It is informative to compare the charge-transfer parameters derived from these studies with those suggested by theory to favor discrimination between the two one-electron components of a two-electron wave. Hinkelmann and Heinze predicted wave splitting for a two-electron couple with $\Delta E^\circ = 0$ V when the second charge transfer is at least $10^2$-fold slower than the first, and the homogeneous disproportionation reaction is slow.[5] The present Ru system, with $E^\circ_2 - E^\circ_1 = +0.02$ V and $k_{s1}/k_{s2} > 10^2$, fulfills these requirements. Presumably, a more positive $\Delta E^\circ$ [further thermodynamic destabilization of the Ru(I) intermediate] would require a greater disparity in charge-transfer rates to see the wave splitting at these scan rates.

Claims of wave splitting for polynuclear metal complexes, interpreted in terms of EE mechanisms, have recently appeared.[16-18] However, the published voltammograms[16] appear to be more diagnostic of an EEC mechanism in which the second electron transfer gives a distinctly new compound or isomer with its own voltammetric behavior.

The present results and the appropriate theory should be helpful in evaluating the important question of the timing of geometric changes relative to electron transfer in multielectron processes, in addition to allowing access in some cases to the electron-transfer parameters of the individual steps making up an overall two-electron change. This method may be particularly appropriate in the study of interactions between weakly coupled identical metal redox sites, which have $\Delta E^\circ$ values inherently close to 0 V.

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## Experimental Modeling of the Priming Mechanism of the Calicheamicin/Esperamicin Antibiotics: Actuation by the Addition of Intramolecular Nucleophiles to the Bridgehead Double Bond

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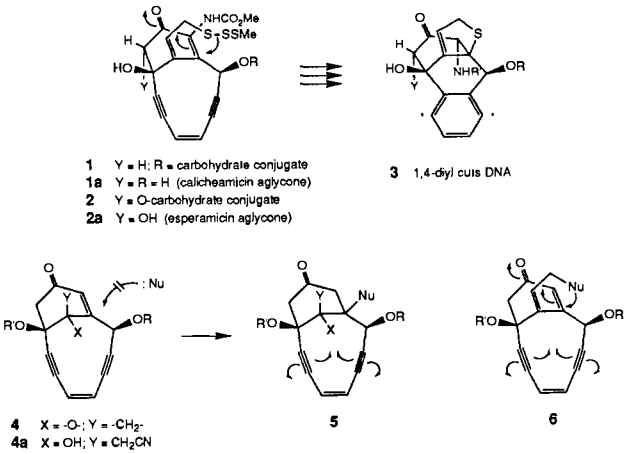
A great deal of effort has been directed toward understanding the mode of action of the enediyne antibiotics, calicheamicin (**1**)[1] and esperamicin (**2**).[2] Such studies might lead to new chemotherapeutic possibilities. The goal is to obtain increasing levels of drug selectivity toward diseased cells without eroding the extraordinary potency of the natural products themselves. Organic synthesis is likely to play a useful role in experimentally based biomodeling, in generating analogues for evaluation, and in elaborating new conjugates for cell targeting.

**Scheme I**




A concise route to compounds of the type **4**, hitherto the most functionalized variants of the hypothetical aglycons **1a** and **2a**, has been described.[3,4] It had been expected that we could trigger cycloaromatization reactions (vide infra) via **5**. Surprisingly, no classical Michael reaction of **4** was achieved with standard nucleophiles (thiolate, cyanide, cuprate).[5,6]

While it will eventually be of interest to determine why this seemingly vulnerable bridgehead double bond has proven to be so resistant to conjugate addition,[7] our next line of attack was to study the feasibility of the intramolecular counterpart. Presumably, the in vivo priming cascade is actuated by intramolecular Michael addition of thiolate. The 1,4-diyl **3**, resulting from Bergman cycloaromatization,[8-11] is likely to be the effector species for the cutting of duplex DNA.[1c,2d,12]

The goal of our synthesis is delineated in construct **6**, wherein an intramolecular *Z*-disposed nucleophile (Nu) is poised to add to the hitherto resistant bridgehead olefin. In this communication we report (i) a solution to this synthetic problem, (ii) the rather facile intramolecular Michael addition of oxygen- and thiol-based nucleophiles to the double bond, and (iii) the reductive cycloaromatization reaction[8] of the resultant enediynes.

