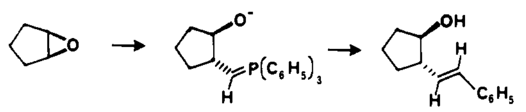
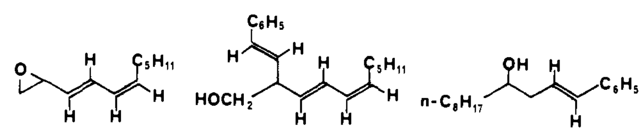


10 11

11 in 65% yield. The selective formation of the trans double bond in **11** is due to the presence of the basic γ-oxido group in **10** and was expected on the basis of previously described reactions of γ-oxido ylides with aldehydes.[7] In contrast to these results with **2**, coupling of cyclopentene oxide and methylenetriphenylphosphorane was unsuccessful even under forcing conditions (50 °C, THF). The conversion of cyclopentene oxide to **11** represents a powerful synthetic construction in that two carbon-carbon bonds, and also three stereocenters are formed in the process. Such a method is potentially well suited for the synthesis of complex trans-homoallylic alcohols, for instance, the macrodiylide asplasmomycin.[8]

Two other examples of the coupling of an epoxide, lithio ylide **2**, and an aldehyde were also investigated. Reaction of the epoxide **12**[9] with **2** (−78 to 25 °C over 2 h and 25 °C for 18 h) followed



12 13 14

by treatment with benzaldehyde (25 °C for 4 h) furnished the triene **13** as major product. In a similar way, the homoallylic alcohol **14** was obtained from 1-decene oxide, lithio ylide **2**, and benzaldehyde in good yield.

A number of other applications of α-lithiated alkylidenetriphenylphosphoranes are now under investigation in our laboratories with special emphasis on new methods for the joining of three components with the formation of two carbon-carbon linkages in one operation. Our work on lithiated ylides complements recent studies on various dicarbanionic species including doubly deprotonated nitro compounds[10] and carbonyl compounds.[11-19] These classes of enhanced carbon nucleophiles provide synthetic capabilities going far beyond those available from conventional reagents.[20]

Registry No. 1, 3487-44-3; **2**, 82537-28-8; **3**, 1195-79-5; **4**, 13567-57-2; **5**, 62668-02-4; **6**, 82537-29-9; **8**, 614-47-1; **10**, 82537-30-2; **11**, 82537-31-3; **12**, 82537-32-4; **13**, 82537-33-5; **14**, 82537-34-6; benzaldehyde, 100-52-7; hexanal, 66-25-1; cyclopentene oxide, 285-67-6; methyltriphenylphosphonium bromide, 1779-49-3; 1-decene oxide, 2404-44-6.

(7) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 790.

(8) (a) Okami, Y.; Okazaki, T.; Kitahara, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 1019. (b) Nakamura, H.; Jitaka, Y.; Kitahara, T.; Okazaki, T.; Okami, Y. *Ibid.* **1977**, *30*, 714.

(9) Corey, E. J.; Kang, J. *J. Am. Chem. Soc.* **1981**, *103*, 4618.

(10) Lehr, F.; Gounermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258 and references cited therein.

(11) Stowell, J. C. "Carbanions in Organic Synthesis"; Wiley: New York, 1979.

(12) Hubbard, J. S.; Harris, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 2110 and references cited therein.

(13) Kawalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 1777.

(14) Cooke, M. P., Jr. *Tetrahedron Lett.* **1981**, *22*, 381 and references cited therein.

(15) Seebach, D.; Pohmakotr, M. *Tetrahedron* **1981**, *37*, 4047.

(16) Adlington, R. M.; Barrett, A. G. M. *Tetrahedron* **1981**, *37*, 3935.

(17) Goswami, R.; Corcoran, D. E. *Tetrahedron Lett.* **1982**, *23*, 1463.

(18) Bilyard, K. G.; Garrett, P. J. *Tetrahedron Lett.* **1981**, *22*, 1755.

(19) Broquet, C. *Tetrahedron* **1975**, *31*, 1331.

