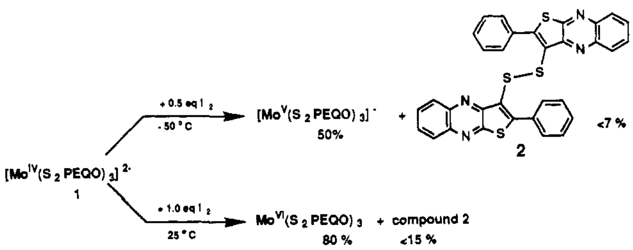
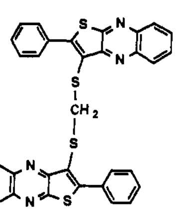
compounds, a third product, compound **2**, was isolated from I_2 oxidation. **2** is yellow and has an infrared spectrum very similar to that of the S_2PEQO dithiolene ligand, but it contains no molybdenum. The ^1H NMR spectrum of **2** shows that all protons of S_2PEQO are intact with the exception of H3.[16] This information led us to speculate that compound **2** was a thiophene derivative of the $[S_2PEQO]^{2-}$ ligand, a hypothesis proven correct by an X-ray crystal structure analysis.[17]



A view of the molecular structure of 2-phenylthieno[2,3-*b*]quinoxaline **2** in Figure 1 reveals the fate of S_2PEQO ligand oxidation. A thiophene ring fused to quinoxaline is formed from cyclization of the β-thiolate at quinoxaline C3. Oxidation of the α-thiolate causes formation of a disulfide bond to a second quinoxalylthiophene moiety. A crystallographic C_2 axis passes through the midpoint of the disulfide bond and relates one quinoxalylthiophene plane to its molecular partner. Bond distances and angles within this molecule are unremarkable since they reproduce values previously reported.[18]

Compound **2** is obtained from **1** using a variety of oxidants (I_2, Ce^{IV}, O_2, and S_8) as well as from solutions of the Mo(V) and Mo(VI) tris(dithiolene) complexes after long exposure to the atmosphere. In fact, we have not yet accomplished an oxidation of $[TEA]_2[Mo(S_2PEQO)_3]$ that does not yield some of compound **2**. Our continued study of these reactions seeks to determine if formation of **2** proceeds through a particular Mo oxidation state and if quinoxaline N-coordination aids a dithiolene cis–trans isomerization that must precede thiophene ring closure.

A second degradation product, compound **3**, has been obtained in small amounts from recrystallization attempts using impure Mo (quinoxalyl)dithiolene complexes. Our preliminary[19] report on this material presents its structure determinated from ^1H and ^{13}C NMR and X-ray analysis. As depicted schematically, **3** is also a thiophene derivative of quinoxaline wherein the exocyclic sulfur is bridged to a second (3-thiothieno)quinoxaline by a methylene group.



3

Decomposition products **2** and **3** isolated from Mo complexes having S_2PEQO dithiolene ligands demonstrate for the first time that thiophene cyclization is a likely decomposition result from such dithiolene complexes. The isolation of both the disulfide-bridged and the S-alkylated products indicates multiple decomposition pathways as has been observed for Mo-co decomposition leading to two fused pterin thiophene compounds, urothione and form B. These results provide the needed experimental support to link the known structures of urothione and form B to the proposed pterinyldithiolene unit in Mo-co.

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Registry No. 1, 137516-72-4; **2**, 137516-68-8; **3**, 137516-69-9; PEQO, 75163-23-4; $[TEA]_2[Mo(S_9)]$, 76581-48-1; $[TEA][Mo^V(S_2PEQO)_3]$, 137516-74-6; $Mo^{VI}(S_2PEQO)_3$, 137516-75-7.

Supplementary Material Available: Listings of analytical and physical properties, crystallographic collection and solution data, atom positions, thermal parameters, and bond distances and angles for **2** (5 pages); tables of observed and calculated structure factors for **2** (19 pages). Ordering information is given on any current masthead page.

