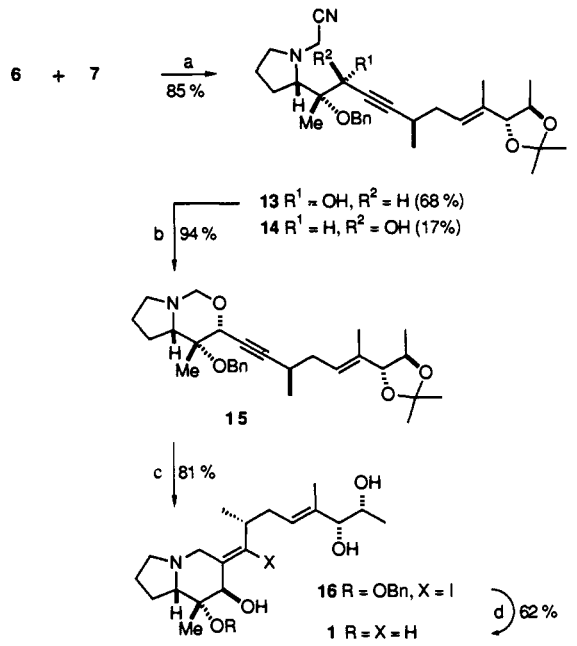
Scheme III. Synthesis of (+)-Allopumiliotoxin 339A[a]



[a] Bn = CH_2Ph. Reaction details: (a) **6** (1.3 equiv), *n*-BuLi (1.3 equiv), THF, −78 °C; **7**, −78 °C, 2.5 h, 85%; (b) $AgOSO_2CF_3$ (2.1 equiv), THF, 23 °C, 94%, **15** $[\alpha]^{22}_D$ −66.5° (*c* 2.2, $CHCl_3$); (c) TsOH (3 equiv), NaI (10 equiv), $(CH_2O)_n$ (5 equiv), 1:10 acetone–H_2O, 100 °C, 2 h, 81%; (d) *n*-BuLi (excess), THF, −78 → 23 °C; MeOH, 81%; Li (excess), NH_3, −78 °C, 3 min, 76%.

provide the desired (−)-alkyne **6** in 30% overall yield from alcohol **8**.

Addition of the alkynyllithium derivative of **6** to the α-benzyloxy aldehyde **7**[13] (THF, −78 °C) occurs in good yield with 4:1 selectivity (Scheme III). The sense of stereoselection was anticipated to arise from attack of the alkynyl nucleophile on the five-membered-ring lithium chelate of the carbonyl and ether oxygens of **7**. The resulting alcohol stereoisomers can be separated on silica gel to provide **13** and **14** in 68% and 17% yields, respectively. Although the corresponding alkynyldiisopropoxytitanium nucleophile[22] derived from **6** reacts with **7** with improved (>10:1) facial selectivity, the yield of this addition reaction is unacceptably low.[23] Treatment of **13** with AgOTf provides the cyclopentaoxazine **15** in high yield and sets the stage for the key cyclization step. Iodide-promoted cyclization of **15** occurs cleanly at 100 °C in acetone–H_2O in the presence of camphorsulfonic acid, with loss of the isopropylidene group, to afford alkylideneindolizidine **16** in 81% yield. No other stereoisomers were detected in the 500-MHz ^1H NMR spectrum of the cyclization product. Deiodination of **16**[14] followed by cleavage of the C(8) benzyl ether by careful treatment with Li–NH_3 at −78 °C provided (+)-allopumiliotoxin 339A (**1**) in 62% overall yield from **16**. Synthetic **1** was indistinguishable from an authentic sample[25] by TLC and 125-MHz ^{13}C NMR analysis. Of greatest significance, a 1:1 mixture of the synthetic and natural toxins is homogenous by 500-MHz ^1H NMR analysis in $CDCl_3$ and CD_3OD.[26] Synthetic (+)-allopumiliotoxin 339A shows optical rotations $[\alpha]^{23}_D$ +68.2° and $[\alpha]^{23}_{546}$ +90.0° (*c* 0.5, $CHCl_3$), while somewhat smaller rotations were measured for a small sample of the natural toxin: $[\alpha]^{22}_D$ +52.0° and $[\alpha]^{22}_{546}$ +75.0° (*c* 0.5, $CHCl_3$).