(20) This research was assisted financially by a grant from the National Science Foundation.

An Intramolecular Diels-Alder Reaction of an Isobenzofuran: A Convergent Synthesis of Resistomycin

B. A. Keay

Department of Chemistry, University of Waterloo
Waterloo, Ontario N2L 3G1, Canada

R. Rodrigo*

Department of Chemistry, Wilfrid Laurier University
Waterloo, Ontario N2L 3C5, Canada

Received May 14, 1982

The gram-positive antibiotic Resistomycin, first isolated[1] from *Streptomyces resistomycificus* by Brockman and Schmidt-Kastner in 1951, was assigned[2,3] the pentacyclic phenalenone structure **1** (Chart I) in 1968. Despite sporadic synthetic forays[4,5] in the intervening years, Resistomycin has not yet been synthesized. Our experience[6] with the use of isobenzofurans as dienes in natural product synthesis led us to explore their applicability in the intramolecular Diels-Alder reaction.[7] A synthesis of Resistomycin is a particularly rigorous test of this idea, for if the complex, highly functionalized isobenzofuran **2** can be elaborated and employed in such a manner, the technique will not only provide a facile route to the antibiotic but also have wider implications for easy synthetic access to a variety of condensed aromatics and hydroaromatic systems. We now report the successful execution of this plan and the first synthesis of Resistomycin.

Our methods of in situ isobenzofuran generation, previously defined,[8] demanded that the precursors of **2** be the two aldehydes **3** and **4**, the former corresponding to carbon atoms 6-10 and the C_9-methyl group and the latter comprising the rest of the Resistomycin molecule. A brief synthesis of **3** was developed[9] from 3,4-dimethylphenol (**5**). Methoxymethylation of **5** was followed by regiospecific deprotonation[10] with *tert*-butyl-lithium and treatment with diethylcarbamoyl chloride to provide **6** exclusively. Hydrolysis and methylation produced **7**, which was oxidized with complete regiospecificity[11] at the C_4-methyl group by ceric ammonium nitrate to **3**. The overall yield for the transformation of **5** to **3** was 72%.

A convergent synthesis of the acetylenic aldehyde **4** was un-

(1) Brockmann, H.; Schmidt-Kastner, G. *Naturwissenschaften* **1951**, *20*, 479.

(2) Brockmann, H.; Reschke, T. *Tetrahedron Lett.* **1968**, 3167. Brockmann, H.; Meyer, E.; Schrempp, K.; Reiners, F.; Reschke, T. *Chem. Ber.* **1969**, *102*, 1224.

(3) Bailey, N. A.; Falshaw, C. P.; Ollis, W. D.; Watanabe, M.; Dhar, M. M.; Khan, A. W.; Vora, V. C. *J. Chem. Soc., Chem. Commun.* **1968**, 374.

(4) Kingston, J. F.; Weiler, L. *Can. J. Chem.* **1977**, *55*, 785.

(5) James, K.; Raphael, R. A. *Tetrahedron Lett.* **1979**, 3895.

(6) Rajapaksa, D.; Rodrigo, R. *J. Am. Chem. Soc.* **1981**, *103*, 6208. Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538. de Silva, S. O.; St. Denis, C.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 995. Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *Ibid.* **1980**, 354.

(7) Intramolecular Diels-Alder reactions of isobenzofurans have not been recorded in the literature. The first report of such a reaction with an isoindole has recently appeared. Ciganek, E. *J. Org. Chem.* **1980**, *45*, 1512.

(8) Keay, B. A.; Lee, D. K. W.; Rodrigo, R. *Tetrahedron Lett.* **1980**, 3663.