(16) ^1H NMR in $CDCl_3$ (δ, ppm) 8.06 (m, 2 H) and 7.78 (m, 2 H) (quinoxaline); 7.36 (m, 2 H), 7.00 (m, 2 H), and 6.92 (m, 1 H) (phenyl).

(17) Crystals of compound **2** possess an orthorhombic cell in space group *Pbcn* ($Z = 4$) with parameters $a = 14.93$ (7) Å, $b = 12.50$ (8) Å, $c = 14.07$ (7) Å for a volume of 2627.4 Å^3. Using 1893 data where $I > 3\sigma(I)$ for 182 variables, refinement produced final agreement factors $R_1 = 0.037$ and $R_2 = 0.052$. Details are in the supplementary material.

(18) (a) Gronowitz, S. *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley-Interscience: New York, 1991; Vol. 44, Part 4, pp 31–37. (b) Barlin, G. *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley-Interscience: New York, 1982; Vol. 41, p 8.

(19) Formation of compound **3** is currently under study to duplicate its production from deliberate decomposition of $Mo(S_2PEQO)_3$ complexes. Physical details (^1H and ^{13}C NMR data, UV spectral data, and preliminary X-ray parameters) are available in the supplementary material.

Novel Enediynes Equipped with Triggering and Detection Devices. Isolation of *cis*-Diol Models of the Dynemicin A Cascade

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The discovery of the enediyne anticancer antibiotics[1] (e.g., neocarzinostatin chromophore,[2] calicheamicin γ_1^{I},[3] esperamicin A,[4] dynemicin A[5]) with their novel molecular structures, fascinating mode of action, and important biological activity sparked a great deal of excitement and research in the areas of chemistry, biology, and medicine.[1] Reports from these laboratories included the first designed mimics[6] of these enediyne natural products and the design and synthesis of a series of dynemicin A models equipped with acid, base, and photosensitive triggering devices[7,8]

(1) For a review, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.*, in press.

(2) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 331.

(3) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

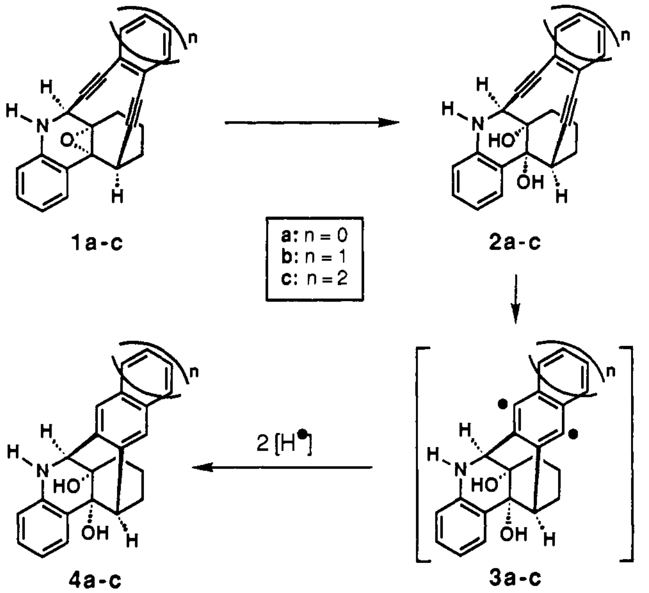
(4) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(5) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. Konishi, M.; Ohkuma, H.; Tsuno, Y.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.

(6) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866. Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247.

(7) (a) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (b) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106. For related synthetic studies in the dynemicin A area, see: (c) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (d) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. (e) Magnus, P.; Fortt, S. M. *J. Chem. Soc., Chem. Commun.* **1991**, 544. (f) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (g) Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chem. Lett.* **1991**, 1271.