Solvolysis of the previously described compound **7**[3] under carefully determined conditions (potassium acetate, acetic acid, DMSO, 50 °C) gave acetoxyhydrin **8**,[13a] in which the enol ether functionality had been preserved. Brief reaction of **8** with dry

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(4) Syntheses of less functionalized versions of the calicheamicin/esperamicin core have been reported. See: (a) Magnus, P.; Lewis, R.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921. (b) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217. (c) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851.
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(6) Unpublished results of N. B. Mantlo.
(7) This immunity may be accountable in terms of steric hindrance afforded by the pseudoaxial substituent of the one-carbon bridge. We do not currently discount, however, the operation of some additional or alternative influence.
(8) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) For earlier explorations in this area, see: Darby, N.; Kim, C. U.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *Chem. Commun.* **1971**, 1516.
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(13) (a) The structure assigned to each new compound is consistent with its infrared and 250 MHz $^1$H NMR spectra as well as parent ion identification by high resolution mass spectrometry. (b) A sample of this new compound obtained by crystallization gave C and H combustion analysis within 0.4%.

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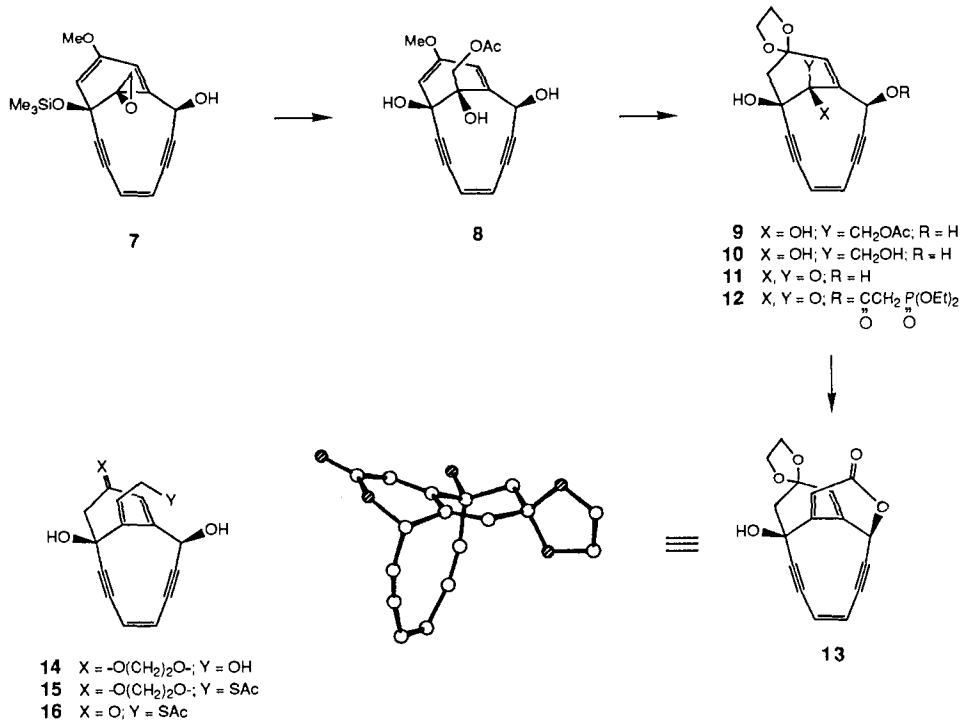
**Scheme II**



