Dohme, and Hoffmann-La Roche.

Registry No. 1, 106799-08-0; **2**, 101417-56-5; **3**, 106799-09-1; **4**, 106820-43-3; **5**, 106799-10-4; **6**, 106799-11-5; **7a**, 106799-13-7; **7b**, 106799-16-0; **8**, 106862-35-5; **9**, 106799-14-8; **10**, 106799-17-1; **11**, 106799-18-2; IIa, 81120-67-4; IIb, 106862-36-6; IIIa, 58-86-6; IIIb, 609-06-3; IV, 81177-24-4; V, 106799-15-9; VI, 106799-19-3; VII, 106799-12-6; VIII, 105172-28-9; IX, 69152-88-1; $Et_2AlC{\equiv}CCH_2OSi$-t-$BuPh_2$, 106799-20-6; $CH_3PPh_3^+Br^-$, 1779-49-3; $(MeO)_2P(O)CH_2Li$, 34939-91-8; amphoteronolide B, 106799-07-9; amphotericin B, 1397-89-3.

Supplementary Material Available: List of R_f, $[\alpha]_D$, IR, and ^1H NMR data for compounds V-VIII (2 pages). Ordering information is given on any current masthead page.

Total Synthesis of Amphoteronolide B

K. C. Nicolaou,* R. A. Daines, and T. K. Chakraborty

Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104

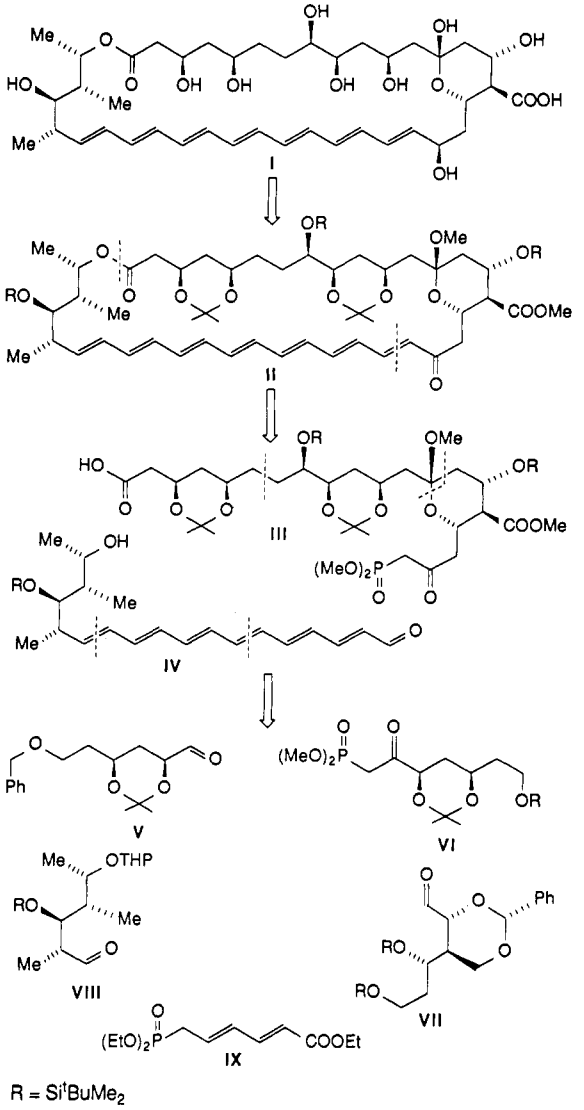
Received October 6, 1986

Amphoteronolide B (I, Scheme I), the aglycon of amphotericin B, has recently been obtained from naturally derived amphotericin B and fully characterized by spectroscopic means.[1] We now report the first total synthesis of this important and long sought target in its optically active form from readily available starting materials and in a highly stereocontrolled manner.[2]

Scheme I outlines a retrosynthetic analysis of the titled molecule. Thus, it was envisioned that amphoteronolide B (I) could be derived from the protected heptaenone II by stereoselective carbonyl reduction and deprotection. This maneuver then allowed disconnection of this precursor at the lactone and unsaturated sites as indicated in structure II. The chosen strategic bond disconnections leading to advanced intermediates III and IV pointed to a highly convergent synthesis and also to two powerful coupling reactions, an esterification and a keto phosphonate-aldehyde condensation, in the synthetic plan to construct II. Finally, subtargets keto phosphonate carboxylic acid III and hydroxy aldehyde IV were retrosynthetically disassembled as indicated in Scheme I, revealing building blocks V-IX as potential starting points for the total synthesis.