Scheme I. Designed Enediynes with Tamed Reactivity and Detection Devices

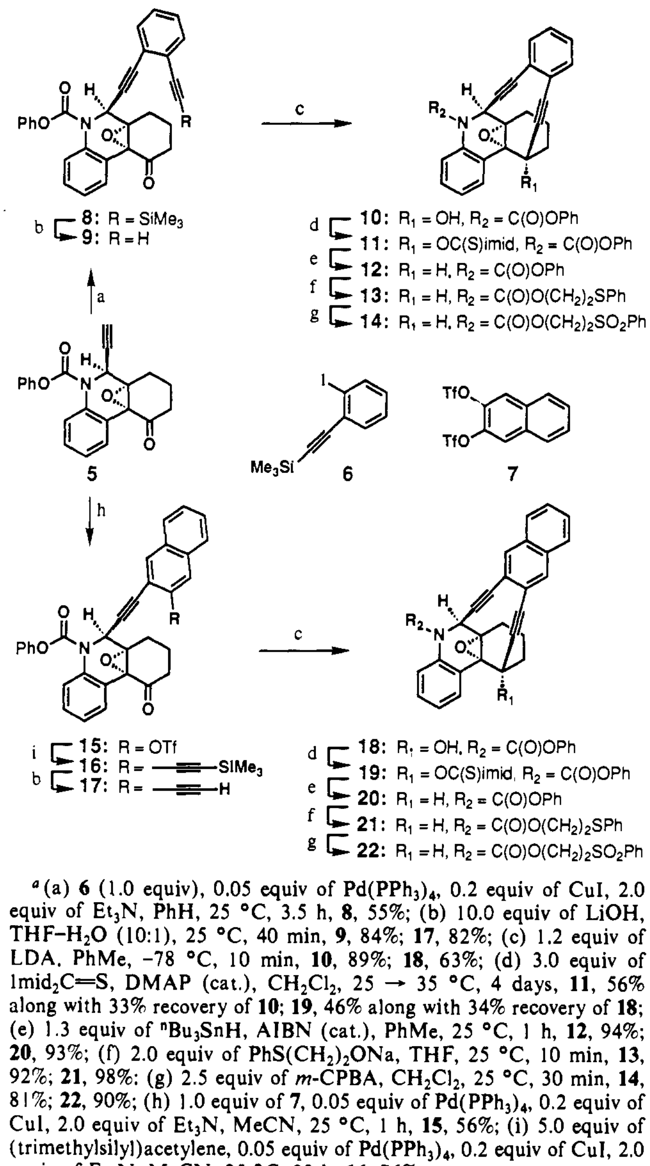


as chemical "warheads".[6] In this communication we report the design and synthesis of two novel series of enediyne systems equipped with such triggering devices and which, in addition, carry functionality that allows their detection by UV and/or fluorescent spectroscopy prior to and/or after the Bergman cycloaromatization.[9] Furthermore, we report the first isolable *cis*-diol models of the dynemicin A cascade.[5,8]

The enediyne systems reported herein were designed for their chemical, spectroscopic, and biological profiles based on the following considerations. Since the parent compound **1a** (Scheme I) was found to be highly reactive,[7b,8] rapidly undergoing the Bergman cyclization through the nonisolable *cis*-diol **2a**, a device was sought to tame its reactivity in the hope that cis-opened systems of type **2a** may be isolated and thereby provide support for the proposed dynemicin A cascade.[5,8] Recalling the resonance energies of benzene (36 kcal/mol), naphthalene (61 kcal/mol), and anthracene (84 kcal/mol), the conjecture was made that compounds **2b** and **2c** should be less reactive than **2a** toward cycloaromatization. Furthermore, these compounds, particularly **2c**, would lead upon cycloaromatization to highly chromophoric systems that should be easily detectable by spectroscopic means.

The synthesis of the titled compounds proceeded as summarized in Scheme II. Thus, coupling of the readily available compounds **5**[7a,b] and **6**[11] using palladium(0)–copper(I) catalysis afforded product **8** in 55% yield. Desilylation of **8** followed by base-induced ring closure led to **10** via **9** (75% overall yield). Conversion of **10** to the thionoimidazolide **11** (84% based on 67% conversion of starting material) followed by deoxygenation with $^nBu_3SnH$ resulted in the formation of **12** (94%). Exchange of the PhO group of **12** with $PhSCH_2CH_2O$ took place smoothly under basic conditions, leading to **13** (92% yield), from which the sulfone **14** was generated by oxidation using *m*-chloroperbenzoic acid (81%). Similar chemistry employing the naphthalene ditriflate **7** led to naphthalene diynes **18–22** via intermediates **15–17** in comparable yields as outlined in Scheme II.

