where increased ^{27}Al hyperfine splittings for H_3SiAlH results in a decrese in $\rho_{Al}(3p)$ to 62% from the 65% found in H_3CAlH and a concomitant decrease in proton superhyperfine interaction results in a drop of almost 7% (11% to 4.4%) in $\rho_H(1s)$. The $\rho_{Al}(3s)$ value of 20% remains the same. As mentioned before, such values are approximate.[6] Similar to the $Al(^2P)\{SiH_4\}$ complex the "missing" spin density is believed to reside on the Si atom of the SiH_3 group.

Acknowledgment. The generous financial support of the Natural Sciences and Engineering Research Council of Canada is greatly appreciated. The award of an Ontario Graduate Scholarship (M.A.L.) is deeply appreciated. Valuable computational assistance from Dr. Douglas McIntosh and Dr. Mike Peterson with various aspects of the EPR simulations and ab initio calculations are gratefully acknowledged.

A Concise Route to the Calicheamicin–Esperamicin Series: The Crystal Structure of a Core Subunit

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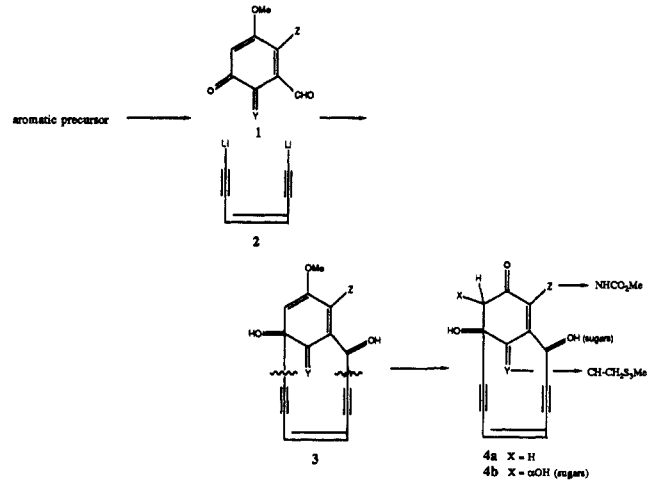
The goal of synthesizing the antitumor antibiotics esperamicin[1a] and calicheamicin[1b,2] is one which will engage the attention of synthetic organic chemists for some time. In addition to addressing the challenge intrinsically posed by these ornate systems, synthesis can be used to generate simpler variants which might mimic the quite extraordinary DNA cleaving properties of the drugs. The ultimate goal is the identification of compounds with greater margins of therapeutic usefulness.

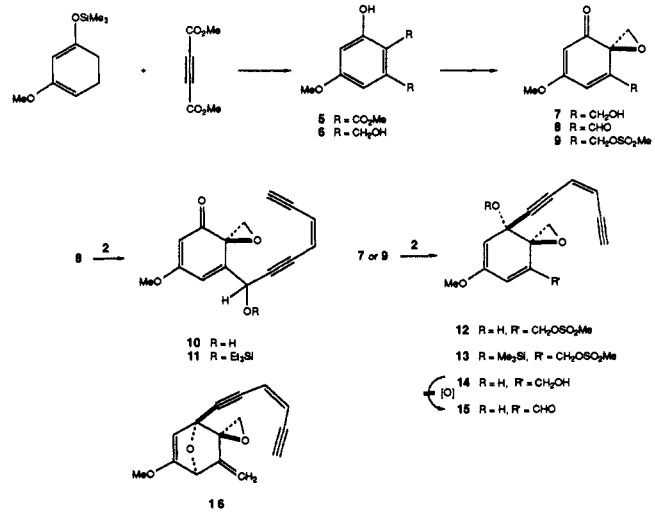
A synthesis of a system containing an enediyne and a bridgehead olefin was accomplished by Schreiber and Kiessling.[3] A recent disclosure by Magnus and Carter provided the first simulation of the cycloaromatization chemistry of a synthetically derived enediyne, related to these antibiotics.[4] We have begun an investigation of the enediyne antibiotics with a view toward total synthesis and medicinal chemistry. *A direct thrust which leads in a few steps to an extensively functionalized core ensemble is now possible.* Moreover, the first crystallographically derived structural information on a prototype system has thus become accessible. Our results are described herein.

A central element of our strategy was the use of a benzenoid matrix to contain the functionality of the eventual cyclohexenone substructure of the natural products. At a strategic point, the system **1** would be exposed. The ketoaldehyde (Y undefined) would be merged with the previously described (*Z*)-dilithioenediyne **2**.[5] Crucial to success would be a productive choice of Y in structure **1**. The selection must harmonize the ease of



liberating **1** from the arene, the amenability of **1** to annulation via dilithium salt **2**, and the feasibility of installing the trisulfide moiety from Y.