The most biologically active of the allopumiliotoxin A alkaloids, (+)-allopumiliotoxin 339A (**1**), has been prepared for the first time by total synthesis. The synthesis is reasonably direct and provides **1** in 16 steps and 15% overall yield from (*R*)-2-methyl-4-pentenol (**8**). The efficiency of the convergent strategy employed will for the first time allow practical access to natural and analogue allopumiliotoxins, thus greatly facilitating ongoing pharmacological studies in this area.

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Supplementary Material Available: Characterization data (IR, ^1H and ^{13}C NMR, [α], MS) for **10**, **12**, **6**, **13–16**, and **1** (5 pages). Ordering information is given on any current masthead page.

Structure of Centrally Bound *angular*-(Terphenylene)chromium Tricarbonyl

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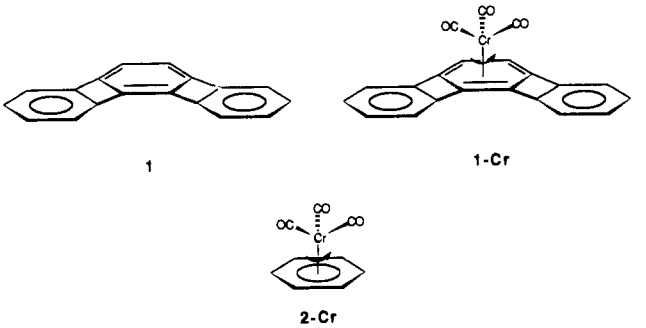
Conformational analysis, by extended Huckel methods, of the chromium tricarbonyl unit bound to cyclohexatriene and arenes with a dominant valence bond resonance form (e.g., naphthalene) reveals a *n*-octahedral geometry for the low-energy conformer.[2] The chromium tricarbonyl complex of *angular*-terphenylene (**1**) shows an unusually high barrier to rotation about the metal–arene bond.[3] This barrier and the chemical shifts of the ^{13}C carbonyl signals, under conditions of slow tripod rotation, support the assertion that **1**-Cr adopts an octahedral conformation in solution.



In the crystal structure of **1**-Cr[4] (Figure 1), the chromium

(22) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.
(23) The corresponding alkynylzinc reagent[24] was not sufficiently nucleophilic to add to the hindered aldehyde **6**.
(24) Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019.
(25) Kindly provided by Dr. John Daly.
(26) The ^1H NMR spectra of **1** is dramatically concentration dependent even in CD_3OD.

(1) (a) University of California, San Diego. (b) California State University, Northridge. (c) San Diego Supercomputer Center.
(2) (a) Albright, T. A.; Hofmann, P.; Hoffmann, R. *J. Am. Chem. Soc.* **1977**, *99*, 7546–57. (b) Albright, T. A. *Acc. Chem. Res.* **1982**, *15*, 149. (c) Rogers, R. D.; Atwood, J. L.; Albright, T. A.; Lee, W. A.; Rausch, M. D. *Organometallics* **1984**, *3*, 263.
(3) Nambu, M.; Siegel, J. S. *J. Am. Chem. Soc.* **1988**, *110*, 3675.

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Table I. Selected Internal Distances and Barrier to Rotation

	X-ray		LDF[a]			MMX/PI[b]			AM1[c]
	1[i]	**1**-Cr	**1**	**1**-Cr	**1**-Cr-ts[j]	**1**	**1**-Cr	**1**-Cr-ts[j]	**1**
C7–C8	1.353	1.383	1.366	1.389	1.403	1.374	1.371	1.371	1.349
C8–C9	1.440	1.440	1.428	1.442	1.428	1.449	1.447	1.446	1.450
C9–C10	1.353	1.373	1.366	1.391	1.403	1.374	1.371	1.371	1.349
C10–C17	1.448	1.462	1.449	1.463	1.448	1.444	1.441	1.441	1.501
C17–C18	1.345	1.368	1.354	1.367	1.385	1.352	1.350	1.350	1.329
C18–C7	1.449	1.465	1.449	1.464	1.448	1.444	1.441	1.441	1.501
av C=C	1.350	1.374	1.363	1.381	1.397	1.367	1.364	1.364	1.342
av C—C	1.446	1.456	1.442	1.456	1.441	1.446	1.443	1.443	1.484
Cr–mnpl[d]		1.700		1.678	1.652		1.738	1.718	
Cr–CO(av)		1.856		1.818	1.816		1.859	1.859	
barrier[e]	9.4[f] (8.3)[g]			6.7			−0.5[h]		