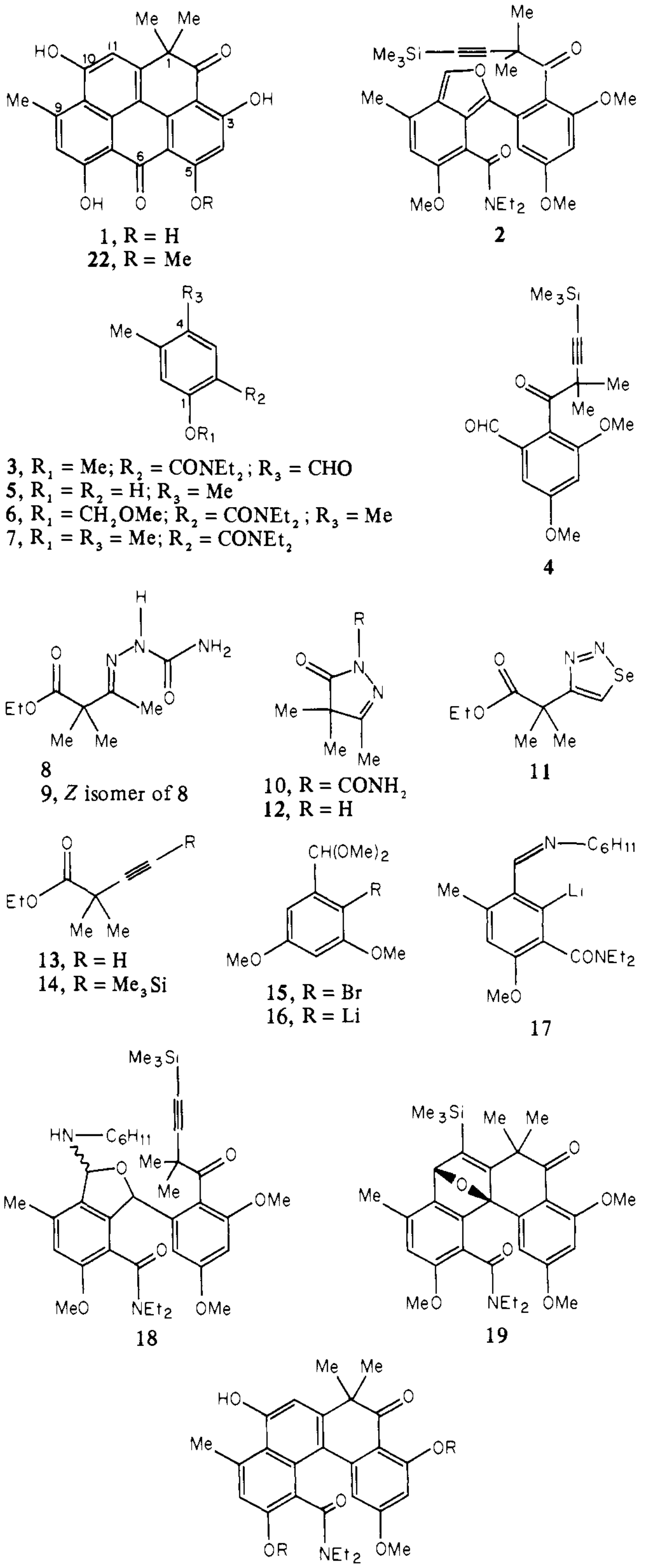
(9) An existing synthesis of the carboxylic acid corresponding to **3** was not efficient enough for our purposes. Meldrum, A. N.; Alimchandani, R. I. *J. Indian Chem. Soc.* **1929**, *6*, 253. **3**: bp 169-172 °C (1 mmHg); ν_{max} 1695, 1635 cm^{-1}; NMR ($CDCl_3$) δ 10.13 (s, 1 H), 7.67 (s, 1 H), 6.77 (s, 1 H), 3.9 (s, 3 H), 3.57 and 3.15 (q, 2 H each), 2.69 (s, 3 H), 1.25 and 1.05 (t, 3 H each, J = 7.0 Hz); M^+ 249 (11), 248 (9), 177 (100).

(10) Christensen, H.; *Synth. Commun.* **1975**, *5*, 65. Ronald, R. C. *Tetrahedron Lett.* **1975**, 3973.

