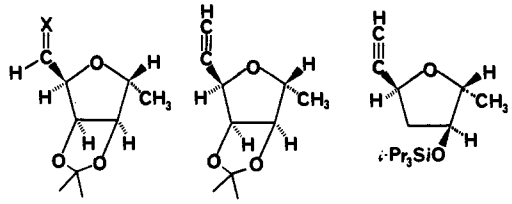
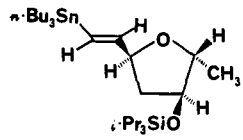


15 X = O
16 X = CCl_2

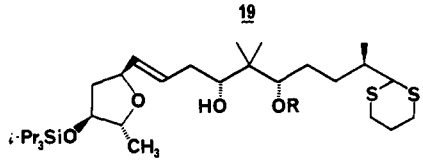
17

18

yield after silica gel chromatography), (2) selective silylation at the hydroxyl further removed from the triple bond using 1.5 equiv of triisopropylsilyl chloride, 2.2 equiv of 4-(dimethylamino)pyridine in methylene chloride at 0 °C for 18 h,[14] (3) triflate ester formation (3 equiv of triflic anhydride and 6 equiv of pyridine in methylene chloride at −10 °C for 5 h (85% yield of pure silyl ether triflate after chromatography on silica gel using ether–hexane for elution), (4) displacement of triflate by iodide (3 equiv of tetra-*n*-butylammonium iodide in benzene at reflux for 2 h; 94% yield),[15] and (5) replacement of iodine by hydrogen with 3 equiv of sodium borohydride and 0.5 equiv of tri-*n*-butyltin chloride in ethanol under sunlamp irradiation[16] at 15 °C for 2 h; 85% yield). Heating of **18** with 1.2 equiv of tri-*n*-butyltin hydride and 0.2 equiv of azobis(isobutyronitrile) at 90 °C for 3 h furnished after chromatography on silica gel the *trans*-vinylstannane **19** in 75% yield.[17]



19



20 R = MTM
21 R = MOM

The coupling of the vinylstannane component **19** and the epoxide **11** was carried out as follows to form **20**, corresponding to the C(3)–C(17) segment of aplasmomycin. Reaction of **19** with 1 equiv of *n*-butyllithium in THF at −78 °C for 1 h and −50 °C for 1.5 h produced the lithium reagent corresponding to **19**, which was sequentially treated with 0.5 equiv of cuprous cyanide (−78 °C for 1 h)[18] and 0.3 equiv of the epoxide **11** (−35 °C for 2 h, −25 °C for 24 h, and −15 °C for 24 h) to form the coupling product **20** (75% yield, 89% yield based on recovered epoxide after chromatographic isolation). In a strictly analogous way the epoxide MOM ether **12** was coupled to **19** to give **21** as product.

The elaboration of **20** and **21** to aplasmomycin has been accomplished as described in the following paper.[19]

Supplementary Material Available: ^{1}H NMR and IR spectral data for compounds **1–21** (3 pages). Ordering information is given on any current masthead page.

(14) The silylation occurred in 96% yield to afford a 12.5:1 ratio, respectively, of bis-homopropargyl and homopropargyl silyl ethers, which were carried through and separated chromatographically as the triflate esters.
(15) Binkley, R. W.; Ambrose, M. G.; Hehemann, D. G. *J. Org. Chem.* **1980**, *45*, 4387.
(16) Corey, E. J.; Suggs, J. W. *Org. Chem.* **1975**, *40*, 2554.
(17) In addition ca. 15% of the isomeric *cis*-vinylstannane could be obtained after chromatography and thermally equilibrated to an 85:15 mixture of the trans and cis isomers, which could be separated to provide more **19**.
(18) Lipschutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305.
(19) This research was assisted financially by a generous grant from the National Institutes of Health.

Total Synthesis of Aplasmomycin

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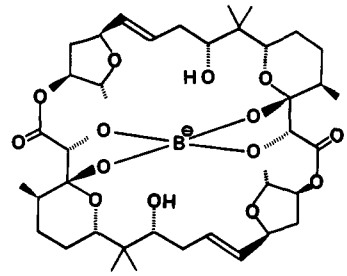
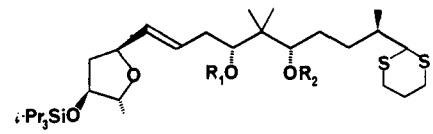
Described herein is the realization of the first total synthesis of the boron-containing antibiotic aplasmomycin (**1**)[1] based on



1



2 R_2 = MTM, R_1 = H
3 R_2 = MOM, R_1 = H
4 R_1 = R_2 = t-BuSi$(CH_3)_2$

the previously reported[2] intermediates **2** and **3**, which correspond to the C(3)–C(17) segment of the two identical C(1)–C(17) molecular subunits. Alternative synthetic routes were developed that utilize *either* **2** or **3** and that involve either sequential coupling of subunits and cyclization or combined, one-step coupling and cyclization. The introduction of borate was effected in the last step. A subsequent publication will deal with the approach in which borate is attached to the subunits prior to coupling to serve as a template for macrocycle formation.

