diffraction[20a,b] uncovered a slight, but regular, bond alternation in the benzene ring.

Thus, in **2**-Cr and in delocalized metal-arene complexes the metal tripod distorts the benzene to meet the needs of the ligand field. In systems where significant bond alternation is already present, such as **1**-Cr, the metal tripod adopts a conformation to meet the needs of the ligand field; the distortions of the arenes upon complexation reflect those of classic π-metal complexes. In no case do we see any need to resort to "superaromaticity"[21] in understanding the stereochemistry of tricarbonylchromium arenes.

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Supplementary Material Available: Experimental details of the data collection and reduction and the structure solution and refinement for **1**-Cr, tables of crystallographic data, bond distances and angles, positional parameters, and general displacement parameter expressions for **1**-Cr, and tables of molecular geometry coordinates for **1** and the ground and transition states of **1**-Cr (19 pages). Ordering information is given on any current masthead page.

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Stereoselective Synthesis of a 1-Azabicyclo[3.1.0]hex-2-ylidene Dehydroamino Acid Derivative Related to the Azinomycin Antitumor Antibiotics

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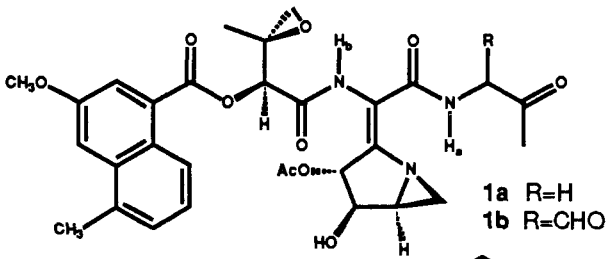
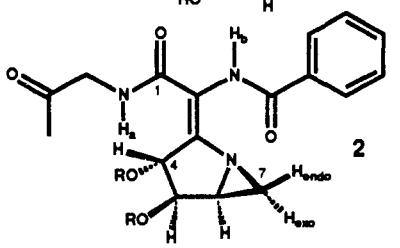
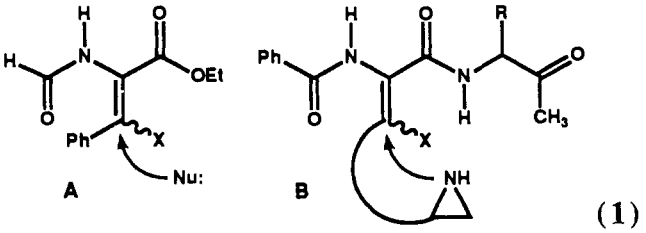
Azinomycins A (**1a**) and B (**1b**) were isolated[1] in 1986 from the fermentation broth of *Streptomyces griseofuscus* and were found to have significant activity against a broad spectrum of tumor systems.[2] These potent metabolites incorporate a novel dehydroamino acid residue containing a 1-azabicyclo[3.1.0]hex-2-ylidene ring system. This unstable group is apparently necessary for the bioactivity of these compounds, since structurally related metabolites lacking this residue and coproduced with **1a** and **1b** exhibit no antibacterial or antitumor activity. Since the effect of azinomycin B on P388 leukemia is comparable to that of the clinically useful drug mitomycin C, an understanding of the chemical events responsible for this activity is of great interest and makes these compounds excellent targets for synthetic studies. The lack of X-ray data for either **1a** or **1b** or derivatives thereof has meant that some structural ambiguities still exist. Specifically, the geometry about the tetrasubstituted olefin and the absolute stereochemistry of the bicyclic pyrrolidine are uncertain. We describe herein a highly stereoselective synthesis of phenacyl derivative **2** containing the azinomycin A amide side chain. The unambiguous assignment of *Z* stereochemistry in **2** provides evidence for the *E* geometry in the natural products.





The instability of the natural product to mild acid suggested that the labile bicyclic aziridine should be introduced under basic conditions. Our strategy centered around formation of the [3.1.0] ring system through an intramolecular addition-elimination reaction on a suitably activated dehydroamino acid derivative. Although highly stereoselective intermolecular vinylic substitution of ethylenimine to β-bromoacrylates is known,[3] the analogous reactions with dehydroamino acids are much less facile due to the deactivating effect of the α-nitrogen atom. These substrates (A) are generally unreactive toward nitrogen and oxygen nucleophiles and add mercaptans with only modest selectivity (3:2 *Z*/*E*) about the olefin.[4] We envisioned that intramolecular substitution (B) would be a much more facile process. Whether the reaction would proceed with good stereoselectivity seemed less certain.