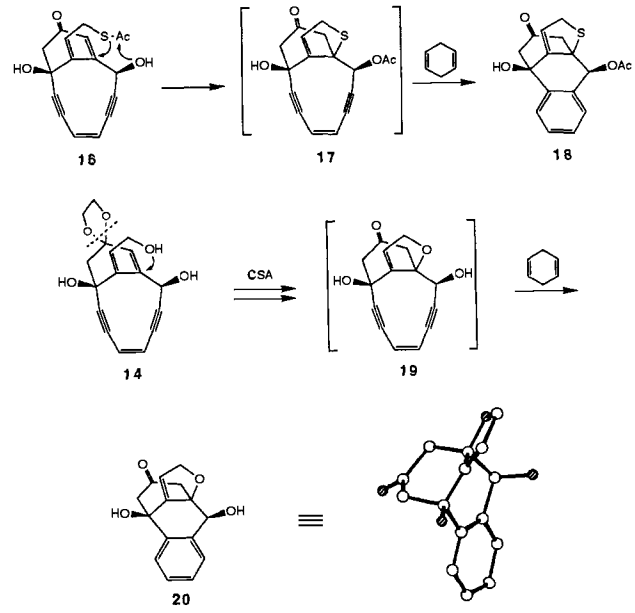

ethylene glycol in the presence of CSA at 50 °C gave ketal **9** in 75% yield from **7**.[13a,14] Deacylation was readily achieved with methanolic ammonia. Resultant tetraol **10**,[13] upon reaction with periodic acid in tetrahydrofuran, afforded ketone **11**[13a] (76% overall yield from **9**). Treatment of **11** with diethylphosphonylacetic acid[15] in the presence of DCC afforded monoester **12**.[13a] This substance underwent intramolecular Emmons condensation under the influence of lithium bromide and triethylamine in THF at room temperature.[16] This gave crystalline (dec > 95°) dienyl lactone **13**[13] in 67% yield from **11**. The structural assignment of this compound was supported by a crystallographic determination.

Treatment of lactone **13** with diisobutylaluminum hydride ($CH_2Cl_2$, −78 °C) afforded the corresponding hemiacetal. The latter could be opened upon further reduction with sodium borohydride in methanol/water. This procedure supplied triol **14**[13a] in 63% yield. The primary alcohol could be selectively mesylated with methanesulfonyl chloride in pyridine. Subsequent addition of thioacetic acid to the reaction mixture resulted in thioacetate **15**.[13a,17] The ketal function was cleaved with camphorsulfonic acid in aqueous THF to provide an 89% yield of enone thioacetate **16**.[13a]

A most interesting result was obtained by treatment of compound **16** with diethylamine in THF in the presence of 1,4-cyclohexadiene.[4a] After 15.5 h at room temperature there was obtained a 71% yield of dihydrothiophene **18**.[13a] It seems reasonable to suppose that this transformation involves acetyl transfer from sulfur to hydroxyl leading to the corresponding thiolate which undergoes intramolecular Michael addition to the double bond. Such a process would afford structure **17**. This compound has not been detected in the reaction mixture. Rather it suffers rapid reductive cycloaromatization (cf. structure **3**) with cyclohexadiene to give the observed **18**.

It was of interest to study the applicability of these findings to an oxygen-based nucleophile. Treatment of compound **14** with camphorsulfonic acid in the presence of cyclohexadiene (aqueous

**Scheme III**




THF, room temperature, 8 h) gave a 58% yield of dihydrofuran **20**.[13] Presumably, the ketal had cleaved and the corresponding enone had been generated. This enone might reasonably undergo in situ Michael addition by the proximal allylic alcohol to produce dihydrofuran **19**. This compound is not detected; rather in the presence of cyclohexadiene it too undergoes reductive cycloaromatization leading to compound **20**. This assignment is also supported by a crystallographic determination.

It has thus been shown that a properly placed intramolecular thiol nucleophile is indeed capable of undergoing Michael addition to the bridgehead double bond. It is further shown that the resultant product (**17**) suffers reductive cycloaromatization. Finally, it has been demonstrated that an oxygen as well as a thiol nucleophile is capable of actuating the cascade. It will be of interest to determine whether diyl intermediates in these processes are capable of cutting DNA. The possibilities of obtaining useful biological activity from these simplified (des-ureido) analogues will also be determined.

(14) Attempts to ketalize the enone derivative of enol ether **8** were unrewarding.

(15) This acid was obtained by saponification of its commercially available ethyl ester (NaOH, EtOH, $H_2O$, room temperature).

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(17) The current yield for this two-step sulfur introduction is a modest but useful 23% of the theoretical. Optimization of the procedure will be reported in due course.

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**Supplementary Material Available:** Spectral data (IR, $^1$H NMR, and MS) for compounds **8–16**, **18**, and **20**, tables of fractional coordinates, bond distances, torsional angles, and anisotropic temperature factors and summary of the X-ray crystallographic determinations and structures of compounds **13** and **20** (17 pages). Ordering information is given on any current masthead page.