The intermediate **2** was converted to the bis-silylated form **4** in 85% overall yield by the sequence (1) silylation with *tert*-butyldimethylsilyl triflate (1.5 equiv)–2,6-lutidine[3] at −20 °C for 2 h, (2) MTM cleavage[4] using silver nitrate–2,6-lutidine in 4:1 tetrahydrofuran (THF)–water at 23 °C for 2 h, and (3) silylation as in step 1.[5,6] Metalation of the dithiane unit in **4** was accomplished by using 1 equiv of *n*-butyllithium and 1 equiv of tetramethylethylenediamine in THF at −30 °C for 2 h to give a lithium reagent which was cooled to −78 °C, treated with 2 equiv of hexamethylphosphorictriamide (HMPA), and then allowed to react with 10 equiv of dimethyl oxalate in THF at −78 °C (30 min), −50 °C (30 min), −30 °C (30 min), and 0 °C (15 min). Extractive isolation and chromatography on silica gel furnished the α-keto ester **5** in 96% yield. Conversion of **5** to the corresponding α-keto acid **6** occurred quantitatively upon heating **5** with 15 equiv of lithium iodide and 2 equiv of 2,6-lutidine in dimethylformamide (DMF); (10 mL/g of **5**) at 75 °C for 18 h. Transformation of **5** to the hydroxy ester **7** was effected in 97%

(1) Nakamura, H.; Sitaka, Y.; Kitahara, T.; Okazaki, T.; Okami, Y. *J. Antibiot.* **1977**, *30*, 714.
(2) For synthesis see: Corey, E. J.; Pan, B.-C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.*, preceding paper in this issue.
(3) Corey, E. J.; Cho, H.; Rücker, Ch.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(4) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269.
(5) All reactions involving air-sensitive components were conducted under an argon atmosphere. Each intermediate was characterized by infrared, proton magnetic resonance (^{1}H NMR), and mass spectral analysis.
(6) The MTM group was replaced by *tert*-butyldimethylsilyl because the MTM unit appeared to interfere with the next step (dithiane metalation).

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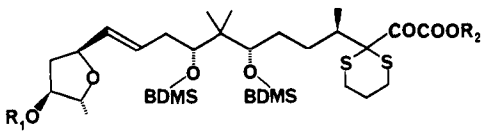
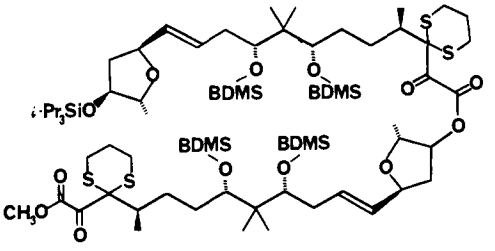


5 R_1 = i-Pr_3Si, R_2 = CH_3
6 R_1 = i-Pr_3Si, R_2 = H
7 R_1 = H, R_2 = CH_3

yield by treatment with 1 equiv of tetra-*n*-butylammonium fluoride in THF at 23 °C for 30 min.[7] Reaction of 1 equiv each of **6** and **7** with 2 equiv of *N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP chloride)[8] and 4 equiv of triethylamine in methylene chloride (12 mL/g of **6**) at 23 °C for 2 h produced the ester **8**



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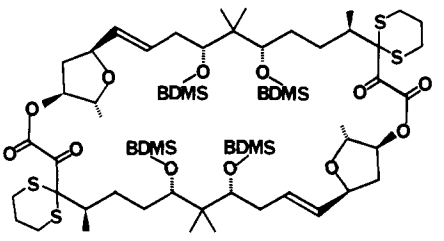
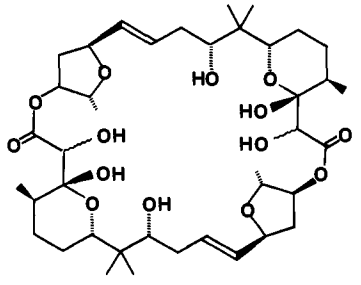


9

in 98% yield. Cyclization of **8** to form the macrocycle **9** was accomplished by the sequence (1) methyl ester cleavage (15 equiv of lithium iodide, 2 equiv of 2,6-lutidine, in DMF at 75 °C for 18 h; 96% yield), (2) triisopropylsilyl ether cleavage (1 equiv of tetra-*n*-butylammonium fluoride in THF at 23 °C for 30 min; 96% yield, and (3) lactonization of the resulting hydroxy acid using 3 equiv of BOP chloride and 7 equiv of triethylamine in methylene chloride (75 mL/g of acid) at 23 °C for 6 h (yield of **9**, 71%). The efficiency of the cyclization to give **9** under conditions of only moderate dilution is noteworthy.