The construction of building blocks V-VIII is reported in the preceeding paper.[3] Their coupling and elaboration to amphoteronolide B is detailed in Scheme II. Thus, coupling of aldehyde V and keto phosphonate VI under basic conditions led to the expected conjugated enone in 94% yield, which was cleanly hydrogenated to the saturated ketone **1** (98%). Molecular models of this ketone suggested that reduction should occur from the opposite side of the adjacent acetonide, particularly by a sterically demanding reagent attacking a frozen conformation of **1**. Indeed, L-selectride at −120 °C produced the single diastereoisomer **2** in 98% yield.[4] The stereochemical outcome of this reduction was

Scheme I[a]



[a] Retrosynthetic analysis of amphoteronolide B (I).

confirmed by X-ray crystallographic analysis (see the ORTEP drawing in Scheme II) of the crystalline *p*-chlorobenzenesulfonate **3** prepared from **2** as outlined in Scheme II. Compound **2** was then functionalized appropriately so as to allow its coupling to the third building block VII as follows. Protection of the secondary hydroxyl of **2** with the more stable t-$BuPh_2Si$ group[5] (91%) followed by selective removal of the t-$BuMe_2Si$ group (84%) from the primary hydroxyl led to compound **5** via **4**. Intermediate **5** was then sequentially converted to iodide **6** (97%) via its mesylate and then to dimethyl phosphonate **7** by displacement with sodium dimethylphosphite.[6] Sulfenation of the anion of **7** then led to a diastereomeric mixture of the α-methylthio phosphonate **8** (73%; ca. 1:1 by ^1H NMR). Condensation of the anion of **8** with aldehyde VII proceeded smoothly, leading to coupling product **9** (84%; mixture of geometrical isomers, ca. 1:1 by ^1H NMR). Desilylation of **9** to the triol **10** (96%) followed by an acid-induced cyclization led to mixed cyclic ketal **11** (64%; ca. 1:1 mixture of anomers by ^1H NMR), which was converted to the methoxy compound **12** by exposure to NBS-MeOH (95%; ca. 1:1 mixture

(1) Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y. *J. Chem. Soc., Chem. Commun.*, in press.

(2) For synthetic studies in this area by other groups, see: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Taeboem, O. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (b) Boscheli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, 5239. (c) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183. (d) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W. *J. Org. Chem.* **1984**, *49*, 2843. (e) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (f) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (g) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (h) Lipshutz, B. H.; Koslowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (i) Hirama, M.; Vie, M. *Tetrahedron Lett.* **1982**, 5307. (j) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, 4991. (k) Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, 2847.

(3) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W.-S.; Papahatjis, D. P.; Chakraborty, T. K., preceeding paper in this issue.