[a] Local density function theory, DMOL. [b] Empirical force field plus π calculation, PCMODEL. [c] Semiempirical theory, MOPAC. [d] Distance from Cr to best plane of the central ring carbon atoms in Å. [e] Barrier to rotation about the Cr–arene bond in kcal/mol. [f] Reference 3. [g] Value was redetermined (Nambu, M.; Siegel, J. S., unpublished results). [h] Wrong ground state. [i] Dierks, R.; Vollhardt, K. P. C. *Angew. Chem.* **1986**, *98*, 268. [j] Transition state.

adopts the predicted octahedral conformation; the three short bonds of the arene define one face of the octahedron, and the three carbonyls define the other. Compared to the uncomplexed arene one sees an elongation of the carbon–carbon bonds in the ring complexed to chromium, with the shorter bonds suffering a greater elongation. The distortions are similar to other chromium–arene[5] and chromium–cycloheptatriene[6] complexes but less drastic than those seen in Pt and Pd olefin complexes[7] (Table I).

Structures containing chromium group transition metals are notoriously difficult computational problems.[8] Comparison of the X-ray structures of **1** and **1**-Cr with ab initio, semiempirical quantum, and empirical/π calculated structures indicates that a high level of theory is necessary to obtain reliable geometric and energetic parameters.[9] Although a reasonable geometry is obtained with MMX calculations, the X-ray conformation is not the predicted ground state. On the basis of root mean square deviations between the predicted and experimental structural fragments,[13] local density functional (LDF) theory best predicts the structure for **1** and **1**-Cr.

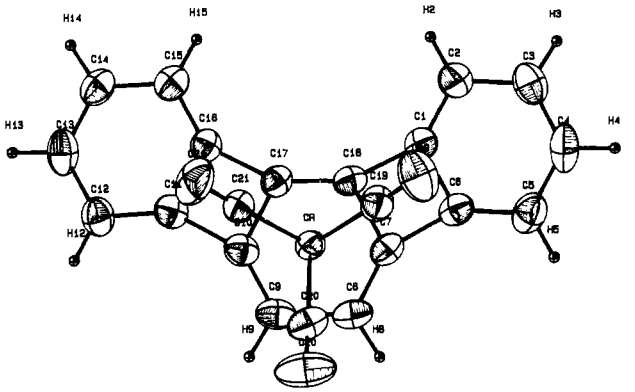

Figure 1. ORTEP representation of **1**-Cr.

LDF calculations show the same bond alternation seen in the X-ray of **1** and predict the differential bond lengthening found on comparison of the structures of **1** and **1**-Cr. Additionally the LDF structure for the transition state shows that elongation of the "double bonds" is more pronounced in the transition state concomitant with a contraction of the "single bonds".

An estimate of the barrier to rotation about the metal–arene bond comes from the difference in energy between the ground state (optimized X-ray structure) and the transition state (the structure with the tripod rotated by 60°, optimized in C_s symmetry). The LDF method predicts a barrier of 6.4 kcal/mol, in good agreement with the value of 9.4 kcal/mol found by NMR methods.[9] The MMX method gives a value close to 0.0 kcal/mol. Neither semiempirical nor pure ab initio methodologies suffice at this time; the former methods lack adequate parameters for chromium, and the latter are too formidable.