(11) Oxidation of **7** to **3** was accomplished with 4 equiv of ceric ammonium nitrate in aqueous acetic acid at 0 °C for 1 h. The oxidation of aryl methyl groups to aryl aldehydes is believed to occur in four stages, each requiring 1 equiv of Ce^{IV} ion (Richardson, W. H. "Oxidation in Organic Chemistry"; Wiberg, K. B., Ed.; Academic Press: New York, 1965; part A, p 271). Our choice of this reagent was prompted by the expectation that a *p*-methoxy substituent would favor oxidation at the C-4 methyl group by stabilizing radical or cationic intermediates in the usual manner.

0002-7863/82/1504-4725$01.25/0 © 1982 American Chemical Society

Chart I



1, R = H
22, R = Me
2
3, R_1 = Me; R_2 = $CONEt_2$; R_3 = CHO
5, R_1 = R_2 = H; R_3 = Me
6, R_1 = CH_2OMe; R_2 = $CONEt_2$; R_3 = Me
7, R_1 = R_3 = Me; R_2 = $CONEt_2$
4
8
9, *Z* isomer of 8
10, R = $CONH_2$
12, R = H
11
13, R = H
14, R = Me_3Si
15, R = Br
16, R = Li
17
18
19
20, R = Me
21, R = H

dertaken. Ethyl acetoacetate was sequentially dimethylated and converted to its semicarbazone **8**. Mother liquors from crystallization of the latter showed (^{1}H NMR) the presence of its *Z*-isomer **9** and the pyrazolone **10**. Treatment of **8** with selenium dioxide in glacial acetic acid[12] provided the selenadiazole **11** and the pyrazolone **10** in equal proportions. After separation, **11** upon brief pyrolysis and distillation gave the desired acetylene **13**[13] which was silylated to **14**.[14] Bromination of 3,5-dimethoxybenzaldehyde and conversion to its dimethyl acetal[15] **15** was followed by metal-halogen exchange with *n*-butyllithium at 0 °C. The lithiated acetal **16**, upon treatment with **14** and subsequent mild acid hydrolysis produced the desired aldehyde **4**.[16]

Convergence of pathways leading to **3** and **4** was now effected by conversion of the aldehyde **3** to its cyclohexylimine and subsequent regiospecific deprotonation between the two ortho-directing groups—the imine[17] and the amide.[18] The resulting lithiated species **17** reacted with **4** to yield[19] the vital intermediate **18**, which is the immediate precursor of isobenzofuran **2**. Our choice of the cyclohexylimine as a masking and directing group was dictated by the need to provide a site for cyclization of the lithium alkoxide formed in the reaction, thus forestalling a possible disastrous alternative: cyclization with the adjacent amide to form a phthalide. When **18** was subjected to the mildly acidic conditions[20] necessary for isobenzofuran generation, the crucial Diels–Alder reaction was realized, and the bridged adduct **19** crystallized in 60% yield. Desilylation and aromatization proceeded smoothly to **20**, which was demethylated to **21** and cyclized[21] to monomethyl Resistomycin **22**. However, **19** (and **22**) may be directly converted into Resistomycin by reaction with pyridinium hydrochloride.[22] This "one-pot" sequence of desilylation, aromatization, demethylation, and cyclization of **19** occurs in a remarkable yield of 84%. Overall, our synthesis provides Resistomycin[23] in 20% yield (from **5**) and clearly demonstrates the feasibility of in situ isobenzofuran generation and its great utility in organic synthesis.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada, Wilfrid Laurier University, and the University of Waterloo for support of this work. We also acknowledge the contributions of B. Kosugi and P. Hubber, who carried out exploratory work on the synthesis of **3** and **13**. We thank Dr. W. G. Rosenbrook and Abbott Laboratories for a sample of natural Resistomycin.

(12) Lalezari, I.; Shafiee, A.; Yalpani, M. *J. Org. Chem.* **1971**, *36*, 2836. For a recent study of *Z*/*E* isomerism in semicarbazones see: Zimmer, O.; Meier, H. *Chem. Ber.* **1981**, *114*, 2938.

(13) Alternative syntheses of **13** and the corresponding acid are available. Tokuda, M.; Nishio, O. *J. Chem. Soc., Chem. Commun.* **1980**, 188. Schexnayder, M. A.; Engel, P. S. *J. Am. Chem. Soc.* **1975**, *97*, 4825.

