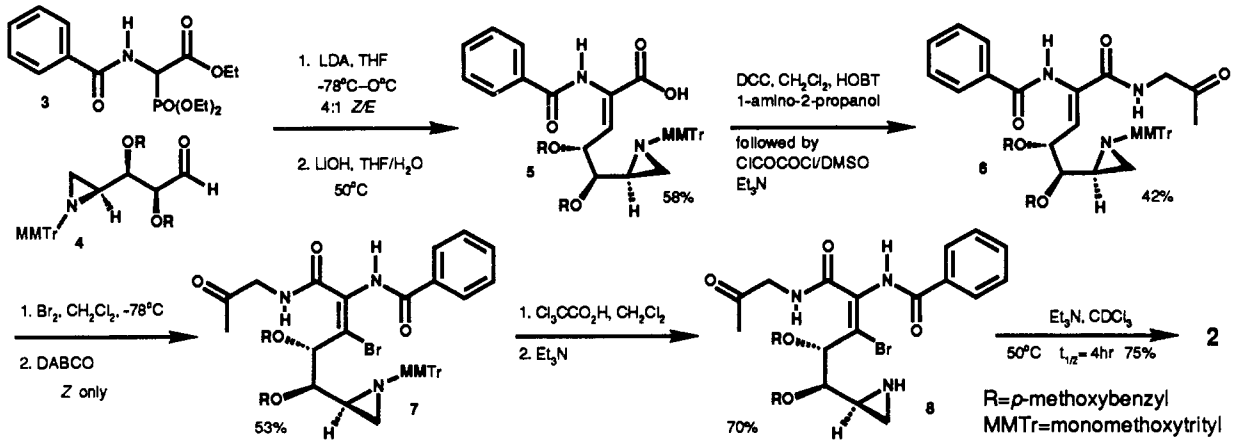
Scheme I



Synthesis of **2** began with the condensation of glycine phosphonate **3**[5] and aldehyde **4**[6] to provide a 4:1 *Z*/*E* mixture of isomers, which was converted to acid **5**[7] in 58% yield (Scheme I). Elaboration to the azinomycin A side chain was accomplished via condensation of **5** with (−)-1-amino-2-propanol under dicyclohexylcarbodiimide/*N*-hydroxybenzotriazole conditions. Due to the instability of the products, the reaction mixture was subjected to Swern oxidation conditions, directly affording ketone **6** in 42% yield. Introduction of the leaving group at the β position was accomplished by addition of 1.1 equiv of bromine (0.1 mM in CH_2Cl_2) at −78 °C followed immediately by DABCO[5] to afford a 53% yield of isomerically pure vinyl bromide **7**. The monomethoxytrityl blocking group could be readily removed by addition of trichloroacetic acid followed by quenching with triethylamine to afford a 70% yield of aziridine **8**. We were pleased to find that this material was stable to isolation and purification using standard methods (flash silica gel chromatography). The cyclization of vinyl bromide **8** was monitored by ^1H NMR spectroscopy using $CDCl_3$ as a solvent. Addition of triethylamine (1.5 equiv) afforded no product at room temperature over a period of 30 min. However, warming to 50 °C resulted in loss of all signals associated with starting material and appearance of a new series of signals consistent with a [3.1.0] bicyclic aziridine. A single diastereomer was produced in high yield (75%) corresponding to the *Z* isomer **2**.[8] Two-dimensional ^1H nuclear Overhauser enhancement (NOE) experiments confirmed the bicyclic nature of the product by showing, among other cross peaks, strong enhancement between $H_{7,endo}$ and H_4. Similar observations are reported for **1a** and **1b**.[1e] Observation of an NOE cross peak between H_4 and the amide H_a hydrogen provided unequivocal evidence for the *E* geometry in **2**. The tentative stereochemical assignment of olefin geometry in **1a** and **1b** by Yokoi et al. was based on the analysis of the chemical shift of the amide hydrogens. Specifically, the downfield shift of H_a in azinomycin A (10.1 ppm) and B (12.3 ppm) was proposed to result from intramolecular hydrogen bonding to the aziridine nitrogen. The analogous H_a resonance in **2** is at a much higher field (6.95 ppm), suggesting that hydrogen bonding is indeed occurring in the natural products. This observation is of great interest since intramolecular protonation is a potential mechanism for activation of the aziridine toward nucleophilic addition.[9]

The intramolecular cyclization of aziridine **8** provides the first synthesis of the strained 1-azabicyclo[3.1.0]hex-2-ylidene ring system (**2**). This highly stereoselective approach affords the bicyclic vinylic aziridine with retention of configuration of the starting vinyl bromide. Assignment of the *Z* geometry in **2** provides evidence for olefin configuration in the natural products. Further synthetic studies of the azinomycins and DNA alkylation profiles for these drugs are currently under investigation in these laboratories.

