_2 species (Scheme III). A similar type of exchange (Scheme IV) has recently been proposed by Ghosh and Bartlett[5] to be operative in the addition of S_3 to norbornene. If the transference mechanism is correct, it would have important and useful stereochemical implications in the construction of chiral 1,2-dithiins. Since several examples of 1,2-dithiins are reported to have anti-AIDS properties[6]

Scheme 1



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