(14) Overall yield of **14** from ethyl acetoacetate was 22.6%. In spite of the diminished yield, a consequence of pyrazolone (**10**) formation, this sequence was preferred for its convenience and adaptability to large-scale operation. The structure of **10** was established by pyrolysis to **12**, which was prepared by treatment of ethyl α,α-dimethylacetoacetate with hydrazine.

(15) Bromination with bromine in glacial acetic acid at 5 °C, also gave a small amount of the 2,6-dibromo derivative. Acetal formation was accomplished with trimethyl orthoformate, methanol, and Dowex-W50-X8.

(16) Overall from 3,5-dimethoxybenzaldehyde in 43% yield of **4**: bp 126–128 °C (0.03 mm Hg); ν_{max} 2120, 1705, 1695 cm^{-1}; NMR ($CDCl_3$) δ 9.85 (s, 1 H), 6.98 and 6.7 (d, 1 H each, J_{meta} = 2.3 Hz), 3.88 and 3.82 (s, 3 H each), 1.53 (s, 6 H), –0.04 (s, 9 H); M^+ 332 (3), 193 (100).

(17) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.

(18) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34.

(19) Lithiated at –78 °C by the addition of *sec*-butyllithium to a solution of the imine and TMEDA in THF. After 10 min. the aldehyde **4** was added and the mixture allowed to come to –50 °C over 1.5 h. Chromatography (silca gel; ethyl acetate, ligroin (7:3)) separated the unreacted starting materials and gave a 60% yield of **18**, which could not be crystallized. Its ^{1}H NMR spectrum was very complex, presumably because of amide tautomerism and the existence of diastereomers in the benzo[*c*]furan system. Mass spectral data: (chemical ionization) $[M + 1]^{+\cdot}$ 663 (12), $[M + 1 - C_6H_{11}NH_2]^{+\cdot}$ 564 (100), $[M - CMe_2C{\equiv}C - Me_3Si]^+$ 523 (20); (electron impact) $[M - C_6H_{11}NH_2]^{+\cdot}$ 563 (43), $[M - CMe_2C{\equiv}CMe_3Si]$ 523 (100).

(20) A variety of acids ranging in pK_a from acetic to *p*-toluenesulfonic were tested. The combination iodoacetic acid–pyridine in refluxing benzene (8 h) gave the best yield of **19**. We believe that the efficacy of this reagent is probably related to alkylation of the nitrogen atom of **18** by the iodoacetic acid.

(21) Desilylation and aromatization with *p*-toluenesulfonic acid in benzene at room temperature (8 h); demethylation with boron trichloride in methylene chloride at 0 °C (0.5 h); cyclization with concentrated sulfuric acid at 120 °C (1.5 h); overall yield of 65%.

(22) Curtis, R. F.; Hassal, C. H.; Parry, D. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 240.

(23) Our product was identical with a sample of natural Resistomycin. All new compounds with the exception of **18** were characterized by spectroscopic data and/or elemental analysis.

Registry No. 1, 20004-62-0; **2**, 82544-89-6; **3**, 82544-90-9; **3** cyclohexylimine, 82544-91-0; **4**, 82544-92-1; **5**, 95-65-8; **6**, 82544-93-2; **7**, 82544-94-3; **8**, 82544-95-4; **9**, 82544-96-5; **10**, 82544-97-6; **11**, 82544-98-7; **13**, 74460-84-7; **14**, 82544-99-8; **15**, 82545-00-4; **16**, 82545-01-5; **17**, 82545-02-6; **18**, 82554-90-3; **19**, 82545-03-7; **20**, 82545-04-8; **21**, 82545-05-9; **22**, 82545-06-0; diethylcarbamoyl chloride, 88-10-8; ethyl acetoacetate, 141-97-9; 3,5-dimethoxybenzaldehyde, 7311-34-4.

Supplementary Material Available: Spectral and analytical data for compounds **1**, **3** and cyclohexylimine thereof, **4**, **7**, **11**, **13–15**, and **19–22** (2 pages). Ordering information is given on any current masthead page.