Acknowledgment. Support from the NSF (CHE 88-58059) and Bristol-Myers Company is gratefully acknowledged. We thank Brian King for technical help.

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(7) Hydrolysis of the unsaturated esters obtained from the condensation of **3** and **4** affords exclusively acid **5** as a result of selective decomposition of the *E* diastereomer.

(8) ^1H NMR (500 MHz, $CDCl_3$, ppm referenced to $CHCl_3$): 2.15 (s, 3 H), 2.18 (d, J = 3.6 Hz, 1 H), 2.40 (dd, J = 1 Hz, J = 5.3 Hz, 1 H), 3.03 (ddd, J = 3.6 Hz, J = 4.9 Hz, J = 5.3 Hz, 1 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 4.03 (dd, J = 4.8 Hz, J = 19.4 Hz, 1 H), 4.18 (dd, J = 4.8 Hz, J = 19.4 Hz, 1 H), 4.42 (dd, J = 1 Hz, J = 4.9 Hz, 1 H), 4.44 (d, J = 11 Hz, 1 H), 4.48 (d, J = 11.0 Hz, 1 H), 4.51 (br s, 2 H), 5.12 (dd, J = 1 Hz, J = 1 Hz, 1 H), 6.84 (m, 2 H), 6.88 (m, 2 H), 6.95 (br dd, 1 H), 7.23 (m, 2 H), 7.25 (m, 2 H), 7.46 (m, 2 H), 7.55 (m, 1 H), 7.88 (m, 2 H), 7.89 (br s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): 202.8, 165.9, 163.5, 159.4, 159.2, 149.5, 133.3, 132.2, 130.0, 129.5, 129.4, 129.3, 128.7, 127.5, 123.3, 113.9, 113.7, 86.1, 81.8, 71.1, 70.8, 55.3, 50.0, 44.0, 37.9, 27.2. HR FABMS: calculated for $C_{33}H_{36}N_3O_7$ 586.2553, found 586.2552.

(9) The lone pair of electrons on the aziridine nitrogen are out-of-plane with respect to the dehydroamino acid system. This implies that there is some rotation about the amide bond containing the side chain to maximize hydrogen bonding to H_2. Subtle conformational changes upon binding could be responsible for activation of the aziridine to alkylation by DNA bases.

Synthesis and Crystal and Molecular Structure of 2,5-Bis(trimethylsilyl)-3,4-dimethyl-1-bismaferrocene: An Aromatic Heterocycle Containing Bismuth

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Heteroferrocenes of the group 15 elements (**1–5**) are of general interest for the study of π-bonding between carbon and the heavier main-group elements. These compounds provide a graded series in which an entire column of elements are incorporated into metallocene rings.[1] A comparison of their properties should provide information about π-bonding as a function of increasing atomic number. Derivatives of azaferrocene **1**,[2,3] phosphaferrocene

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Table I. Comparison of Selected Distances (Å) of Group 15 Heteroferrocenes

compd	E	d(EFe)	d(EC$_2$)	d(E out of ring plane)	d(C$_2$C3)	d(C$_3$C$_4$)	ref
10	Bi	2.64	2.24	0.39	1.42	1.43	this work
6	Sb	2.56	2.11	0.18	1.41	1.43	11
7	As	2.40	1.90	0.07	1.40	1.42	8
8	P	2.28	1.76	0.02	1.42	1.42	5
9	N	2.09	1.39	0	1.42	1.41	3

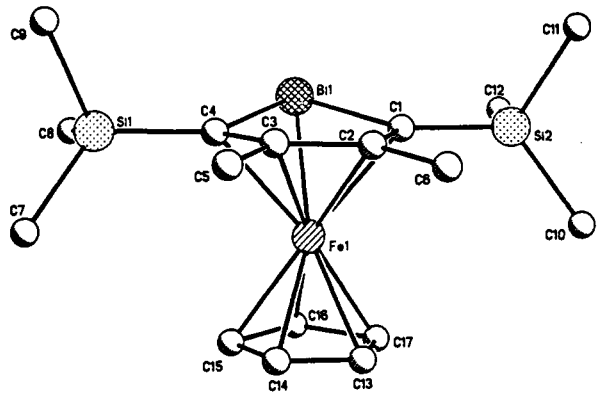
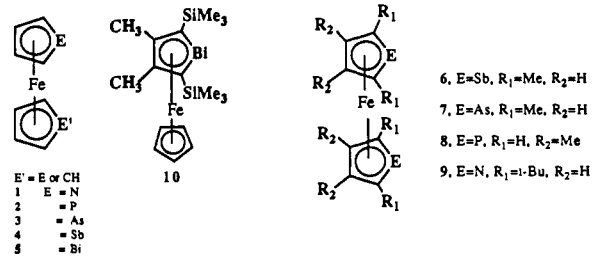
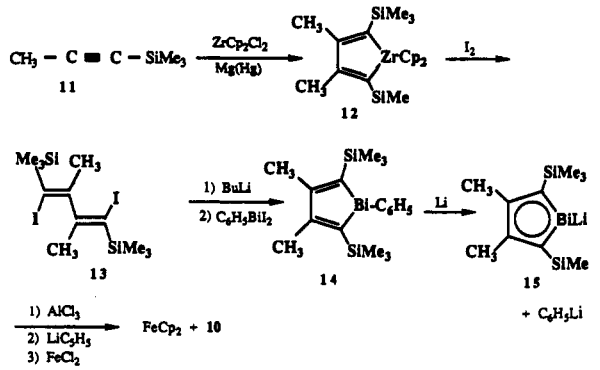


