Scheme III. Summary of the Reductive Activation-Alkylation Reactions of \(N\)-Methylmitomycin A

![Diagram of Scheme III]

complicated by uncertainties in the sequence of the various alkylation steps. Hornemann and Kohn had previously examined the reaction of MMC with potassium ethyl xanthate (9) under reductive (\(\text{Na}_2\text{S}_2\text{O}_4\)) conditions.\(\text{a},\text{b}\) Apomitosones, arising from the non-stereospecific ring opening of the aziridine by nucleophile at C9, were encountered. It was implicitly assumed that reaction had occurred via the MMC derived version of 3a. In the N-MeMMA series, we could evaluate the reactivity of the aziridine-containing compounds 7 and 3a, generated as discrete entities by our methodology.\(\text{c},\text{d}\) Reactions were conducted in aqueous pyridine. From this series of reactions, three products could be obtained and identified. These were the C1 and C10 xanthates 10 and 12, as well as the dimethoxime 11. When reaction was conducted with 3a (10 min, 0 °C) followed by subsequent air oxidation, a 20% yield of the three products in the indicated ratio was obtained. When reaction was conducted on 7, a trace of 10 (ca. 5%) could be detected and ca. 95% of 7 was recovered. Maximum yield was realized from the reaction of 7 with \(\text{Na}_2\text{S}_2\text{O}_4\) in the presence of 9. Oxidation (air) after the 10-min incubation period afforded a 35% yield of 10 and a 25% yield of 11. Thus the process of reductive priming of 7 with sodium dithionite gave a substantially higher yield than was realized from the two-electron reduction product (3a) itself. Furthermore, attempted reduction of 7 with dithionite (aqueous pyridine) in the absence of nucleophile 9 led to very slow reaction and the product was not 3a, but rather the ene pyrrole 4 (NMR analysis). The rate of formation of 3a is too slow for it to be the primary alkylating agent. Hence the formulation whereby the two electron reduction product, 3a, acts as the active alkylating agent, producing 10, 11, and 12, is untenable. The sequence embodied in Scheme III, wherein mitosene semiquinone 6 alkylates nucleophile 9, accounts very well for the observed result. Further support for the proposal comes from the reaction of aziridinomitosene 7 with a catalytic amount (0.3 equiv) of \(\text{Na}_2\text{S}_2\text{O}_4\) in the presence of nucleophile 9. Workup after 35 min yielded an 80% combined yield of xanthate alkylated products.\(\text{e}\) Thus the extent of alkylation substantially exceeds the availability of reducing agent. These data in the aggregate point toward the intervention of a steady-state reactive intermediate (cf. semiquinone 6) as the active electrophile.

A parallelism is noted between the intervention of semiquinone equivalent 6 in the xanthate alkylations and the involvement of species 5 in the C9 methoxy-etherification event (1 → 7).\(\text{f}\) The rough vinylogy between the two processes is indicated (cf. arrows). Our data do not preclude significant alklylation properties for compound 3a. They also do not define the precise species involved in the remarkable transformation of 3a → 4.\(\text{f}\) They do, however, provide a basis for proposing a very concise sequence for bioactivation of mitomycins, as shown in Scheme III. A natural consequence of these findings is that new departures in mitomycin drug development might well center on substitutions which will favor species generically related to 6. This proposition will now be pursued.

Acknowledgment. This work was supported by PHS Grant CA 24824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. We also thank Dr. Terry Doyle of the Bristol Pharmaceutical Co. for supplying us with mitomycin C.

Supplementary Material Available: Experimental data for compounds 2a,b, 3a,b, 4, 7, 8a,c and 10–12 (3 pages). Ordering information is given on any current masthead page.