"Triple-Decker Sandwich" with a Planar As_5 Ring. Synthesis and Crystal Structure of $CpMo[\mu\text{-}(\eta^4\text{-}As_5)]MoCp$

Arnold L. Rheingold,* Michael J. Foley, and Patrick J. Sullivan

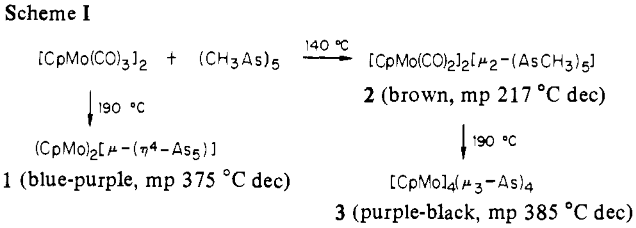
Department of Chemistry, University of Delaware Newark, Delaware 19711

Received February 4, 1982

Unusual configurations of homoatomic main-group catenates can be stabilized by coordination to transition-metal centers. The generation of novel structures containing arsenic atom catenates has been particularly fruitful due to a convenient balance between bond energies low enough to allow facile transformations and high enough to confer sufficient stability for isolation of both intermediates and final products. Structures containing organically substituted linked arsinidene fragments, RAs, have been reviewed by West.[1] We now report the preparation and crystallographic characterization of the first transition-metal complex containing a ring of five unsubstituted arsenic atoms in a triple-decker sandwich structure, $CpMo[\mu\text{-}(\eta^4\text{-}As_5)]MoCp$ (**1**).

Complex **1** is one member of a series of cluster products obtained from reactions of *cyclo*-$(AsCH_3)_5$ and $[CpMo(CO)_3]_2$, as shown in Scheme I. $[CpMo(CO)_2]_2(AsCH_3)_5$ (**2**) is obtained

Scheme I



after 4 days as a brown, crystalline solid in high yield (>50%) from equimolar quantities of reactants in dilute toluene solution in a sealed tube at 140 °C.[5] The same reactants at 190 °C for 2 days produce **1** in somewhat lower yield (20–30%).[6] Since both **1** and **2** contain the same 2Mo/5As ratio, we tested the reasonable assumption that **1** was derived from **2**; however, heating isolated samples of **2** at 190 °C for 2 days in toluene produced only **3**.[7]

Blue-purple (nearly black) crystals of **1** belong to the monoclinic space group $P2_1/c$, with $a = 14.884$ (5) Å, $b = 12.639$ (3) Å, $c = 15.576$ (5) Å, $\beta = 90.50$ (3)°, $D_c = 3.16$ g cm^{-3}, and $Z = 8$ (two independent molecules form the asymmetric unit). The final R_F value was 0.043 on the basis of 2435 independent observed reflections with $I \geq 3\sigma(I)$ (3.5° ≤ 2θ ≤ 45°, Mo Kα).

The molecular configuration of **1**, as determined at 23 °C, is shown in Figure 1, and selected bond distances and angles are given in Table I. The two independent molecules differ only in the rotational orientation of one Cp ring to the other two rings. All rings are essentially eclipsed in one molecule (see Figure 2); in the other molecule, one Cp ring is rotated 22° relative to the other eclipsed rings. No other structural parameters show significant differences between molecules.

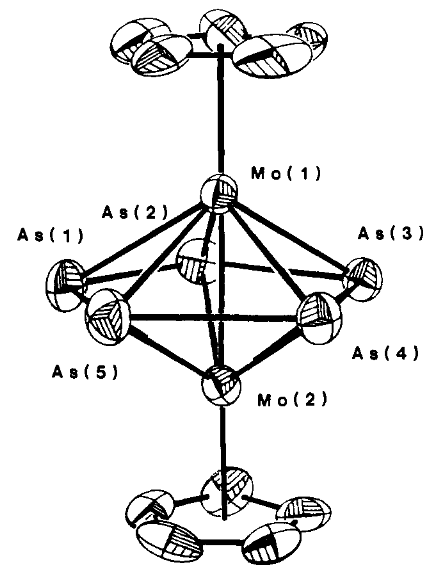


Figure 1. Molecular geometry and labeling scheme for $(CpMo)_2[\mu\text{-}(\eta^4\text{-}As_5)]$ (**1**). Hydrogen atoms have been omitted, and thermal elipsoids are drawn at the 50% probability level.