Scheme II. Synthesis of Novel Enediynes[a]



[a] (a) **6** (1.0 equiv), 0.05 equiv of $Pd(PPh_3)_4$, 0.2 equiv of CuI, 2.0 equiv of Et_3N, PhH, 25 °C, 3.5 h, **8**, 55%; (b) 10.0 equiv of LiOH, THF–H_2O (10:1), 25 °C, 40 min, **9**, 84%; **17**, 82%; (c) 1.2 equiv of LDA, PhMe, –78 °C, 10 min, **10**, 89%; **18**, 63%; (d) 3.0 equiv of $Imid_2C{=}S$, DMAP (cat.), CH_2Cl_2, 25 → 35 °C, 4 days, **11**, 56% along with 33% recovery of **10**; **19**, 46% along with 34% recovery of **18**; (e) 1.3 equiv of $^nBu_3SnH$, AIBN (cat.), PhMe, 25 °C, 1 h, **12**, 94%; **20**, 93%; (f) 2.0 equiv of $PhS(CH_2)_2ONa$, THF, 25 °C, 10 min, **13**, 92%; **21**, 98%; (g) 2.5 equiv of *m*-CPBA, CH_2Cl_2, 25 °C, 30 min, **14**, 81%; **22**, 90%; (h) 1.0 equiv of **7**, 0.05 equiv of $Pd(PPh_3)_4$, 0.2 equiv of CuI, 2.0 equiv of Et_3N, MeCN, 25 °C, 1 h, **15**, 56%; (i) 5.0 equiv of (trimethylsilyl)acetylene, 0.05 equiv of $Pd(PPh_3)_4$, 0.2 equiv of CuI, 2.0 equiv of Et_3N, MeCN, 25 °C, 20 h, **16**, 76%.

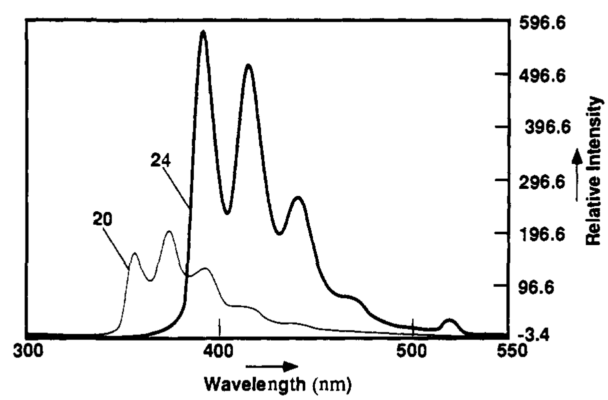


Figure 1. Fluorescence spectra of arene diyne **20** and cycloaromatization product **24**. Spectra were recorded in EtOH (1 μM) at 25 °C, excitation at 260 nm.

The cycloaromatization of enediynes **12** and **20** was then studied in order to determine the precise structural and spectroscopic changes taking place. Thus, whereas cycloaromatization of **12** (ca. 0.02 M solution) under acidic conditions (1.2 equiv of $TsOH{\cdot}H_2O$, benzene–cyclohexadiene = 4:1, 25 °C, 4 h) produced smoothly the corresponding naphthalene derivative **23** in 78% yield, no dramatic changes in the UV and fluorescent spectra were

(8) Nicolaou, K. C.; Dai, W.-M.; Wendeborn, S. V.; Smith, A. L.; Torisawa, Y.; Maligres, P.; Hwang, C.-K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1032.

(9) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091.

(10) For previous examples of arene diynes and their cycloaromatizations, see: (a) Darby, N.; Kim, C. V.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. *Chem. Commun.* **1971**, 1516. (b) Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217.

(11) Compound **6** was prepared from 1,2-diiodobenzene and (trimethylsilyl)acetylene by a standard Pd(0)–Cu(I) catalyzed coupling reaction.