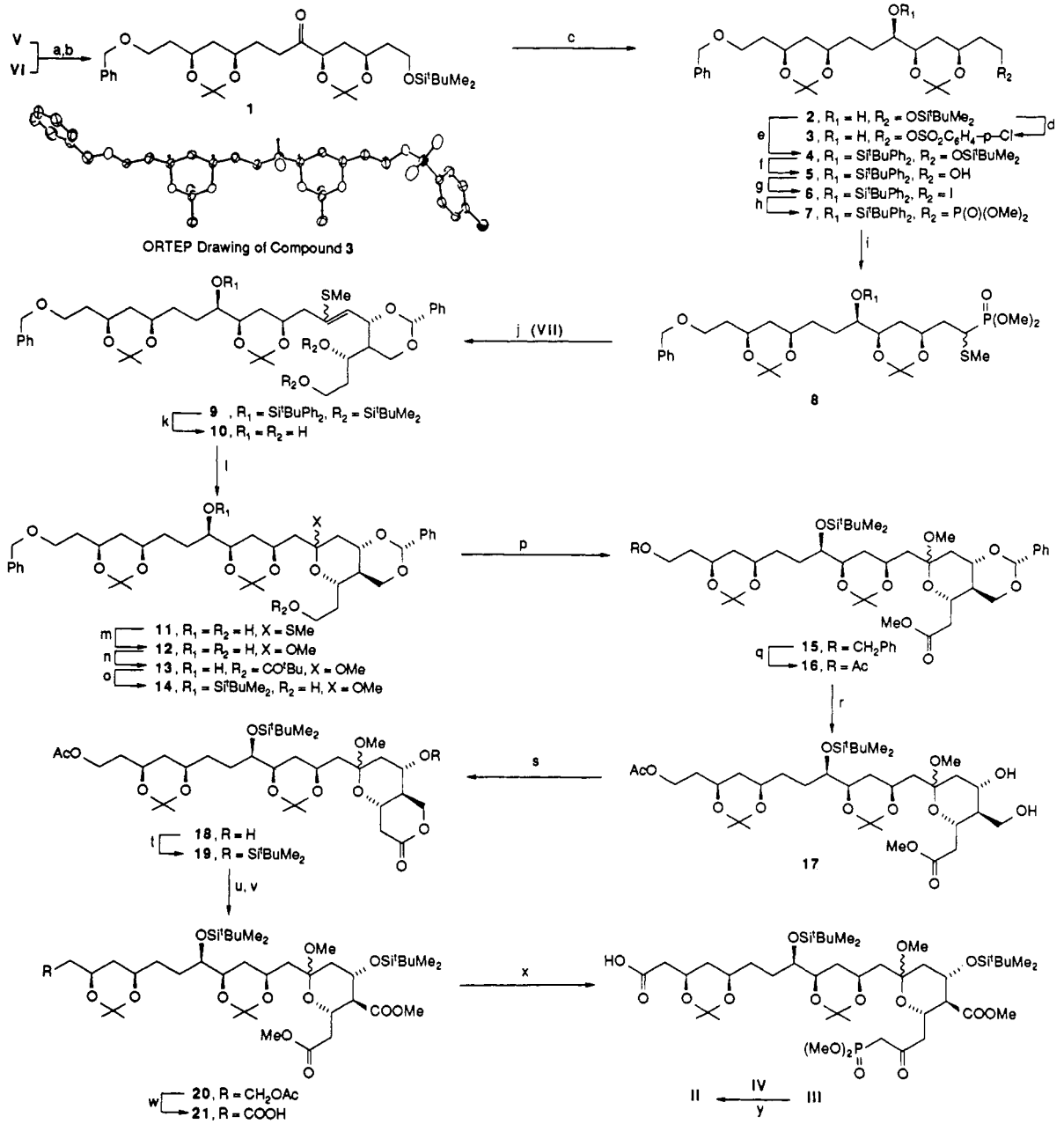
(4) At least 98% pure, as checked by ^1H NMR spectroscopy (250 MHz). A variety of other reduction conditions gave mixtures of **2** and its epimer (e.g., L-selectride, THF, −78 °C, ca. 5:1 ratio; L-selectride, Et_2O, −78 °C, ca. 1.3:1 ratio; $Zn(BH_4)_2$, Et_2O, 0 or −78 °C, ca. 1:1 ratio; DIBAL, CH_2Cl_2, −78 °C, ca. 2.7:1 ratio; t-$BuNH_2{\cdot}BH_3$, THF, −40 °C, ca. 1.2:1 ratio).

(5) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(6) Sturtz, G. *Bull. Chim. Fr.* **1964**, 2340.

0002-7863/87/1509-2208$01.50/0

Scheme II[a]

