^{3}Fl is responsible for both hydrogen atom abstraction and for formation of the ether products.

The reaction of DAF in acetonitrile with methanol can be sensitized with triplet thioxanthone. Irradiation of an 8×10^{-4} M solution of thioxanthone containing 9.2×10^{-4} M DAF and 0.5 M methanol at 380 nm gives the ether in 92% yield. When 0.05 M 2,5-dimethyl-2,4-hexadiene is included in the reaction mixture as a quencher of thioxanthone triplet, the formation of the ether is slowed by a factor of ca. 40, indicating that the diene and DAF are competing for the sensitizer triplet. These findings also *appear* to show that ^{3}Fl is responsible for formation of ethers from alcohols.

The dilemma generated by the observation of singlet reactivity from a carbene that appears to be a triplet can be resolved if at room temperature ^{3}Fl is in very rapid equilibrium with the as yet unseen ^{1}Fl.[12] The rate of equilibration between the two spin states in this model is faster than any reaction we have yet examined in relatively dilute acetonitrile or spiropentane solution. Assuming that reaction of the singlet carbene with methanol can be no faster than diffusion controlled, the kinetics suggest that the equilibrium mixture in acetonitrile at room temperature contains at least 5% ^{1}Fl. Equilibration between a singlet and triplet carbene has been suggested previously to account for the chemistry of diphenylmethylene.[13]

These new findings necessitate a reinterpretation of the chemical properties attributed earlier to ^{1}Fl and ^{3}Fl.[2,3,14–16] The previous assignments of ^{1}Fl and ^{3}Fl rested in large part on the analysis of competition reactions between methanol and various olefins for the carbene. These studies confirmed that a species generated prior to the one responsible for the 400-nm absorption in acetonitrile formed products appropriate for ^{1}Fl with the anticipated yields. The present results indicate that there are at least two species preceding the one that absorbs at 400 nm, the triplet carbene and its unseen precursor and companion, which is presumably the singlet. The competition experiments reported earlier, although confirming the measured rate constants, cannot indicate which spin state is responsible for the observed products if their equilibration is more rapid than their reaction. Indeed, in this circumstance the observed chemical properties of the carbene may simply reflect the nature of the reagent used as the probe. Alcohols react with the singlet carbene and drain the equilibrium from that side, and hydrocarbons react with ^{3}Fl to give free radical products. At high concentration a very reactive probe may intercept the precursor to ^{3}Fl before equilibration has been achieved. In this case spin-specific reactivity might be observed.[1]

Acknowledgment. This work was supported by grants from the National Science Foundation and from the National Institutes of Health. We particularly wish to thank Cynthia Teeters for her help with the low-temperature optical spectroscopy and M. Hendrich and Dr. P. DeBrunner of the Physics department for their assistance with the low-temperature EPR spectroscopy. We also thank Drs. D. Griller and J. Scaiano of NRC, Canada, and M. Platz of Ohio State University for discussion of this work and for sharing with us their results prior to publication.

Registry No. DAF, 832-80-4; FlH·, 2762-16-5; H, 1333-74-0; ethanol, 64-17-5; methanol, 67-56-1; thioxanthone, 492-22-2; 2,5-dimethyl-2,4-hexadiene, 764-13-6; cyclohexane, 110-82-7.

(12) Another possibility, suggested by D. Griller and J. C. Scaiano of NRC, Canada, is that the alcohols react with ^{3}Fl to give the observed ether products.

(13) Closs, G. L.; Rabinow, B. E. *J. Am. Chem. Soc.* **1976**, *98*, 8190. Eisenthal, K. B.; Turro, N. J.; Aikawa, M.; Butcher, J. A., Jr.; DuPuy, C.; Hefferson, G.; Hetherington, W.; Korenowski, G. M.; McAuliffe, M. J. *Ibid.* **1980**, *102*, 6563. Gaspar, P. P.; Whitsel, B. L.; Jones, M., Jr.; Lambert, J. B. *Ibid.* **1980**, *102*, 6108. DuPuy, C.; Korenowski, G. M.; McAuliffe, M.; Hetherington, W. M.; Eisenthal, K. B. *Chem. Phys. Lett.* **1981**, *27*, 272.

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(15) Zupancic, J. J.; Grasse, P. B.; Schuster, G. B. *J. Am. Chem. Soc.* **1981**, *103*, 2423.