## Molecular Sieve Sensors for Selective Detection at the Nanogram Level

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Zeolites have long been known for their molecular sieving properties based upon crystalline pore structures of molecular dimensions.[1] We explore strategies to introduce *molecular sieving functions into inorganic thin films* and membranes which are of current interest for sensor coatings and gas-phase separations.[2-4] The zeolite films offer high thermal stability (>770 K) and chemical resistance. Surface acoustic wave (SAW, Figure 1A) devices[5] can be operated as highly sensitive piezoelectric balances that respond to small fractions of single-crystal monolayer adsorption via frequency changes of an oscillator circuit. Since the response is nonselective, a number of organic and organometallic coatings on SAW devices have previously been explored to impart chemical selectivity.[6] The SAW device[7,8] (97 MHz, detection limit ca. 100 pg/cm$^2$) used in the present study to measure selective adsorption of organic vapors (0.1% of saturation in nitrogen flow, 295 K) consists of a single-crystal quartz substrate with interdigital transducers which was coated with zeolite-silica thin films and mounted in a test chamber with gas inlet and outlet.

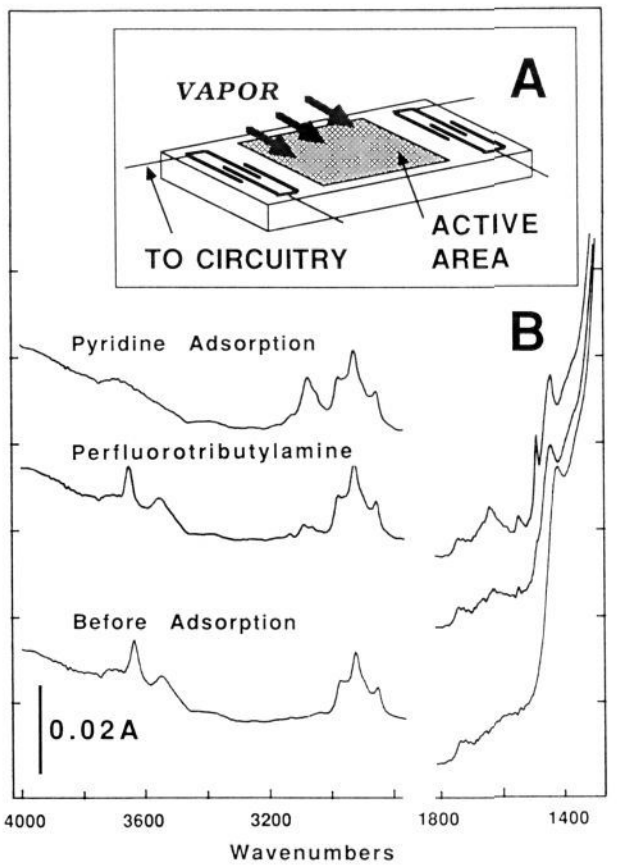


**Figure 1**. A. Schematics of the surface acoustic wave device. B. Adsorption of pyridine and perfluorotributylamine vapor (1 Torr at 295 K) on HY-zeolite film embedded in silica matrix derived from base-catalyzed sol (B2), degassed at 570 K, $10^{-7}$ Torr. FTIR spectra were taken at 8-cm$^{-1}$ resolution in a stainless steel UHV cell, equipped with $CaF_2$ windows and connected to a steel apparatus with turbomolecular pump and mass spectrometer. The features in the C–H stretch region (ca. 2800–3000 cm$^{-1}$) are due to decomposition products of the sol matrix deposited on the cell windows after initial heating.

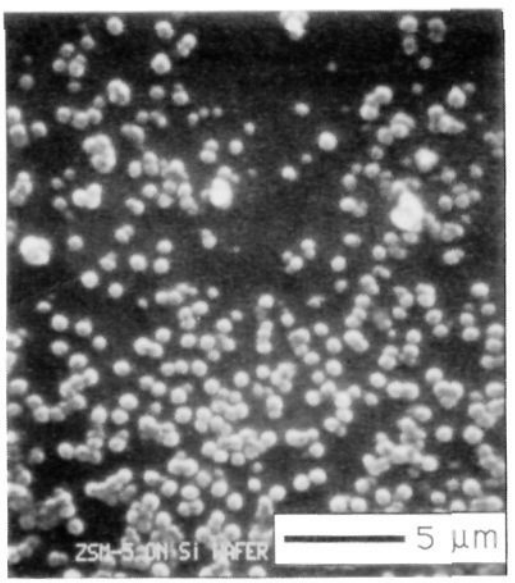


**Figure 2**. Scanning electron micrograph of crystals of zeolite H-ZSM-5 embedded in an A2-sol derived matrix[16] on a Si wafer.

The zeolite-silica composites are prepared from suspensions of small zeolite crystals in alcoholic solutions of tetraethylorthosilicate (TEOS) that is hydrolyzed and polymerized by acid- and base-catalyzed reactions resulting in extended, weakly branched

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