Figure 1. The structure of 2,5-bis(trimethylsilyl)-3,4-dimethyl-1-bismaferrocene (**10**), showing the atom-labeling scheme. Hydrogen atoms are omitted for clarity. Selected interatomic distances (Å) and angles (deg) are as follows: Bi–Fe, 2.643 (2); C1–Fe, 2.07 (1); C2–Fe, 2.061 (9); C3–Fe, 2.06 (1); C4–Fe, 2.09 (1); C(Cp)–Fe(av), 2.01 (1); Bi–C1, 2.23 (1); Bi–C4, 2.24 (1); C1–C2, 1.42 (1); C2–C3, 1.43 (2); C3–C4, 1.42 (1); C1–Bi–C4, 76.6 (4); Bi–C1–C2, 112.7 (7); C1–C2–C3, 117.9 (9); C2–C3–C4, 119 (1); C3–C4–Bi, 112.1 (8).

2,[4-6] arsaferrocene **3**,[4,7-9] and stibaferrocene **4**[9-11] are available, while structural data have been reported for derivatives **6**,[11] **7**,[8] **8**,[5] and **9**.[3] We report here on the first synthesis of a bismaferrocene and on structural data which show that the bismolyl group serves as an η^5-aromatic ligand.



In view of the known lability of bismuth-containing heterocycles,[12] we chose the sterically hindered bismaferrocene **10** as a target. Compound **10** was prepared by an extension of the Fagan–Nugent heterole synthesis.[13] Thus the reaction of 1-(trimethylsilyl)-1-propyne (**11**) with zirconocene dichloride and magnesium amalgam in THF gave 96% of the yellow crystalline zirconocycle **12**. Iodonolysis of **12** with I_2 afforded an 80% yield of the white crystalline diiodide **13**. Dilithiation of **13** with butyllithium in ether followed by treatment with a suspension of phenylbismuth diiodide gave a nearly quantitative yield of the 1-phenyl-2,5-bis(trimethylsilyl)-3,4-dimethylbismole (**14**). Because of its lability, the bismole was used directly without extensive purification. Reaction of **14** with lithium metal in THF at 0 °C for 3 h gave a deep red solution of bismolyl anion **15** and phenyllithium. Addition of $^1/_3$ equiv of $AlCl_3$ to remove phenyllithium, followed by sequential treatment with 1 equiv of LiC_5H_5 and $FeCl_2$, afforded a mixture of ferrocene and the desired bismaferrocene **10**. After removal of ferrocene by sublimation, the residue was recrystallized from pentane to give 25% of **10** as mildly air sensitive red/black crystals. The bismaferrocene **10** has been thoroughly characterized spectroscopically and by X-ray diffraction.[14]



The structure of **10** illustrated in Figure 1 shows a metallocene-like arrangement which closely resembles its lighter pnicogen analogues **6**–**9**. Relevant data are compared in Table I.

The iron atom of **10** is slightly closer to the Cp carbons (2.01 Å av) than to the bismolyl ring carbons (2.07 Å av), while the FeBi distance is considerably greater (2.64 Å). The four carbon atoms of the bismolyl ring lie in a plane parallel to the Cp ring, but the bismuth atom is displaced away from iron above the plane by 0.38 Å. Heteroferrocenes **6**–**8** show a similar displacement of the heteroatom which correlates with its size. Thus this displacement appears to be a consequence of simultaneously accommodating the π-bonding to the large heteroatoms and the smaller carbons.

The C–C bonding distances of the bismolyl ring are not significantly different (1.42, 1.43 Å) and are typical of those of heteroferrocenes **6**–**9**. The BiC bonds (2.23, 2.24 Å) are quite long in comparison to C–C ring bonds. However, they are slightly shorter than the sum of the covalent radii of C and Bi (2.29 Å)[15] and the average (2.27 Å) found in two structurally characterized diphenylbismuth derivatives with σ-metal bonds.[16,17] Thus the

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BiC bond lengths suggest multiple-bond character as has been previously found for the E-C bonds of heteroferrocenes **6-9**.