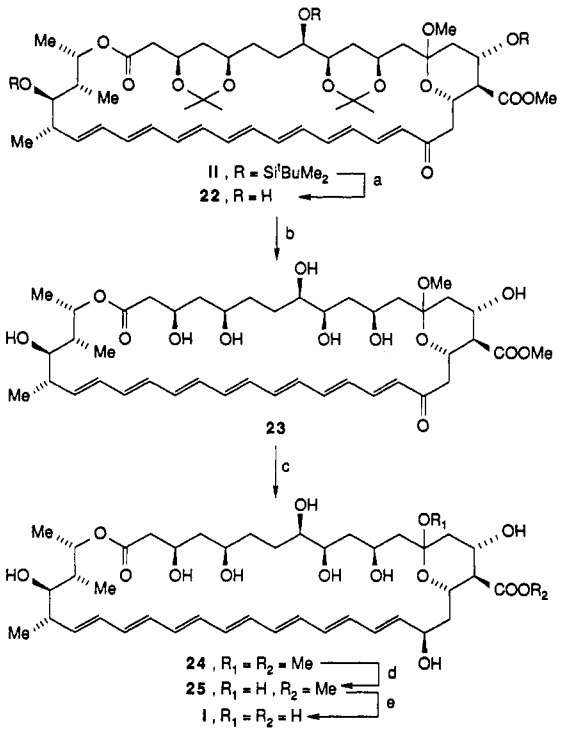


[a] Reagents and conditions. (a) VI, 1.1 equiv of NaH, DME, 0 °C, then 1.0 equiv of aldehyde V, −60 → −20 °C, 4 h, 94%. (b) 5% Pd–C catalyst, H_2, EtOAc, 25 °C, 3 h, 98%. (c) 5.0 equiv of L-Selectride, THF, −120 °C, 2 h, 98%. (d) 1.5 equiv of *n*-Bu_4NF, THF, 1 h, 25 °C, then 1.1 equiv of *p*-Cl-$C_6H_4SO_2Cl$, 1.5 equiv of Et_3N, DMAP catalyst, CH_2Cl_2, 0 °C, 4 h, 90%. (e) 1.2 equiv of *t*-$BuPh_2SiCl$, 1.5 equiv of imidazole, DMF, 0–25 °C, 4 h, 91%. (f) 1.1 equiv of *n*-Bu_4NF, THF, 0 °C, 6 h, 84%. (g) 1.1 equiv of MsCl, 1.3 equiv of Et_3N, CH_2Cl_2, −15 °C, 15 min then excess NaI, acetone, 25 °C, 8 h, 97% overall. (h) 1.2 equiv of $(MeO)_2P(O)H$, 1.2 equiv of NaH, DME:DMF (3:2), 45 °C, 4 h, 97%. (i) 1.1 equiv of LDA, THF, −78 °C then 1.1 equiv of MeSSMe, −78 °C, 5 min, 73%. (j) 1.3 equiv of LDA, THF, −78 °C then 1.1 equiv of aldehyde VII, −78 → 25 °C, 2 h, 84%. (k) 3.0 equiv of *n*-Bu_4NF, THF, 8 h, 25 °C, 96%. (l) 1.1 equiv of CSA, CH_2Cl_2 (0.05 M), 0–25 °C, 20 min, 64%. (m) 1.1 equiv of NBS, 3 Å molecular sieves, CH_2Cl_2–MeOH (10:1), 0 °C, 10 min, 95%. (n) 1.1 equiv of *t*-BuCOCl, pyr, 0–25 °C, 8 h, 86%. (o) 1.1 equiv of *t*-$BuMe_2SiOTf$, 1.3 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 89% then 2.5 equiv of DIBAL, CH_2Cl_2, −78 °C, 15 min, 98%. (p) 5.0 equiv of PDC, DMF, 25 °C, 12 h, then CH_2N_2, Et_2O, 0 °C, 82% overall. (q) 10% Pd–C catalyst, H_2, absolute EtOH, 25 °C, 3 days, then 1.2 equiv of Ac_2O, 3.0 equiv of DMAP, CH_2Cl_2, 0 °C, 15 min, 67% overall. (r) 10% Pd–C catalyst, H_2, absolute MeOH, 25 °C, 2 days, 76%. (s) 5.0 equiv of imidazole, CH_3CN, 25 °C, 10 h, 76%. (t) 1.1 equiv of *t*-$BuMe_2SiOTf$, 1.3 equiv of 2,6-lutidine, CH_2Cl_2, 10 min, 0 °C, 80%. (u) 1.1 equiv of aqueous LiOH (1.0 M), THF, 0–25 °C, 20 min, then CH_2N_2, Et_2O, 0 °C, 98% overall. (v) 5.0 equiv of PDC, DMF, 25 °C, 12 h, then CH_2N_2, Et_2O, 0 °C, 76%. (w) 5.0 equiv of K_2CO_3, MeOH, 0 °C, 30 min, 95% then 5.0 equiv of PDC, DMF, 12 h, 79%. (x) 3.0 equiv of $CH_3P(O)(OCH_3)_2$, 3.0 equiv of *n*-BuLi, THF, −78 °C, then add **21**, −78 °C, 15 min, 62%. (y) see ref 8.