The variation which we explored here is one where Y corresponds to a spiroepoxide, generated by the elegant chemistry of Adler and Becker.[6,7a,b] Compound **6** available by reduction ($LiAlH_4$) of **5**[8] when oxidized with sodium periodate in THF–H_2O



afforded **7** (65% overall yield). Reaction of **7** with the Dess–Martin periodinane gave a 70% yield of **8**.[9] Mesylation of **7** ($MeSO_2Cl$; Et_3N) afforded **9**. Seco systems **10**, **12**, and **14** were obtained in good yield by the monoaddition of dilithioenediyne **2** to compounds **8**, **9**, and **7**, respectively. Compounds **10** and **12** as well as their silylated derivatives **11** and **13** failed to undergo cyclization in the desired sense after treatment with lithium diisopropylamide. The product arising from **12** was the 7-oxanorbornene derivative **16**. *A remaining possibility to be screened was one in which cyclization would be attempted on an enediyne aldehyde of the type* ***15***. However, we were unable to reach this compound by oxidation of **14**.

Success was achieved by an adaptation of the Comins concept of in situ aldehyde protection.[10] Treatment of starting ketoaldehyde **8** in THF at −40 °C with lithio *N*-methylanilide generated what we surmised to be the corresponding lithio α-aminoalkoxide adduct. Administration of 2 equiv of dilithioenediyne

(1) (a) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. *J. Am. Chem. Soc.* **1987**, *109*, 3462. (b) Lee, M.; Dunne, T.; Siegel, M.; Chang, C.; Morton, G.; Borders, D. *J. Am. Chem. Soc.* **1987**, *109*, 3464, 3466. Zein, N.; Sihha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science (Washington, D.C.)* **1988**, *240*, 1198.

(2) The revision in stereochemistry at C_{12} in calicheamicin from that initially published[1b] was suggested in a personal communication by Dr. M. Lee of the Lederle group.

(3) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631.

(4) Magnus, P.; Carter, P. *J. Am. Chem. Soc.* **1988**, *110*, 1626.

(5) Danishefsky, S. J.; Yamashita, D. S.; Mantlo, N. B. *Tetrahedron Lett.*, in press.

(6) Adler, E.; Brasen, S.; Miyake, H. *Acta Chem. Scand.* **1971**, *35*, 2055. Becker, H.; Bremholt, T.; Adler, E. *Tetrahedron Lett.* **1972**, *41*, 4205.

(7) (a) Berchtold, G. A.; Sher, F. T. *J. Org. Chem.* **1977**, *42*, 2569. (b) Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256. We note that the stereochemical course of the addition of dilithio salt **2** to compound **15** parallels that observed for a related process in this reference.

(8) McMurry, J.; Erion, M. *J. Am. Chem. Soc.* **1985**, *107*, 2712.

(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(10) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *44*, 1078.

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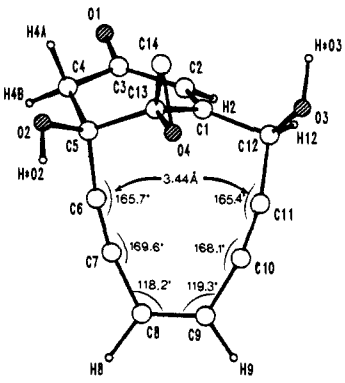
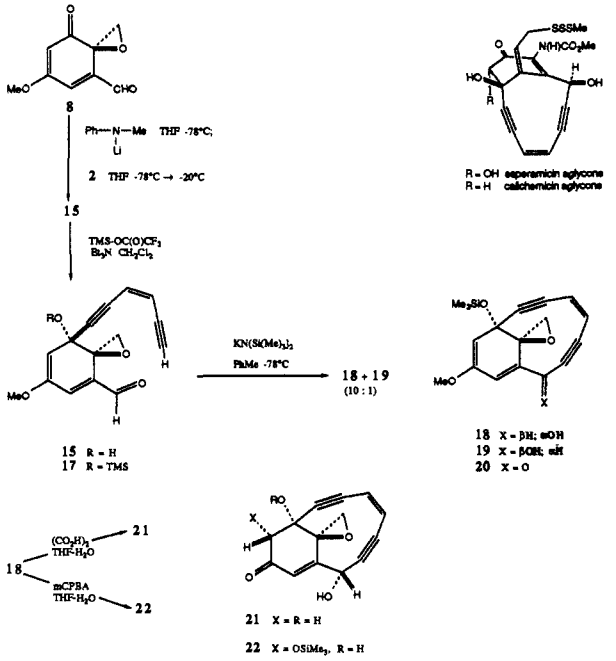


Figure 1. Molecular structure of **21**.

2[5] to a THF solution (−78 °C) of the protected **8**, followed by workup, afforded a 50–60% yield of **15**.[7b] This compound was converted to its trimethylsilyl derivative **17** (70% yield), as shown.