One of the early notions in theoretical structural organometallic chemistry was that metal–arene complexes would show significant bond alternation due to the energy gained by creating a formal octahedral field around the metal.[14,15] Although the molecular symmetry of (benzene)chromium tricarbonyl (**2**-Cr) permits such a distortion,[18] the room temperature structure of **2**-Cr showed no evidence for any such effect.[19] Reinvestigation of the structure at liquid nitrogen temperature using both X-ray[20] and neutron

(4) Crystal data: Room temperature data were collected on an orange crystal of **1**-Cr (0.27 × 0.13 × 0.08 mm from hexanes) using Mo Kα radiation (λ = 0.71073 Å). The crystal was monoclinic: a = 6.125 (2) Å, b = 7.251 (2) Å, c = 17.707 Å, β = 91.89 (3)°, V = 786 (1) Å^3, Z = 2. A total of 1625 reflections (maximum 2θ of 50°) were collected, on an Enraf-Nonius CAD4 diffractometer using the ω scan method, of which 1299 were considered observed ($F_o > 3\sigma(F_o)$). A secondary extinction correction was applied. Anomalous dispersion effects were included in F_c. The structure was solved in P21 with SHELXS-86 using the Patterson heavy atom method followed by successive difference Fourier syntheses and least-squares refinement (226 parameters, GOF = 1.13, R = 0.034, R_w = 0.041). Heavy atoms were refined anisotropically. Hydrogens were refined isotropically under riding-model constraints. The largest peak in the final difference Fourier had a height of 0.13 e/Å^3.

(5) Muetterties, E. L.; Bleeke, J. R.; Wucherer, E. J.; Albright, T. A. *Chem. Rev.* **1982**, *82*, 499.

(6) Reynolds, S. D.; Albright, T. A. *Organometallics* **1985**, *4*, 980–5.

(7) Lukehart, C. M. *Fundamental Transition Metal Organometallic Chemistry*; Brooks/Cole: Monterey, 1985; Chapter 5.

(8) Langhoff, S. R.; Bauschlicher, E. W., Jr. *Annu. Rev. Phys. Chem.* **1988**, *39*, 181–2.

(9) Calculations were done at several levels of theory using the following computational packages and techniques: DMOL (local density function theory);[10] MOPAC/AM1 (semiempirical theory);[11] PCMODEL/MMX (empirical force field–Huckel theory).[12]

(10) For further information on LDF theory, see: (a) DMOL: BIOSYM Technologies, Inc., 10065 Barnes Canyon Rd., Suite A, San Diego, CA 92121. (b) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864. (c) Kohn, W.; Sham. L. J. *Phys. Rev.* **1965**, *140*, A1133. (d) Wimmer, E.; Freeman, A. J.; Fu, C.-L.; Cao, P.-L.; Chou, S.-H.; Delley, B. In *Supercomputer Research in Chemistry and Chemical Engineering*; Jensen, K. F., Truhlar, D. G., Eds.; ACS Symposium Series 353; American Chemical Society: Washington, DC, 1987; Chapter 4. (e) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651.

(11) MOPAC: (a) Stewart, J. J. P. *Quantum Chem. Exchange Bull.* **1985**, *5*, 126, 133, QCPE Program 455, Version 5.01. (b) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Steward, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–9.

(12) PCMODEL: Serena Software, Box 3076, Bloomington, IN 47402-3076.

(13) Structural data manipulation and fragment comparison were done with MacMoMo, a crystallographic analysis program available from Prof. Max Dobler, Department of Organic Chemistry, ETH-Zurich.

(14) Ruch, E. *Elektronentheorie Homoopolaren Bindungen, Ber. Hauptjahestag. chem. Ges. Deut. Demokrat. Rep.*; Leipzig, 1955; pp 125–31.

(15) This concept in conjunction with conflicting X-ray results stimulated a discussion over whether the structure of bis(benzene)chromium had D_{3h}[16] or D_{6h}[17] symmetry.

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(17) (a) Weiss, E.; Fischer, E. O. *Z. Anorg. Allg. Chem.* **1956**, *286*, 142–5. (b) Cotton, F. A.; Dollase, W. A.; Wood, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1543–4. (c) Ibers, J. A. *J. Chem. Phys.* **1964**, *40*, 3129. (d) den Boer, D. H. W.; den Boer, P. C.; Longuet-Higgens, H. C. *Mol. Phys.* **1962**, *5*, 387–90.