(1)

(1) The spectral properties of carzinophilin and azinomycin B are identical (unpublished results). For isolation and proposed structures of carzinophilin: (a) Hata, T.; Koga, F.; Sano, Y.; Kanamori, K.; Matsumae, A.; Sugawara, R.; Shima, T.; Ito, S.; Tomizawa, S. *J. Antibiot., Ser. A* **1954**, *107*, 7. (b) Lown, J. W.; Hanstock, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 3212. (c) Onda, M.; Konda, Y.; Hatano, A.; Hata, T.; Omura, S. *J. Am. Chem. Soc.* **1983**, *105*, 1995. (d) Onda, M.; Konda, Y.; Hatano, A.; Hata, T.; Omura, S. *Chem. Pharm. Bull.* **1984**, *32*, 2995. For isolation and proposed structures of azinomycins A and B: (e) Yokoi, K.; Nagaoka, T.; Nakashima, T. *Chem. Pharm. Bull.* **1986**, *34*, 4554. (f) Nagaoka, K.; Matsumoto, M.; Oono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527.

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(4) Nunami, K.-I.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467. When the *N*-formyl group in structure A was replaced by the more electron withdrawing isocyano group, benzylamine addition products were observed in modest yields and low stereoselectivity.

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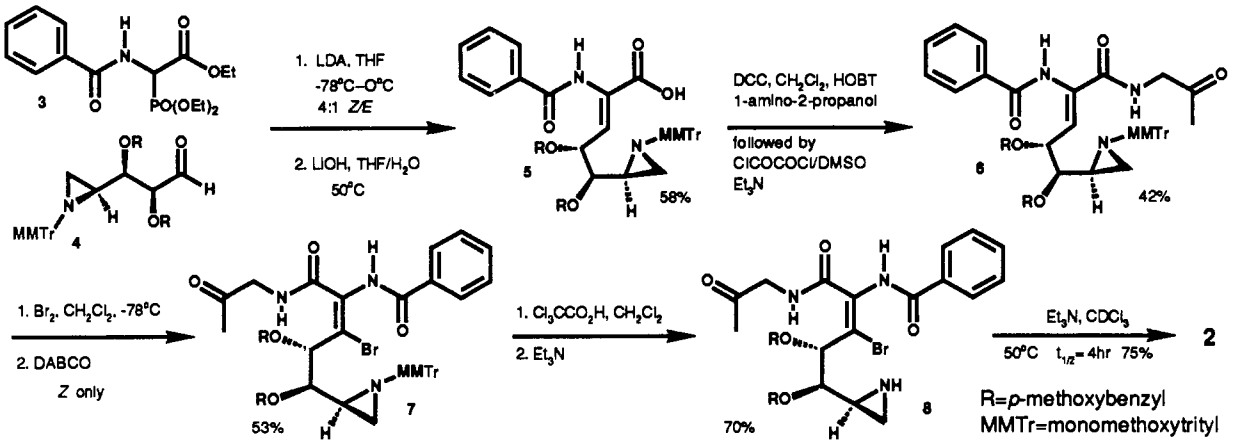
Scheme I



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.

(5) Olsen, R. K.; Hennen, W. J.; Wardle, R. B. *J. Org. Chem.* **1982**, *47*, 4605.

(6) Moran, E. J.; Tellew, J. E.; Armstrong, R. W., submitted for publication.

(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

(1) For a detailed discussion on the analogous heterobenzene series, see: (a) Jutzi, P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 232. (b) Ashe, A. J., III. *Acc. Chem. Res.* **1978**, *11*, 153. (c) Ashe, A. J., III. *Top. Curr. Chem.* **1982**, *105*, 125.

(2) King, R. B.; Bisnette, M. B. *Inorg. Chem.* **1964**, *3*, 796. Joshi, K. K.; Pauson, P. L.; Qazi, A. R.; Stubbs, W. H. *J. Organomet. Chem.* **1964**, *1*, 471.

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