

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; $\text{Et}_2\text{AlC}\equiv\text{CCH}_2\text{OSi-}t\text{-BuPh}_2$, 106799-20-6; $\text{CH}_3\text{PPh}_3^+\text{Br}^-$, 1779-49-3; $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{Li}$, 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

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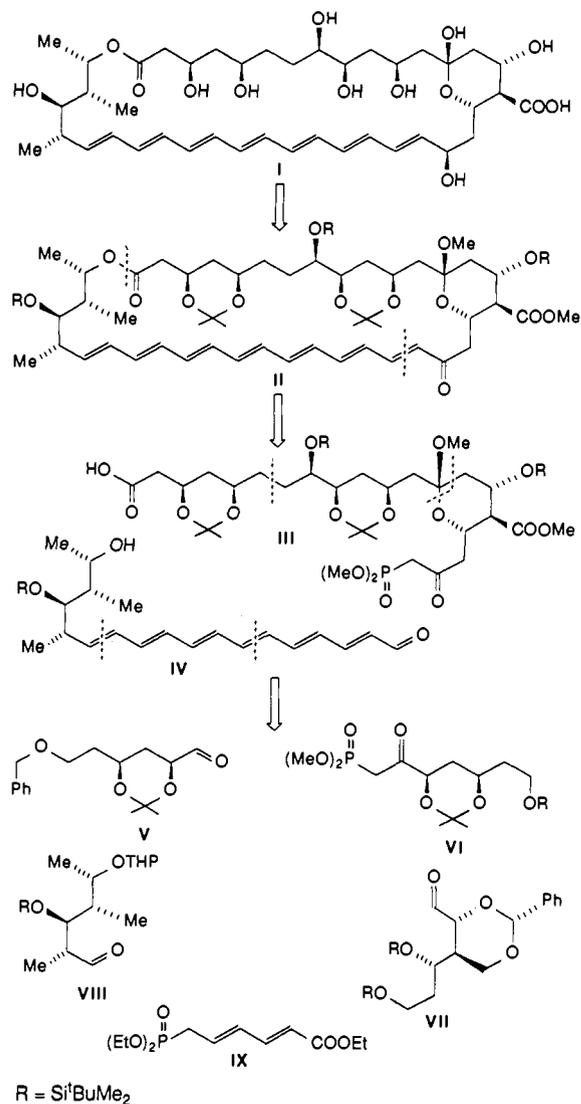
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Amphoteronolide B (I, Scheme I), the aglycon of amphotericin B, has recently been obtained from naturally derived amphotericin B and fully characterized by spectroscopic means.¹ We now report the first total synthesis of this important and long sought 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 preceding 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



^aRetrosynthetic 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*-BuPh₂Si group⁵ (91%) followed by selective removal of the *t*-BuMe₂Si 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 Sulfonation 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.