(18) Fritz, H. P.; Manchot, J. *Spectrochim. Acta* **1962**, *18*, 171.

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.

Acknowledgment. We thank the National Science Foundation Presidential Young Investigator Award Program (CHE-8857812), the American Cancer Society Junior Faculty Fellowship Program (C-58024), and the donors of the Petroleum Research Fund (20776-G1), administered by the American Chemical Society, for support of this work. We greatly appreciate additional support of our program from Exxon, Hoffmann-La Roche, Rohm+Haas, Monsanto, Zambon, Sterling, and Eli Lilly. We thank the SDSC for a grant of supercomputer time.

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.

(19) (a) Corradini, P.; Allegra, G. *J. Am. Chem. Soc.* **1959**, *81*, 2271-2. (b) Bailey, M. F.; Dahl, L. F. *Inorg. Chem.* **1965**, *4*, 1314-9.

(20) (a) Rees, B.; Coppens, P. *J. Organomet. Chem.* **1972**, *42*, C102-5. (b) Rees, B.; Coppens, P. *Acta Crystallogr., Sect. B* **1973**, *B29*, 2516-28. (c) Wang, Y.; Angermund, K.; Goddard, R.; Kruger, C. *J. Am. Chem. Soc.* **1987**, *109*, 587-9.

(21) The recent NMR results reported by Mitchell et al.[22] on tricarbonylchromium dihydrobenzpyrene are equally well explained by assuming that the Cr tripod adopts a specific ground-state conformation and thereby alters the contribution from the various resonance forms of the dihydropyrene fragment. A more extensive study is forthcoming.[23]

(22) (a) Mitchell, R. H.; Zhou, P. Z.; Venugopalan, S.; Dingle, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 7812-3. (b) Mitchell, R. H.; Zhou, P. *Tetrahedron Lett.* **1990**, *31*, 5277-80.

(23) Nambu, M.; Hardcastle, K.; Baldridge, K. K.; Siegel, J. S., manuscript in preparation.

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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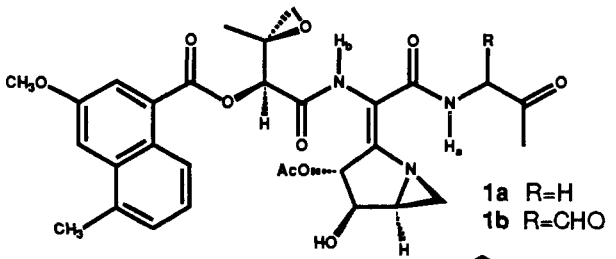
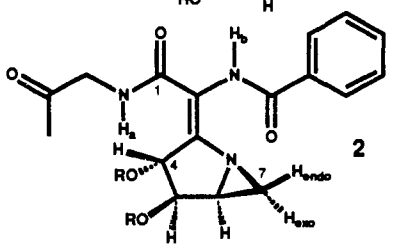
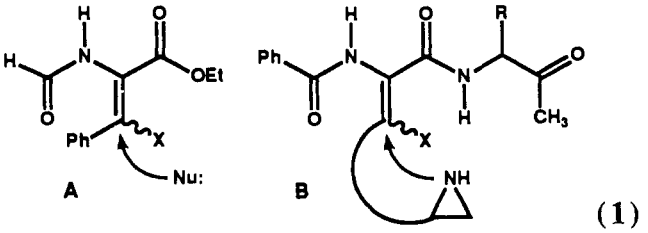
Received September 23, 1991

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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(3) (a) Bromination of acrylates and subsequent addition of ethylenimine has afforded vinyl aziridines with retention of geometric configuration with respect to the starting vinyl halide: Truce, W. E.; Gobarty, M. L. *J. Org. Chem.* **1970**, *35*, 2113. (b) Nucleophilic vinylic substitution of β-bromo α,β-unsaturated esters and nitriles under analogous conditions also affords vinyl aziridines in high yields and similar stereoselectivity: De Ancos, B.; Maestro, M. C.; Martin, M. R.; Farinza, F. *Synthesis* **1988**, 136.

(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.

0002-7863/92/1514-371$03.00/0