\(\text{16}\) The similarities of “electron flow” inherent in the formation of xanthate adducts 10, 11, 12, and of ene pyrrole 4 make tempting the possibility that semiquinone 6 is intervening in the formation of 4.
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of the carboxylic acid (RuO4 catalyst-NaIO4),* methyl ester was then cleaved (aqueous HCl), and the resulting lactol was converted to olefin 10 by a Wittig reaction (58% overall). Engagement of the 1,3-diol system of 10 as an acetonide, followed by hydroboration and silylation, led to compound 11 in 73% overall yield. Finally, debenzylation, oxidation of the liberated hydroxyl group to the carboxylic acid (RuO4 catalyst-NaIO4),15 methyl ester formation, and nucleophilic attack by L-(CH2)3P(O)(OMe)3 furnished the desired keto phosphate VI in 71.5% overall yield. Alternative syntheses of fragments V and VI starting with the prochiral allylic alcohol IX are summarized in Scheme IV. As mentioned above, (−)- and (+)-DET were utilized in conjunction with the Sharpless asymmetric epoxidation reaction14 to induce the desired asymmetry. Thus, according to our previously reported general method for building 1, 3, 5, ..., (2n + 1) polyols,15 IX was converted to the enantiomeric triols IIa and IIb. Protecting group manipulation of IIa as detailed in Scheme IV then led to intermediate 9 (52% overall yield), which was converted to V as already described above. In parallel, IIb was transformed to the protected derivative II by selective silylation and acetonide formation (85.5% overall yield) and thence to VI as described above. In conclusion, focusing on subtle and repeated structural units, the described retrosynthetic analysis allows the utilization of readily available enantionicemic structures as starting points for an eventual total synthesis of both amphoteronolide B and amphotericin B. Thus, four major building blocks (V–VIII) have been synthesized in optically active forms and by highly efficient and concise sequences using (−)- and (−)-xylene and (+)- and (−)-DET as sources of chirality. The strategy is now set for a highly convergent total synthesis of both amphoteronolide B and amphotericin B. The following paper describes the accomplishment of the former goal.14,15

Acknowledgment. We express our many thanks to Drs. George Furst and John Dykins in this department for their superb NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp &

The route to building block VI started from (−)-xylene (IIb) and proceeded through derivative 7b, obtained as described above for its enantiomer (7a). The silyl protecting group in 7b was then exchanged with a benzyl group, the acetone was removed (aqueous HCl), and the resulting lactol was converted to olefin 10 by a Wittig reaction (58% overall). Engagement of the 1,3-diyl system of 10 as an acetonide, followed by hydroboration and silylation, led to compound 11 in 73% overall yield. Finally, debenzylation, oxidation of the liberated hydroxyl group to the carboxylic acid (RuO4 catalyst-NaIO4), methyl ester formation, and nucleophilic attack by L-(CH2)3P(O)(OMe)3 furnished the desired keto phosphate VI in 71.5% overall yield. Alternative syntheses of fragments V and VI starting with the prochiral allylic alcohol IX are summarized in Scheme IV. As mentioned above, (−)- and (+)-DET were utilized in conjunction with the Sharpless asymmetric epoxidation reaction14 to induce the desired asymmetry. Thus, according to our previously reported general method for building 1, 3, 5, ..., (2n + 1) polyols,15 IX was converted to the enantiomeric triols IIa and IIb. Protecting group manipulation of IIa as detailed in Scheme IV then led to intermediate 9 (52% overall yield), which was converted to V as already described above. In parallel, IIb was transformed to the protected derivative II by selective silylation and acetonide formation (85.5% overall yield) and thence to VI as described above. In conclusion, focusing on subtle and repeated structural units, the described retrosynthetic analysis allows the utilization of readily available enantionicemic structures as starting points for an eventual total synthesis of both amphoteronolide B and amphotericin B. Thus, four major building blocks (V–VIII) have been synthesized in optically active forms and by highly efficient and concise sequences using (−)- and (−)-xylene and (+)- and (−)-DET as sources of chirality. The strategy is now set for a highly convergent total synthesis of both amphoteronolide B and amphotericin B. The following paper describes the accomplishment of the former goal.14,15

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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 via stereoselective carbonyl reduction and deprotection. This maneuver then allowed disconnection of this precursor at the lactone and unsaturated sites as indicated in structure III. The chosen strategic bond disconnections led to advanced intermediates III and IV which 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, subunits ketophosphate 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 phosphate VI under basic conditions led to the expected conjugated enone in 94% yield, which was cleanly hydrogenated to the saturated ketone I (98%). Molecular models of this ketone suggested that reduction should occur from the opposite side of the adjacent acetonide, particularly by a sterically hindered reduction from the tertiary hydroxy group.4 The stereochemical outcome of this reduction was confirmed by X-ray crystallographic analysis (see the ORTEP drawing in Scheme II) of the crystalline p-chlorobenzensulfonate 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 phosphate 7 by displacement with sodium dimethylphosphite.6 Sulfenation of the anion of 7 then led to a diastereomeric mixture of the α-methylthio phosphate 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 3,4,7,9).