In conclusion, the overall structural data on **10** emphasizes its close relationship to the series of the heteroferrocenes.

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Supplementary Material Available: Full experimental details for the procedures described herein, tables of complete crystallographic data, atomic coordinates, bond lengths and angles, anisotropic thermal parameters, hydrogen atom coordinates, and planes of **10**, and an ORTEP plot of **10** (14 pages); tables of observed and calculated structure factors of **10** (13 pages). Ordering information is given on any current masthead page.

^{2}H Mims Pulsed ENDOR of Hydrogen Bonds and Exogenous Ligands to the Metal Clusters of Iron-Sulfur Proteins

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Hydrogen bonding to the [*m*Fe-*n*S] clusters in Fe-S proteins is of interest because this interaction may well modulate cluster function.[1] In addition, multimetal clusters in proteins can act in a catalytic role,[2] and thus it is important to probe their interaction with exogenous ligands, such as those that come from solvent, H_xO (HO^-, H_2O). We report that Mims[3a,4] deuteron pulsed electron-nuclear double resonance (ENDOR) spectroscopy of H/D exchanged Fe-S proteins provides significant new opportunities both for probing H bonding to metal clusters and for examining exogenous ligands to such clusters. We find that frozen solutions of H/D exchanged proteins give extremely well resolved deuteron Mims ENDOR spectra[3a,4] from small samples (~10-20 μL), and that the data permits direct measurements of ^{2}H hyperfine and quadrupole couplings for individual interacting deuterons. Indeed, these unmatched opportunities exist for *any* nucleus that experiences small hyperfine couplings.[4c,e,5e] As the first applications of this approach, we report that the [2Fe-2S]$^+$ cluster in *Anabaena* 7120 ferredoxin (Fd)[6] is involved in at least one direct H bond with significant covalency, and we provide data supporting the suggestion based on multifrequency continuous wave (CW) ENDOR that the [4Fe-4S]$^+$ cluster of aconitase binds OH^- in the absence of substrate, but H_2O in its presence.[5c]

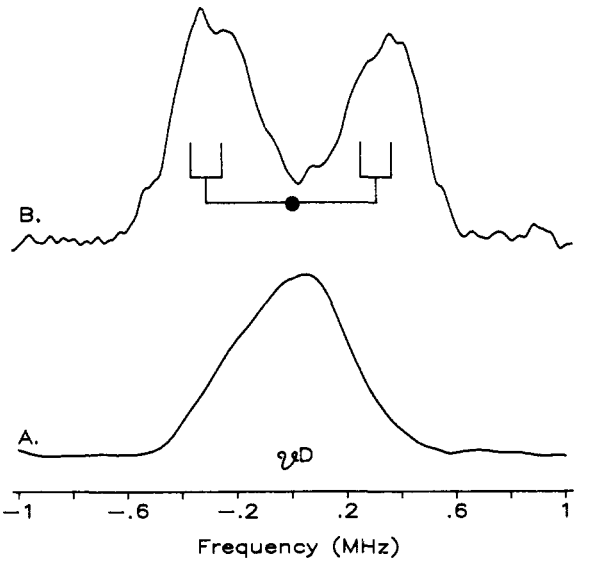

Figure 1. CW ENDOR (A) and Mims ENDOR (B) spectra of the [2Fe-2S]$^+$ cluster of *Anabaena* ferredoxin in D_2O solvent. For comparison, spectra are plotted as $\delta\nu = \nu - \nu_D$. Experimental conditions for spectrum A: ν_e = 34.54 GHz; H_0 = 12670 G; ν_D = 8.3 MHz; scan rate 0.25 MHz/s; 200 scans. For spectrum B: ν_e = 9.15 GHz; H_0 = 3357 G; microwave pulse width, 16 ns; rf pulse width, 40 μs; τ_{12} = 420 ns; ν_D = 2.2 MHz; 64 scans.

The [2Fe-2S]$^+$ cluster of *Anabaena* Fd exhibits a rhombic EPR spectrum with $g_{1,2,3}$ = 2.00, 1.96, 1.92. A ^{2}H Q-band CW ENDOR spectrum[7a] (Figure 1A) of the D_2O-exchanged protein[8] shows only a featureless signal at the deuterium Larmor frequency, ν_D (7.9 MHz at H_0 = 12000 G), and one cannot determine to what extent this signal is due to "distant ENDOR"[9] from deuterons that are not hyperfine-coupled to the cluster. The electron spin echo envelope modulation (ESEEM) technique also typically shows ^{2}H modulation only with a frequency ν_D.[3] In contrast, the Mims pulsed ENDOR technique yields highly resolved local ^{2}H

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