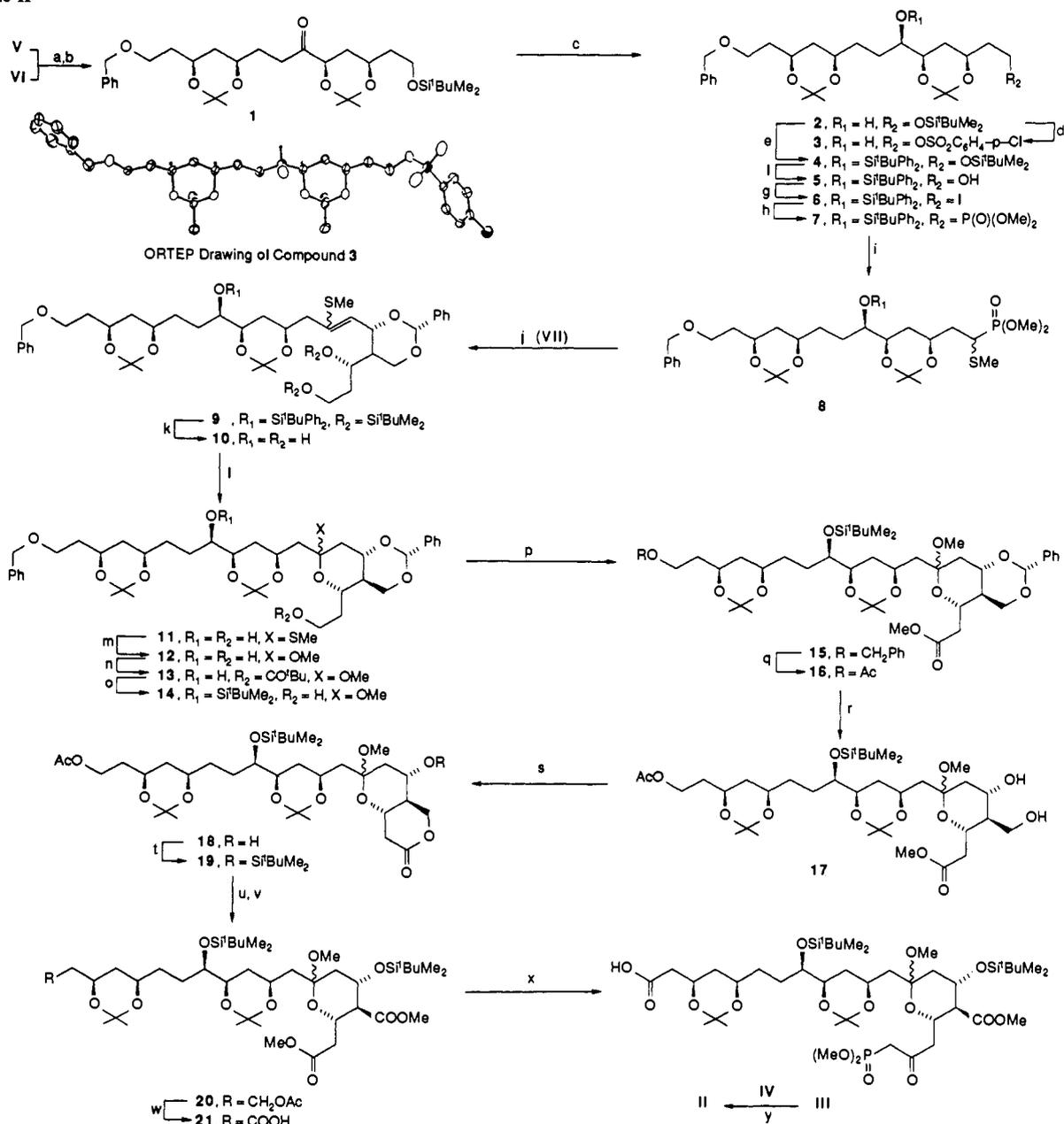
(2) For synthetic studies in this area by other groups, see: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Taeboem, O. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (b) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, 5239. (c) Blanchette, M. A.; 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.; Vitil, 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) Hiram, 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.

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(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; $\text{Zn}(\text{BH}_4)_2$, Et_2O , 0 or -78°C , ca. 1:1 ratio; DIBAL, CH_2Cl_2 , -78°C , ca. 2.7:1 ratio; $t\text{-BuNH}_2\text{BH}_3$, THF, -40°C , ca. 1.2:1 ratio).

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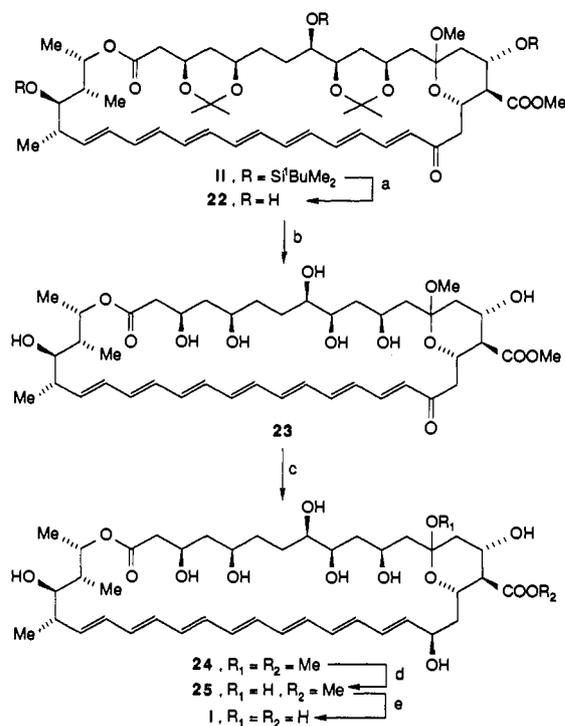
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Scheme II^a