Reaction of a toluene solution of **17** with potassium hexamethyldisilazide (toluene −78 °C, 20 min) afforded a 52% yield[11] of a 10:1 ratio of **18**:**19**. The somewhat unstable ketone **20**, obtained by oxidation[9] of **19**, upon reduction with potassium triisopropoxyborohydride, afforded alcohol **18**, thus allowing for "retrieval" of the minor cyclization product. The stereochemistry of **18** (and therefore **19**) initially surmised from NMR (NOE) measurements was fully established by X-ray crystallographic determinations of compounds **21** and **22**. These products were obtained in 90% and 50% yields, respectively, by hydrolysis or oxidation of **18** as shown.[12] It will be noted that **21** represents a highly functionalized version of calicheamicin. The siloxyketone **22** contains the additional oxygen required for esperamicin, though an inversion at carbon 4 would be required.

The crystal structures of both **21** and **22** are the first obtained in the esperamicin–calicheamicin series wherein the enediyne and bridgehead olefin functionalities are present. The molecular parameters of the two compounds are very similar. An ORTEP view and some of the more interesting data for compound **21** are provided in Figure 1. This compound has many interesting features. The distortion of the acetylenic bond angles is substantial relative to the only modest deviations in the connecting C_8–C_9 vinylene unit. The distance between C_6 and C_{11} is compressed[14] to 3.44 Å. Bonding between these centers is assumed to occur during the bioactivation process.[1,2] Also noteworthy are the deviation from planarity of the enediyne[15] and the boat-like conformation of the cyclohexenone. The C_3 oxygen is tipped syn to C_{13}, and the deviation from planarity of the enone is 17°.

The results of continuing research in this area will be disclosed in due course.

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Supplementary Material Available: Tables of fractional coordinates, bond distances, torsional angles, and anisotropic temperature factors, protocols for the X-ray crystallographic determination of compound **21** and a structure (6 pages). Ordering information is given on any current masthead page.

(11) This yield is based on 18% recovered starting material. The ratio reflects predominant attack of the acetylide on the S-trans conformer of the enal. When the reaction was performed in THF with lithium hexamethyldisilazide as base, a 2.5:1 ratio of **18**:**19** ensued.

(12) The X-ray crystallographic analysis indicated a transfer of the trimethylsilyl group from the oxygen at C_5 to the newly introduced oxygen at C_4.

(13) Cf. dibenzo-1,5-cycloocta-3,7-diyne has acetylenic bond angles of 155.8°: Destro, R.; Simonetta, M. *J. Am. Chem. Soc.* **1975**, *97*, 658. Benzocyclodeca-3,9-diyne has a $C_{2,3,4}$ bond angle of 166.7° and a $C_{3,4,5}$ bond angle of 176.3°: Bennet, M. J.; Smith, R. A. *Acta Crystallogr., Sect. B*: **1977**, *33B*, 1123.

(14) In an analogous acyclic system, 1,2-bis(trimethylstannylacetylene)-benzene, the distance between the distal acetylene carbons is 4.17 Å: Adiwidjaja, G.; Grouhi-witte, G. *J. Org. Met. Chem.* **1980**, *91*, 188.

(15) The torsion angles of $C_{5\text{-}6\text{-}7\text{-}8}$, $C_{6\text{-}7\text{-}8\text{-}9}$, $C_{7\text{-}8\text{-}9\text{-}10}$, $C_{8\text{-}9\text{-}10\text{-}11}$, and $C_{9\text{-}10\text{-}11\text{-}12}$ are −38°, −7°, −2.8°, −8°, and −23°, respectively.

Dependence of Disulfide Vibrational Frequencies on Internal Rotation Geometry: An ab Initio and Normal Mode Study of Dimethyl Disulfide

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Correlations of disulfide vibrational frequencies, such as the S–S [ν(SS)] and C–S [ν(CS)] stretch modes, with the internal rotation angles associated with this group have been the subject of numerous investigations since Lord and Yu noted the conformation dependence of these modes in the Raman spectra of proteins.[1] We have completed ab initio force constant and normal mode calculations as a function of τ(SS), the CS–SC dihedral angle, on dimethyl disulfide, the simplest of a series of such molecules that we are studying, that provide a rigorous basis for evaluating some of these relationships.

There have been contradictory claims regarding the dependence of ν(SS) on τ(SS). According to Sugeta and co-workers,[2-4] ν(SS) is independent of τ(SS), a conclusion supported by Bastian and Martin.[5,6] On the other hand, Van Wart, Scheraga, and coworkers initially proposed[7] that ν(SS) varies linearly with τ(SS) in the range of 0 to ~90°, subsequently, on the basis of CNDO/2[8]

(1) Lord, R. C.; Yu, N.-T. *J. Mol. Biol.* **1970**, *50*, 509–524.
(2) Sugeta, H.; Go, A.; Miyazawa, T. *Chem. Lett.* **1972**, 83–86.
(3) Sugeta, H.; Go, A.; Miyazawa, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3407–3411.
(4) Sugeta, H. *Spectrochim. Acta* **1975**, *31A*, 1729–1737.
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(6) Martin, R. B. *J. Phys. Chem.* **1974**, *78*, 855–856.
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