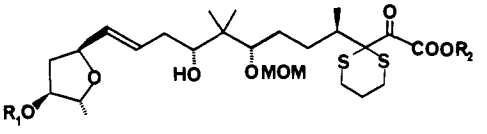
The protected macrocyclic dilactone **9** was transformed into "deboro" aplasmomycin **10**, obtained as a mixture of diastereomers



10

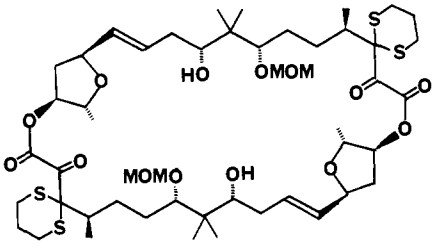
differing in configuration at the carbons α to the lactone carbonyls, by the sequence (1) reduction of the α-keto groups (8 equiv of sodium borohydride in ethanol at −20 °C for 2 h; 88% yield), (2) desilylation using 7:3 acetonitrile–48% hydrofluoric acid at −10 °C for 20 min and 23 °C for 120 min (95% yield), and (3) dithiane cleavage using 12 equiv of mercuric chloride, 24 equiv of calcium carbonate in 4:1 acetonitrile–water at 23 °C for 9 h, (94% yield after purification by flash chromatography on silica gel).[9] The ^{1}H NMR spectrum of synthetic **10** showed each of the peaks exhibited by a sample of deboro aplasmomycin (obtained by citric acid treatment of aplasmomycin)[10] and in addition another set of peaks indicative of a second diastereomer in equal amount. Treatment of synthetic **10** as the mixture of diastereomers (not separable by thin-layer chromatography) with 10 equiv of trimethyl borate in methanol at reflux for 5 h afforded after flash chromatography on silica gel pure synthetic aplasmomycin (75% yield), $[\alpha]^{20}_D$ +202° (*c* 0.05 in chloroform).[11,12] Identity of synthetic and naturally derived aplasmomycins was established by the correspondence of proton (270 MHz) and ^{13}C nuclear magnetic resonance spectra and infrared and mass spectra, as well as by thin-layer chromatographic comparison on silica gel plates with 1:1 ethyl acetate–hexane, 20:1 chloroform–methanol, or 2:1 hexane–THF for elution.

The MOM ether **3** was converted to aplasmomycin by an even shorter route. Direct metalation of **3** with butyllithium and reaction with dimethyl oxalate (as described above for **4**) gave α-keto ester **11**, which was hydrolyzed and desilylated (as described above

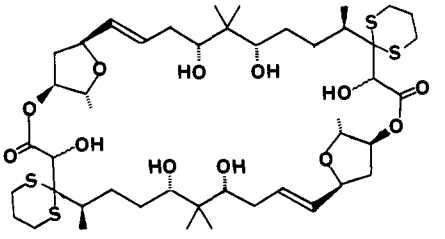


11 R_1 = i-Pr_3Si, R_2 = CH_3
12 R_1 = R_2 = H

for **5**) to afford the dihydroxy acid **12**. Reaction of **12** in methylene chloride (100 mL/g of **12**) with BOP chloride (4 equiv) and triethylamine (8 equiv) at 23 °C for 12 h afforded in 25% yield the macrocycle **13**. In addition the various byproducts when



13



14

saponified by base were cleanly converted to the starting dihydroxy acid **12**, making this one-step coupling and cyclization procedure highly effective; sodium borohydride (−20 °C in methanol) selectively reduced the two α-keto groups in **13** to afford a macrocyclic bis-MOM ether tetraol. Cleavage of the MOM ether groups was effected in 80% yield by using 6 equiv of diiso-

(7) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(8) Diago-Mesequer, J.; Palomo-Coll, A. L.; Fernandez-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547.
(9) Mercuric salts were precipitated prior to workup of the reaction mixture by the addition of sodium sulfide.
(10) Sato, K.; Okazaki, T.; Maeda, K.; Okami, Y. *J. Antibiot.* **1978**, *31*, 632.
(11) Under the same conditions a sample of naturally derived aplasmomycin showed $[\alpha]^{23}_D$ +205°.
(12) Clearly equilibration at C(2) (via enolization) accompanies borate bridging, the formation of aplasmomycin being thermodynamically favorable.

propylthioboron bromide[13] in methylene chloride at −78 °C for 3 h to give after quenching with aqueous sodium bicarbonate, extractive isolation, and chromatography on silica gel the macrocycle **14**. This intermediate was identical in all respects (TLC, IR, ^{1}H NMR) with the product obtained from **9** by sodium borohydride reduction and desilylation (as described above); intermediate **14** is convertible to aplasmomycin in two steps, dithiane cleavage and borate complexation.