Table I. Selected Bond Distances and Angles for $[CpMo]_2[\mu\text{-}(\eta\text{-}As_5)]$ (**1**)[a]

	Bond Distances (Å)		
Mo(1)–Mo(2)	2.764 (2)	As(4)–Mo(2)	2.577 (2)
As(1)–Mo(1)	2.721 (2)	As(5)–Mo(1)	2.571 (2)
As(1)–Mo(2)	2.731 (2)	As(5)–Mo(2)	2.551 (2)
As(2)–Mo(1)	2.549 (2)	As(1)–As(2)	2.397 (3)
As(2)–Mo(2)	2.553 (2)	As(2)–As(3)	2.751 (3)
As(3)–Mo(1)	2.541 (2)	As(3)–As(4)	2.570 (2)
As(3)–Mo(2)	2.554 (2)	As(4)–As(5)	2.762 (3)
As(4)–Mo(1)	2.580 (2)	As(5)–As(1)	2.389 (2)
	Bond Angles (deg)		
As(5)–As(1)–As(2)	107.8 (1)	Mo(1)–As(1)–Mo(2)	61.2 (1)
As(1)–As(2)–As(3)	112.0 (1)	Mo(1)–As(2)–Mo(2)	65.6 (1)
As(2)–As(3)–As(4)	104.4 (1)	Mo(1)–As(3)–Mo(2)	64.7 (1)
As(3)–As(4)–As(5)	103.0 (1)	Mo(1)–As(4)–Mo(2)	65.7 (1)
As(4)–As(5)–As(1)	112.7 (1)	Mo(1)–As(5)–Mo(2)	65.6 (1)
av	108.0 (1)	av	64.6 (1)

[a] Data are for the configuration shown in Figure 2. Deviations between independent molecules, except as noted in the text, are not significant.

(1) West, B. O. In "Homoatomic Rings, Chains and Macromolecules of Main-Group Elements"; Rheingold, A. L., Ed.; Elsevier; Amsterdam, 1977; p 409.

(2) Two examples of structures containing three-membered arsenic rings are known: $Co(CO)_3As_3$[3] and $[(triphos)Co]_2As_3(BPh_4)_2$.[4]

(3) Foust, A. S.; Foster, M. S.; Dahl, L. F. *J. Am. Chem. Soc.* **1969**, *91*, 5631.

(4) Di Vaira, M.; Midollini, S.; Sacconi, L.; Zanobini, F. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 676.

(5) Complex **2** contains a 1,5-*catena*-$(AsCH_3)_5$ bridge symmetrically linking both $CpMo(CO)_2$ units without metal–metal bonding. Rheingold, A. L.; Churchill, M. R., submitted to *J. Organomet. Chem.*

(6) Mass spectral data (**1**): $M^{+\cdot}$ = base peak, $m/e = 695$ (all other peaks ≤17.0% of base).

(7) Structural characterization of **3** is incomplete. Elemental and mass spectral analysis support the formula $(CpMoAs)_4$, and the crystallographic arrangement of As and Mo atoms is unambiguously displayed as a cubanelike structure symmetrically equivalent to the structure of $[(CO)_3FeAsCH_3]_4$ (Röttinger, E.; Vahrenkamp, H. *J. Organomet. Chem.* **1981**, *213*, 1). Complex **3** crystallizes in the cubic space group $P\bar{4}3n$, which imposes a disordered threefold rotational axis along the CpMo···As vector. Preparation and characterization of the methylcyclopentadienyl derivative will, we hope, reduce crystallographically demanded symmetry.

0002-7863/82/1504-4727$01.25/0 © 1982 American Chemical Society