(16) Wong, P. C.; Griller, D.; Scaiano, J. C. *Chem. Phys. Lett.* **1981**, *83*, 69.

(17) Wilson, P. D.; Edwards, T. H. *Appl. Spectrosc. Rev.* **1976**, *12*, 1.

Total Synthesis of Aplasmomycin. Stereocontrolled Construction of the C(3)–C(17) Fragment

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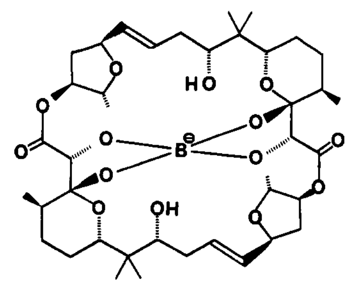
Received August 10, 1982

Aplasmomycin, isolated from a marine-derived strain of *Streptomyces griseus*, is a boron-containing antibiotic ($C_{40}H_{60}O_{14}BNa$) that exhibits activity against Gram-positive bacteria and also Plasmodia.[1] It belongs to the family of borate-bridged macrocycles of which boromycin was the first known member.[2] X-ray crystallographic analysis of aplasmomycin silver salt revealed a beautifully symmetrical C_2 structure composed of two identical subunits bound together as indicated in formula **1**.[3] The



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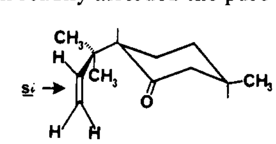
unique structure and biological activity of aplasmomycin distinguish this molecule as an unusually interesting target for synthesis. Reported in this and the following paper is the first total synthesis of aplasmomycin. In overall outline the synthesis was conducted by the construction of precursors corresponding to the C(3)–C(10) fragment (starting with inexpensive commercial (+)-pulegone) and the C(11)–C(17) fragment (starting from D-mannose). Coupling of these intermediates and chain extension with dimethyl oxalate formed the entire C(1)–C(17) chain of the aplasmomycin subunit, from which the antibiotic was obtained by coupling, macrolactonization, adjustment of functionality, and introduction of borate.

Reaction of (+)-pulegone with the reagent from 2.5 equiv of vinylmagnesium bromide and 1.25 equiv of cuprous iodide in terahydrofuran (THF) at −30 °C for 1 h afforded after extractive isolation a 1:1 mixture of *trans*- and *cis*-5-methyl-2-(1,1-dimethylallyl)cyclohexanones (88%), which was equilibrated by exposure to 0.1 equiv of sodium methoxide in methanol to an 85:15 trans–cis mixture.[4] Chromatography on silica gel using a Waters Associates Model 500 preparative machine with 1% ether in hexane for elution readily afforded the pure trans isomer (**2**) as



2

a colorless oil.[5] In the next step a crucial 1,3-stereorelationship was established by taking advantage of the sizeable steric inter-

† Formerly written as Pan Pei-Chuan.

(1) Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176.

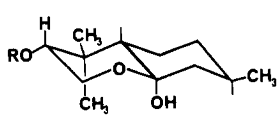
(2) Dunitz, J. D.; Hawley, D. M.; Mikloš, D.; White, D. N. J.; Berlin, Y.; Marušić, R.; Prelog, V. *Helv. Chim. Acta* **1971**, *54*, 1709.

(3) Nakamura, H.; Sitaka, Y.; Kitahara, T.; Okazaki, T.; Okami, Y. *J. Antibiot.* **1977**, *30*, 714.

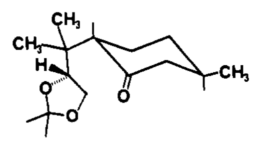
(4) Reactions involving air-sensitive reagents, intermediates, or products were conducted under dry argon.

(5) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each stable intermediate by using chromatographically purified and homogeneous samples.

actions between the cyclohexanone unit and the attached α-tertiary appendage. Assuming a chair-formed cyclohexanone, a staggered appendage-ring bond with the appendage methyls at a maximum distance from the carbonyl oxygen, and further, an *s*-trans arrangement of vicinal vinyl C–H and C–CH_3 bonds, we expected attack by osmium tetraoxide on the vinyl group to occur at the sterically more accessible *si*[6] face. In fact, catalytic hydroxylation of **2** by using 0.002 equiv of osmium tetraoxide and 1.1 equiv of *N*-methylmorpholine *N*-oxide in 2:1 acetone–water at 23 °C for 12 h afforded after recrystallization from ether 76% yield of the cyclic hemiketol **3**, mp 147 °C, which showed hydroxyl but not