^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, H₂, 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*-Bu₄NF, THF, 1 h, 25 °C, then 1.1 equiv of *p*-Cl-C₆H₄SO₂Cl, 1.5 equiv of Et₃N, DMAP catalyst, CH₂Cl₂, 0 °C, 4 h, 90%. (e) 1.2 equiv of *t*-BuPh₂SiCl, 1.5 equiv of imidazole, DMF, 0-25 °C, 4 h, 91%. (f) 1.1 equiv of *n*-Bu₄NF, THF, 0 °C, 6 h, 84%. (g) 1.1 equiv of MsCl, 1.3 equiv of Et₃N, CH₂Cl₂, -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*-Bu₄NF, THF, 8 h, 25 °C, 96%. (l) 1.1 equiv of CSA, CH₂Cl₂ (0.05 M), 0-25 °C, 20 min, 64%. (m) 1.1 equiv of NBS, 3 Å molecular sieves, CH₂Cl₂-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*-BuMe₂SiOTf, 1.3 equiv of 2,6-lutidine, CH₂Cl₂, 0 °C, 10 min, 89% then 2.5 equiv of DIBAL, CH₂Cl₂, -78 °C, 15 min, 98%. (p) 5.0 equiv of PDC, DMF, 25 °C, 12 h, then CH₂N₂, Et₂O, 0 °C, 82% overall. (q) 10% Pd-C catalyst, H₂, absolute EtOH, 25 °C, 3 days, then 1.2 equiv of Ac₂O, 3.0 equiv of DMAP, CH₂Cl₂, 0 °C, 15 min, 67% overall. (r) 10% Pd-C catalyst, H₂, absolute MeOH, 25 °C, 2 days, 76%. (s) 5.0 equiv of imidazole, CH₃CN, 25 °C, 10 h, 76%. (t) 1.1 equiv of *t*-BuMe₂SiOTf, 1.3 equiv of 2,6-lutidine, CH₂Cl₂, 10 min, 0 °C, 80%. (u) 1.1 equiv of aqueous LiOH (1.0 M), THF, 0-25 °C, 20 min, then CH₂N₂, Et₂O, 0 °C, 98% overall. (v) 5.0 equiv of PDC, DMF, 25 °C, 12 h, then CH₂N₂, Et₂O, 0 °C, 76%. (w) 5.0 equiv of K₂CO₃, MeOH, 0 °C, 30 min, 95% then 5.0 equiv of PDC, DMF, 12 h, 79%. (x) 3.0 equiv of CH₃P(O)(OCH₃)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 monopalmitate ester 13 (86%), which was silylated (89%) and deprotected to afford primary alcohol 14 (98%). PDC oxidation⁷ 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

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 NaBH₄, MeOH, 0 °C, 98%. (d) 0.1 equiv of CSA, MeOH–H₂O (9:1), 0–25 °C, 97%. (e) 10.0 equiv of 1 N LiOH, H₂O, 0–25 °C, 1 h, 80% (75% conversion).

and the resulting hydroxy acid was converted to the dimethyl ester **20** by sequential methylation (CH₂N₂), PDC oxidation, and a second methylation (CH₂N₂) (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 VIII³ 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 laboratories⁸ 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 studies¹ 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

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(9) Both synthetic II and degradatively derived⁸ II (two methoxy anomers, chromatographically separated) were found to be spectroscopically and chromatographically identical. Compounds II–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.

methyl ester **25**. Thus, the total synthesis of amphoteronolide B (**1**) was accomplished.¹²

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

(11) After chromatographic purification (silica, 25–75% MeOH in CH₂Cl₂) and spectroscopic characterization, the aglycon I was methylated (CH₂N₂, Et₂O–Me₂SO, 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 (NEt₄)₂[V₄S₂(SCH₂CH₂S)₆] and Its Structural and Electronic Relationship to the Li_xVS₂ Phases

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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 catalysis³ 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_xVS₂ polymeric phases (0 ≤ x ≤ 1).⁶

Reaction of VCl₃, Li₂S, Na₂edt (edt is ethane-1,2-dithiolate), and NEt₄Br 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 (NEt₄)₂[V₄S₂(edt)₆]·2MeCN in analytical purity.⁷ A single-crystal structure determination⁷ shows the anion (Figure 1) to possess a V₄S₂ central core with two

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(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; α = 112.04 (1), β = 94.82 (1), γ = 93.44 (1)°; *Z* = 1; *R* = 0.0459, *R_w* = 0.0467, using 3290 unique intensities with *F* > 3σ(*F*). All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located in a difference Fourier and refined isotropically. Anal. Calcd for C₃₂H₇₀N₄S₄V₄: C, 33.03; H, 6.06; N, 4.82. Found: C, 32.77; H, 6.01; N, 4.60.