It is worthy of note that cleavage of the MOM ethers in **13** is not realizable by conventional acid-catalyzed hydrolysis since a six-membered cyclic formal results under these conditions from participation of the neighboring hydroxyl at C(9). In the method of cleavage using diisopropylthioboron dibromide, the C(9) hydroxyl serves to faciliate MOM ether cleavage by formation of a diisopropylthioborate ester which by coordination to the hydroxyl at C(7) catalyzes MOM ether cleavage.[14]

The total synthesis of aplasmomycin reported herein is convergent, stereocontrolled, and efficient. It leads to the natural product without the need for resolution.

Further results on other methods of macrocycle formation and on the extension of this work to the synthesis of boromycin will be discussed in subsequent papers.[15]

Supplementary Material Available: ^{1}H NMR and IR data for compounds **4-14** (2 pages). Ordering information is given on any current masthead page.

(13) Goubeau, J.; Wittmeier, H. W. *Z. Anorg. Allgem. Chem.* **1952**, *270*, 16.

(14) For further examples and a more complete discussion of boron-assisted cleavage of MOM ethers of 1,3- and 1,2-diols see: Corey, E. J.; Seitz, S. *Tetrahedron Lett.*, in press.

(15) This work was assisted financially by a grant from the National Institutes of Health. We are indebted to Professor Hamao Umezawa and Dr. Yoshiro Okami of the Institute of Microbial Chemistry, Tokyo, and to Professor Heinz G. Floss of Purdue University for providing reference samples of aplasmomycin.

Formation of Perthiocarbonate Ligands following the Addition of CS_2 to Binary Mo-S Complexes. Crystal and Molecular Structures of the $(Ph_4P)_2[(CS_4)_2MoS]\cdot DMF$ and $(Ph_4P)_2[(CS_4)Mo_2S_4(CS_4)]\cdot{}^1/_2DMF$ Complexes

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The hydrogenolysis of organosulfur compounds in petroleum products (hydrodesulfurization) is facilitated by heterogeneous catalysts that often contain "sulfided" molybdenum and cobalt salts supported on alumina. Although it has been proposed that a molybdenum sulfide surface is the catalytic site,[1] little is known about the mechanistic course and intermediates of this important reaction. A basic understanding of the likely interactions between organosulfur compounds and Mo-S surfaces conceivably could be obtained from reactivity studies on well-defined Mo-S complexes. Various binary molybdenum thioanions have been synthesized and structurally characterized in recent years. In compounds such as $[Mo_2(S_2)_6]^{2-}$,[2] $[Mo_3S(S_2)_6]^{2-}$,[3] $[(MoS_4)_2MoS]^{2-}$,[4] $[(S_4)_2MoS]^{2-}$,[5] $[(S_4)Mo_2S_4(S_2)]^{2-}$,[5b,6] and $[(S_4)Mo_2S_4(S_4)]^{2-}$,[5b] the molybdenum atoms are coordinated by sulfide (S^{2-}), persulfide (S_2^{2-}), or tetrasulfide (S_4^{2-}) ligands.

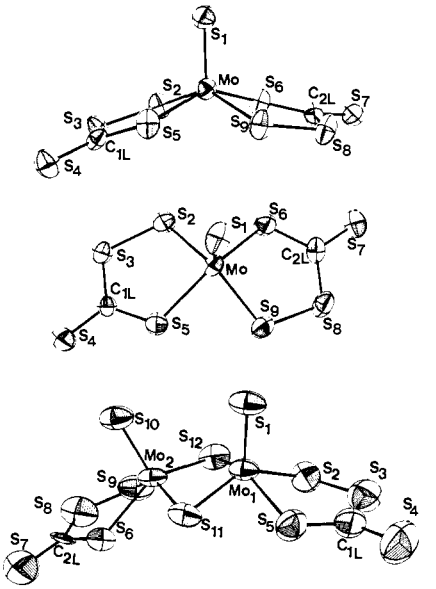

Figure 1. Structures of the $[(CS_4)_2MoS]^{2-}$ and $[(CS_4)Mo_2S_4(CS_4)]^{2-}$ anions showing the atom labeling scheme. Thermal ellipsoids are drawn by ORTEP (Johnson, C. K., ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965) and represent the 50% probability surfaces.