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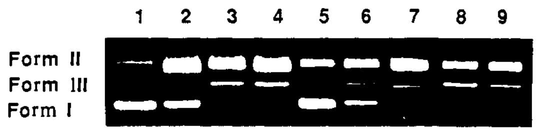
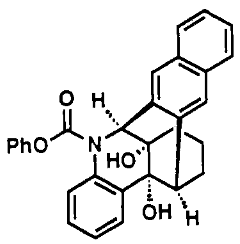


Figure 2. Supercoiled DNA interaction with selected model compounds. ΦX174 DNA was incubated for 48 h at 37 °C with compounds **14**, **1b**, **2b**, **22**, **1c**, **2c**, **1a**, and A (the corresponding N-protected sulfone of **1a**) in buffer (50 mM Tris·HCl, pH 8.5) and analyzed by electrophoresis (1% agarose gel, ethidium bromide stain). Lane 1: DNA control. Lane 2: **14** [10.0 mM]. Lane 3: **1b** [10.0 mM]. Lane 4: **2b** [10.0 mM]. Lane 5: **22** [10.0 mM]. Lane 6: **1c** [10.0 mM]. Lane 7: **2c** [10.0 mM]. Lane 8: **1a** [0.1 mM]. Lane 9: A [1.0 mM]. Key: I, form I DNA; II, form II DNA; III, form III DNA.

observed for the starting benzene diyne (**12**) and cycloaromatized product (**23**). In contrast, however, the naphthalene diyne **20** produced, upon acid-induced Bergman cycloaromatization, the anthracene derivative **24** (49% yield), which exhibited, as expected, strong and characteristic UV and fluorescence profiles. These profiles were distinct from those of its precursor [UV (EtOH), **20**, λ_{max} (log ϵ) 304 (3.47), 294 (4.01), 284 (4.26), 267–240 (4.53–4.55), 214 (4.50) nm; **24**, λ_{max} (log ϵ) 390 (3.74), 369 (3.78), 351 (3.66), 333 (3.45), 318 (3.20), 267–244 (4.43–4.46), 215 (4.43) nm; fluorescence (EtOH, 1 μM, excitation at 260 nm), **20**, λ_{max} 435, 412, 393, 374, 357 nm; **24**, λ_{max} 520, 466, 442, 413, 392 nm, see Figure 1]. Figure 1 shows the fluorescence spectra of **20** and **24**, demonstrating the striking and potentially useful differences between the arene diyne **20** and its Bergman cyclization product **24**.



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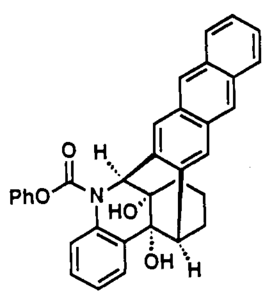

24

Epoxides **1b** and **1c** (Scheme I) were generated from their corresponding precursors **14** and **22** by treatment with DBU in benzene, and although rather labile, they exhibited enhanced stability relative to the parent epoxide **1a**.[7b] Treatment of **1b** and **1c** with silica gel in wet benzene led smoothly to the *cis*-diols **2b** and **2c**. The benzene diyne **2b** was stable enough to be detected by TLC and ^{1}H NMR spectroscopy but cyclized readily on standing at ambient temperatures [half-life ($t/2$) in THF-d_8 at 20 °C, ca. 2.5 h]. On the other hand, the naphthalene diyne **2c** exhibited enhanced stability compared to **2b** and could be purified by chromatography and characterized by the usual means. Its half-life ($t/2$) in THF-d_8 at 37 °C was determined by ^{1}H NMR spectroscopy to be ca. 44 h. Thus, the energy gains in forming the cycloaromatized products from these (ar)enediynes were approximately reflected in their observed rates of cyclization.