of anomers by ^1H NMR). Differentiation between the primary and secondary hydroxyls of **12** was achieved via monopivalate ester **13** (86%), which was silylated (89%) and deprotected to afford primary alcohol **14** (98%). PDC oxidation[7] of **14** followed by diazomethane treatment led to methyl ester **15** (82%); the benzyl ether protection of **15** was then selectively removed and replaced with an acetate group, leading to **16** (67% overall yield) so as to allow for subsequent differentiations. Removal of the benzylidene group from **16** furnished diol **17** (76%), which underwent smooth lactonization to **18** by treatment with imidazole (76%), thus temporarily engaging the primary hydroxyl group. Subsequent silylation of the remaining free hydroxyl of **18** led to the disilyl ether **19** (80%). The highly sensitive lactone functionality of **19** was then dismantled (without acetate removal) by aqueous base

(7) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

Scheme III[a]



[a] Reagents and conditions. (a) excess HF-pyr, MeOH, 45 °C, 48 h, 55%. (b) 0.1 equiv of CSA, MeOH, 0-25 °C, 1 h, 50% based on recovered starting material (10%) and a monoacetonide (25%, as yet unidentified isomeric structure). (c) 10 equiv of $NaBH_4$, MeOH, 0 °C, 98%. (d) 0.1 equiv of CSA, MeOH-H_2O (9:1), 0-25 °C, 97%. (e) 10.0 equiv of 1 N LiOH, H_2O, 0-25 °C, 1 h, 80% (75% conversion).

and the resulting hydroxy acid was converted to the dimethyl ester **20** by sequential methylation (CH_2N_2), PDC oxidation, and a second methylation (CH_2N_2) (76% overall yield). The acetate was then removed from **20** (95%) and the carboxylic acid **21** was obtained by PDC oxidation of the resulting primary alcohol (79%). Finally, differentiation among the three carboxyl groups in **21** (anion formation at C-1, steric congestion at C-16) was observed in the one-step, chemoselective conversion of this intermediate to the requisite keto phosphonate acid III by attack of dimethyl (lithiomethyl)phosphonate at C-19 (62%). The second requisite key intermediate, hydroxy aldehyde IV, was constructed from synthetic VIII[3] and two units of phosphonate IX (Scheme I) as recently described.[8] Finally, coupling of III and IV (esterification, 70%) followed by macrocyclization (intramolecular keto phosphonate-aldehyde condensation, 70%) according to the procedures recently reported from these laboratories[8] led to heptaenone II.[9] Heptaenone II was then converted to I as outlined in Scheme III. Thus, desilylation of II (HF·pyr-MeOH) afforded triol **22** (55%), which was then subjected to deacetonization (CSA-MeOH) leading to heptahydroxy heptaenone **23** (50% yield based on ca. 50% conversion). Sodium borohydride reduction of **23** led, stereospecifically,[1] to the amphoteronolide derivative **24** (98%). The 19*R* configuration of the reduction product was confirmed by CD studies[1] and by comparisons of materials derived from **24** and amphotericin B.[10] Finally, sequential demethylation of **24** (CSA-MeOH, 97% followed by LiOH hydrolysis, 80% yield based on ca. 75% conversion) led to amphoteronolide B (**1**)[11] via its methyl ester **25**. Thus, the total synthesis of amphoteronolide B (**1**) was accomplished.[12]

Acknowledgment. We express our many thanks to Dr. C. Cimarusti, The Squibb Institute for Medical Research, for generous samples of amphotericin B, and to Drs. George Furst, Patrick Carroll, and John Dykins for their superb NMR, X-ray crystallographic, and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp and Dohme, and Hoffmann-La Roche.