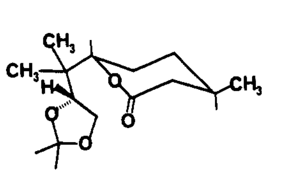
3 R = H
4 R = CH_3CO



5

carbonyl stretching absorption in the infrared. The stereochemistry of this product, which corresponds to hydroxylation at the *si* face of the double bond, was ascertained simply by monoacetylation to **4** and proton magnetic resonance (^1H NMR) analysis. The acetoxymethine proton (HCOAc) of **4** was clearly axial as shown by couplings of 10.6 and 5.3 Hz with the adjacent methylene protons.[7] The high degree of 1,3-diastereoselection of the hydroxylation step suggests that this approach could be of value in other synthetic applications.

Reduction of **3** with 2 equiv of lithium aluminum hydride in THF at reflux for 2 h afforded quantitatively a triol, which after ketalization (acetone, tosic acid catalyst at 23 °C for 4 h) and oxidation with 2 equiv of pyridinium chlorochromate[8] in methylene chloride in the presence of 3-Å molecular sieve at 20 °C for 8 h gave the keto acetonide **5** (70% from **3**). Baeyer–Villiger oxidation of **5** (1.5 equiv of 0.25 M *m*-chloroperbenzoic acid in benzene at 23 °C for 6 days) produced ketal lactone **6** (83%),



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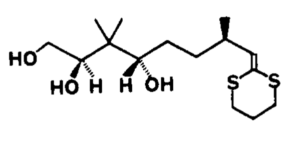

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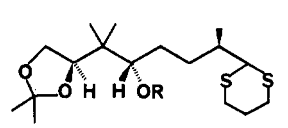
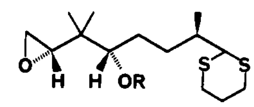


8 R = H
9 R = MTM
10 R = MOM

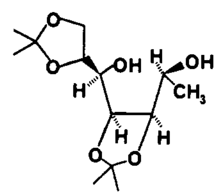
which upon treatment in methylene chloride at 23 °C for 24 h with a reagent prepared from 4 equiv of trimethylaluminum and 2 equiv of propane-1,3-dithiol[9] gave the ketenethioacetal triol **7** (87% yield). The triol **7** was transformed into the hydroxy ketal thioketal **8** by the following sequence: (1) ozonolysis at –78 °C in methanol (slight excess of ozone), addition of dimethyl sulfide to reduce peroxides, replacement of methanol with methylene chloride, and reaction with propane-1,3-dithiol–boron trifluoride etherate (23 °C for 30 min) to form the noraldehyde thioacetal (72%); (2) acetonide formation (2,2-dimethyoxypropane, tosic acid, 23 °C for 2 h; 80% yield). The hydroxyl group of **8** was protected in two alternative ways: (1) as the methylthiomethyl (MTM) ether (**9**; excess dimethyl sulfoxide–acetic acid–acetic anhydride[10] containing sodium acetate at 23 °C for 20 h; yield 73%); (2) as the methoxymethyl (MOM) ether **10** (4 equiv of chloromethyl methyl ether, 10 equiv of triethylamine, 2 equiv of 4-(dimethylamino)pyridine in dimethylformamide at 60 °C for 4 h; yield 80%). The MTM ether **9** was transformed in 80% overall yield into the epoxide **11** without purification of inter-



11 R = MTM
12 R = MOM

mediates by the sequence (1) selective acetonide cleavage to a 1,2-diol in 93% yield using 3:1 acetic acid–water at 50 °C for 45 min, (2) selective benzoylation at the primary hydroxyl using 1.1 equiv of benzoyl cyanide[11] and 1.2 equiv of triethylamine in acetonitrile at –10 °C for 10 min followed directly by reaction with 1.5 equiv of methanesulfonyl chloride and 2 equiv of triethylamine in ether at 0 °C for 3 h to form the primary benzoate, secondary mesylate of the 1,2-diol, and (3) benzoate cleavage and epoxide closure using tetra-*n*-butylammonium hydroxide in ether containing a little methanol at 23 °C. The epoxide MOM ether **12** was made in an analogous fashion.