Compounds **1b**, **1c**, **2b**, **2c**, **14**, and **22** exhibited significant DNA-cleaving activity when incubated with supercoiled ΦX174 at pH 8.5 at 37 °C (Figure 2). Noteworthy in these experiments is the diminished activity of these arene diynes toward DNA relative to the enediyne **1a**, which is in line with their chemical and steric profiles. Compounds **14** and **22** exhibited potent anticancer activities against a variety of cell lines such as Molt-4 leukemia [IC_{50} ca. 10^{-7} M for **14** and IC_{50} ca. 10^{-8} M for **22**].[12]

The described designed molecules or modified analogues may serve as tools in following the reactions and distributions of enediyne-type agents both in vitro and in vivo. In addition, modulation of the enediyne reactivity toward Bergman cyclization allowed for the first time the isolation of *cis*-diol systems of the dynemicin A type. Finally, the powerful anticancer properties of these systems endow them with considerable therapeutic potential.

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Supplementary Material Available: A listing of selected spectroscopic data for compounds **1b**, **1c**, **2b**, **2c**, **12**, **14**, **20**, **22**, **23**, and **24** (7 pages). Ordering information is given on any current masthead page.

(12) We thank Dr. W. Wrasidlo of The Scripps Research Institute for these assays.

Organosamarium-Mediated Synthesis of Bismuth Bismuth Bonds: X-ray Crystal Structure of the First Dibismuth Complex Containing a Planar $M_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}Bi_2)$ Unit

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Increased interest in p-block chemistry in the past few years has led to many advances in the synthesis and reaction chemistry of main-group elements and complexes. One of the more challenging synthetic problems in this area is the controlled construction of molecules containing bonds between the heavier p-block elements, which have lower bond strengths than their lighter congeners. For example, in group 15, RE=ER compounds (E = P, As, Sb, Bi) containing unsupported multiple bonds are known for phosphorus and arsenic,[1] but analogous antimony and bismuth species have been observed only when stabilized by transition-metal carbonyl anions.[2–8] Compounds containing E–E single bonds involving the heavier congeners in group 15 are known, but can be accessed by only a few synthetic routes: by reduction of the elements to form Zintl ions,[9,10] by incorporation into transition-metal carbonyl clusters,[11–14] and by reduction of R_3E and R_2EX

(1) Cowley, A. H.; Norman, N. C. *Prog. Inorg. Chem.* **1986**, *34*, 1–63.
(2) Huttner, G.; Weber, U.; Sigwarth, B.; Scheidsteger, O. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 215–216.
(3) Huttner, G.; Weber, U.; Zsolnai, L. *Z. Naturforsch.* **1982**, *37b*, 707–710.
(4) Plössl, K.; Huttner, G.; Zsolnai, L. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 446–447.
(5) Clegg, W.; Compton, N. A.; Errington, R. J.; Norman, N. C. *Polyhedron* **1988**, *7*, 2239–2241.
(6) Arif, A. M.; Cowley, A. H.; Norman, N. C.; Pakulski, M. *J. Am. Chem. Soc.* **1985**, *107*, 1062–1063.
(7) Weber, U.; Huttner, G.; Scheidsteger, O.; Zsolnai, L. *J. Organomet. Chem.* **1985**, *289*, 357–366.
(8) Arif, A. M.; Cowley, A. H.; Norman, N. C.; Pakulski, M. *Inorg. Chem.* **1986**, *25*, 4836–4840.
(9) Critchlow, S. C.; Corbett, J. D. *Inorg. Chem.* **1984**, *23*, 770–774.
(10) Corbett, J. D. *Chem. Rev.* **1985**, *85*, 383–397.
(11) Whitmire, K. H.; Raghuveer, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 2778–2780.
(12) Whitmire, K. H.; Churchill, M. R.; Fettinger, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 1056–1057.
(13) Ang, H. G.; Hay, C. M.; Johnson, B. F. G.; Lewis, J.; Raithby, P. R.; Whitton, A. J. *J. Organomet. Chem.* **1987**, *330*, C5–C11.
(14) Martinengo, S.; Ciani, G. *J. Chem. Soc., Chem. Commun.* **1987**, 1589–1591.

0002-7863/91/1513-9880$02.50/0