Supplementary Material Available: Listing of R_f, $[\alpha]_D$, IR, UV, and ^1H NMR data for compounds **4**, **8**, **9**, **14**, **17**, **19**, **21**, II, III, IV, and **25** and a ^{13}C NMR spectrum of **25** (7 pages). Ordering information is given on any current masthead page.

(8) Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 413.

(9) Both synthetic II and degradatively derived[8] II (two methoxy anomers, chromatographically separated) were found to be spectroscopically and chromatographically identical. Compounds **11-21** and III were carried through the sequence as mixtures of methoxy anomers.

(10) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.*, in press.

(11) After chromatographic purification (silica, 25-75% MeOH in CH_2Cl_2) and spectroscopic characterization, the aglycon I was methylated (CH_2N_2, Et_2O-Me_2SO, 25 °C) back to amphoteronolide B methyl ester, identical with an authentic sample, thus further confirming its structure.

(12) All new compounds exhibited satisfactory spectral and analytical/exact mass spectral data. Yields refer to spectroscopically and chromatographically homogeneous materials.

Preparation and Structure of $(NEt_4)_2[V_4S_2(SCH_2CH_2S)_6]$ and Its Structural and Electronic Relationship to the Li_xVS_2 Phases

Joanna K. Money, John C. Huffman, and George Christou*

Department of Chemistry and the Molecular Structure Center, Indiana University Bloomington, Indiana 47405

Received October 15, 1986

The polymeric sulfides of the early transition metals often display interesting magnetic and electrical properties[1,2] and have proven to be of considerable importance to many areas, not least of which are heterogeneous catalysis[3] and employment as battery electrodes.[4] A current and important challenge to the synthetic inorganic chemist is the preparation of soluble, discrete structural counterparts of the polymeric metal-sulfide phases to allow parallel characterization of both the reactivity characteristics in homogeneous solution and the intrinsic properties of the basic building block of the extended lattice. Such efforts have resulted in considerable progress, particularly in the chemistry of soluble molybdenum sulfides.[5] We herein report the preparation and properties of the first tetranuclear vanadium-sulfur-thiolate species. We believe this complex presages a rich new area of high nuclearity V/S/SR chemistry. In addition, we describe its structural and electronic correspondence to the Li_xVS_2 polymeric phases ($0 \leq x \leq 1$).[6]

Reaction of VCl_3, Li_2S, Na_2edt (edt is ethane-1,2-dithiolate), and NEt_4Br in a 3:4:3:6 ratio in MeCN yields an intensely brown solution that, after filtration and addition of diethyl ether, deposits large black prismatic crystals of $(NEt_4)_2[V_4S_2(edt)_6]\cdot 2MeCN$ in analytical purity.[7] A single-crystal structure determination[7] shows the anion (Figure 1) to possess a V_4S_2 central core with two

(1) Hullinger, F. *Struct. Bonding (Berlin)* **1968**, *4*, 83.

(2) Whittingham, M. S. *J. Electrochem. Soc.* **1976**, *123*, 315.

(3) Weisser, O.; Landa, S. *Sulfide Catalysts: Their Properties and Applications*; Pergamon: New York, 1973.

(4) Rouxel, J.; Brec. R. *Annu. Rev. Mater. Sci.* **1986**, *16*, 137-162.

(5) Muller, A. *Polyhedron* **1986**, *5*, 323.

(6) Murphy, D. W.; Cros, C.; DiSalvo, F. J.; Waszczak, J. V. *Inorg. Chem.* **1977**, *16*, 3027.

(7) Crystallographic data at -155 °C: triclinic; space group $P\bar{1}$; $a = 11.130$ (3), $b = 11.424$ (3), $c = 10.748$ (3) Å; $\alpha = 112.04$ (1), $\beta = 94.82$ (1), $\gamma = 93.44$ (1)°; $Z = 1$; $R = 0.0459$, $R_w = 0.0467$, using 3290 unique intensities with $F > 3\sigma(F)$. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located in a difference Fourier and refined isotropically. Anal. Calcd for $C_{32}H_{70}N_4S_{14}V_4$: C, 33.03; H, 6.06; N, 4.82. Found: C, 32.77; H, 6.01; N, 4.60.

0002-7863/87/1509-2210$01.50/0