Supplementary Material Available: List of R0, [x], 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**


*Department of Chemistry, University of Pennsylvania
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Received October 6, 1986

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(2) For synthetic studies in this area by other groups, see: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, O.; Taeboem, 0.; Chakraborty, T. K., preceeding paper in this issue.
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**Scheme II**

![Diagram](image)

Reagents and conditions. (a) VI, 1.1 equiv of NaH, DME, 0 °C, then 1.0 equiv of aldehyde V, –60 to –50 °C, 4 h, 94%. (b) 5% Pd–C catalyst, H2, EtOAc, 25 °C, 3 h, 98%. (c) 5.0 equiv of L-Selectride, THF, –70 °C, 2 h, 98%. (d) 1.5 equiv of n-Bu4NF, THF, 1 °C, then 1.1 equiv of aldehyde VII, –70 °C, 4 h, 91%. (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 MeCl, 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, 1.1 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 Me3SiC1, 86%, which was silylated (89%) and deprotected to afford primary alcohol 14 (98%). PDC oxidation of 14 followed by diazomethane treatment led to methyl ester 15 (82%); the benzylic 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

The polymeric sulfides of the early transition metals often display interesting magnetic and electrical properties, and have proven to be of considerable importance to many areas, not least of which are heterogeneous catalysis and employment as battery electrodes. A current and important challenge to the synthetic inorganic chemist is the preparation of soluble, discrete 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. 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/CR chemistry. In addition, we describe its structural and electronic correspondence to the Li3VS2 polymer phases (0 ≤ x ≤ 1).

Reaction of VCl5, 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(SCH2CH2S)6].2MeCN. Structural and electronic correspondence to the Li3VS2 phases is proven to be of considerable importance to many areas, not least of which are heterogeneous catalysis and employment as battery electrodes. A current and important challenge to the synthetic inorganic chemist is the preparation of soluble, discrete 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. 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/CR chemistry. In addition, we describe its structural and electronic correspondence to the Li3VS2 polymer phases (0 ≤ x ≤ 1).

(7) Crystallographic data at -155 °C: triclinic; space group P1; a = 11.130 (3), b = 11.424 (3), c = 10.748 (3); α = 112.04 (1), β = 94.82 (1), γ = 94.82 (1); Z = 1; R = 0.0459, R1 = 0.0467, using 3290 unique intensities with R > 3σ(F). All non-hydrogen atoms were refined anisotropically; hydrogen atoms were located in a difference Fourier and refined isotropically.
(9) Both synthetic II and degradatively derived I (two methoxy anions, chromatographically separated) were found to be spectroscopically and chromatographically identical. Compounds I-11 and III were carried through the sequence as mixtures of methoxy anions.

预备和结构研究

**（NEt₄)₂[V₄S₂(SCH₂CH₂S)₆]** 和其结构和电子关系到 **Li₃VS₂** 阶段

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 preparatory work of the early transition metals often displays interesting magnetic and electrical properties, and have proven to be of considerable importance to many areas, not least of which are heterogeneous catalysis and employment as battery electrodes. A current and important challenge to the synthetic inorganic chemist is the preparation of soluble, discrete 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. 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/CR chemistry. In addition, we describe its structural and electronic correspondence to the Li₃VS₂ polymer phases (0 ≤ x ≤ 1).

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Supplementary Material Available: Listing of Rₓ, [α]ₓ, IR, UV, and ['H 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.

(1) After chromatographic purification (silica, 25-75% MeOH in CH₂Cl₂) and spectroscopic characterization, the aglycon I was methylated (CH₃₂N₂, 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 Li₃VS₂ Phases**

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