In this communication we report on the reactions of the $(Ph_4P)_2[(S_4)_2MoS]$ (I) and $(Ph_4P)_2[(S_4)Mo_2S_4(S_2)]$ (II) complexes with CS_2 and on the crystal and molecular structures of the CS_2 addition products. The formation and isolation of either I or II, from dimethylformamide (DMF) solutions of $(Ph_4P)_2MoS_4$ and dibenzyl trisulfide (BzSSSBz) in a 1:5 molar ratio at ambient temperatures, depend on the concentration of the reagents. From DMF solutions 0.011 M in $(Ph_4P)_2MoS_4$ and 0.055 M in BzSSSBz, II and $(Ph_4P)_2[(S_4)Mo_2S_4(S_4)]$ (as a minor component) can be isolated as crystalline solids in good yields.[5b] A 4-fold increase in the concentrations of both reagents affords I in excellent yields. Both I and II react with CS_2 (in large excess) in DMF solution at ambient temperatures. Crystalline products are obtained from the reaction mixtures by the addition of diethyl ether to incipient crystallization and standing. Red-orange crystals of $(Ph_4P)_2[(CS_4)_2MoS]\cdot DMF$ (III) are obtained from I in 76% yield. Anal. Calcd for $MoS_9P_2ONC_{53}H_{47}$: C, 54.87; H, 4.06; Mo, 8.28; P, 5.35; S, 24.85. Found: C, 54.79; H, 4.26; Mo, 7.79; P. 5.36, S, 24.48. The orange-red, crystalline $(Ph_4P)_2[(CS_4)Mo_2S_4(CS_4)]\cdot{}^1/_2DMF$ complex (IV) is obtained from II in 75% yield. Anal. Calcd for $Mo_2S_{12}P_2O_{1/2}N_{1/2}C_{51.5}H_{43.5}$: C, 47.01; H, 3.31; Mo, 14.61; S, 29.21. Found: C, 46.25; H, 3.37; Mo, 14.97; S, 30.12. The visible spectrum of III is characterized by absorptions at 430 nm (ϵ 20,980) and 334 (ϵ 36,200) nm. In the electronic spectrum of IV absorptions are observed at 610, 470, 365, and 314 nm as shoulders on a broad band. In both III and VI the presence of a strong absorption in the infrared at ca. 980 cm^{-1} is attributed to the C=S asymmetric stretching vibration of the CS_4^{2-} ligand. Cyclic voltammetry in CH_2Cl_2[7] shows irreversible oxidations at 0.47 and 0.87 V and an irreversible reduction at −0.28 V for III. An irreversible reduction at −1.13 V is found for IV.

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(2) Müller, A.; Nolte, W. O.; Krebs, B. *Inorg. Chem.* **1980**, *19*, 2835-2836 and references trherein.

(3) (a) Müller, A.; Bhattacharyya, R. G.; Pfefferkorn, B. *Chem. Ber.* **1979**, *112*, 778-780. (b) Müller, A.; Pohl, S.; Dartmann, M.; Cohen, J. P.; Bennet, J. M.; Kirshner, R. M. *Z. Naturforsch., B. Anorg. Chem., Org. Chem.* **1979**, *34B*, 434-436.

(4) (a) Pan, W. H.; Stiefel, E. I. 2nd National Meeting of the American Chemical Society, New York, Aug 23-28, 1981; Abstracts. (b) Stiefel, E. Proceedings "Nitrogen Fixation; The Chemical-Biochemical-Genetics Interface"; Universität Bielefeld, June 29-July 1, 1981; Plenum Press, in press.

(5) (a) Simhon, E. D.; Baenziger, N. C.; Kanatzidis, M.; Draganjac, M.; Coucouvanis, D. *J. Am. Chem. Soc.* **1981**, *103*, 1218-1219. (b) Draganjac, M.; Simhon, E. D.; Chan, L. T.; Kanatzidis, M. Baenziger, N. C.; Coucouvanis, D. *Inorg. Chem.* **1982**, *21*, 3321-3332.

(6) Clegg, W.; Christou, G.; Garner, C. D.; Sheldrick, G. M. *Inorg. Chem.* **1981**, *20*, 1562-1566.

(7) On a platinum electrode vs. SCE, solutions were 1 × 10^{-3} M in electroanalyte and 0.1 M in Bu_4NClO_4.

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