Reaction of the readily available bis-acetonide of D-mannose[12] in THF with 2.2 equiv of methyllithium in ether at –40 °C for 1 h and 0 °C for 6 h proceeded stereospecifically to give 99% yield of the diol expected from addition of methyl to the *si* face of formyl chelated by lithium to the α-ketal oxygen (**13**). The stereo-



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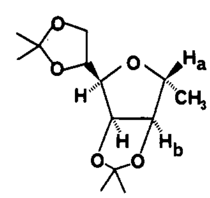

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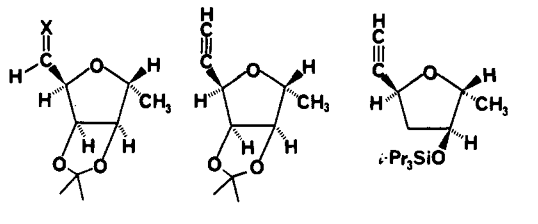
chemistry of **13** was clarified by ^1H NMR analysis of the product of the next step, **14**, which was formed in 91% yield by reaction of **13** with 2 equiv of tosyl chloride in pyridine at 50 °C for 34 h. The conversion of **13** to **14** proceeds via tosylation of the methyl carbinol unit as shown by isolation of this intermediate from experiments at lower temperature. ^1H NMR decoupling revealed J_{ab} in **14** to be 0.8 Hz (H_a at δ 4.20), demonstrating a trans arrangement of H_a and H_b. Since the carbon of **14** holding H_a was the site of internal S_N2 displacement the predecessor must be formulated as **13**. The bis-acetonide **14** is a colorless liquid, bp 120 °C (0.2 torr), $[\alpha]^{23}_D$ –39° (*c* 2 in $CHCl_3$). The acetonyl group attached to the side chain was selectively hydrolyzed in 90% yield at 60% conversion (30:2:1 methanol–water–12 N hydrochloric acid, 4 °C, 24 h), and the resulting diol (easily separated from **14** by rough column chromatography on silica gel) was treated with 1.2 equiv of sodium periodate and 1.2 equiv of sodium bicarbonate in water at 0 °C for 1 h to give the aldehyde **15**, infrared max in CCl_4 1733 cm^{-1} (96% yield).

Reaction of **15** with 1.5 equiv of bromotrichloromethane and 3.3 equiv of tris(dimethylamino)phosphine (–50 °C for 2 h, –10 °C for 1 h, and 5 °C for 0.5 h) produced the dichloroolefin **16** (75%), which after reaction with 2 equiv of *n*-butyllithium in THF at –78 °C for 1.5 h afforded the acetylene **17** in 99% yield.[13]

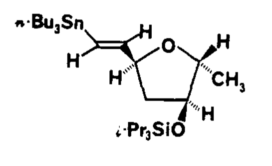
Acetylene **17** was converted to the silylated deoxy derivative **18** in 56% overall yield by the sequence (1) acetonide cleavage using 10:1 methanol–4 N hydrochloric acid at 23 °C for 24 h (92%

(6) Prelog, V.; Helmchen, G. *Helv. Chim. Acta* **1972**, *55*, 2581. Epoxidation with peracid was less selective.
(7) The expected trans fusion for **3** and **4** is indicated by ^1H NMR data.
(8) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(9) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829.
(10) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.
(11) Tanaka, M. *Tetrahedron Lett.* **1980**, *21*, 2959.
(12) Lee, J. B.; Nolan, T. J. *Tetrahedron* **1967**, *23*, 2789.
(13) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

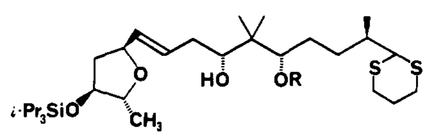


15 X = O **16** X = CCl$_2$ **17** **18**

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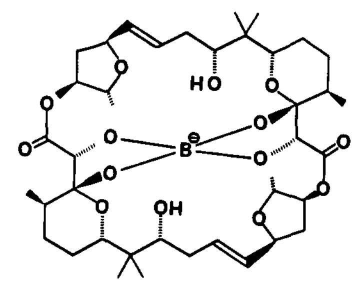
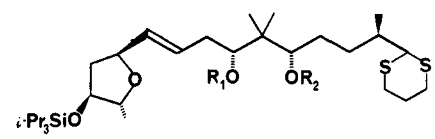
Described herein is the realization of the first total synthesis of the boron-containing antibiotic aplasmomycin (**1**)[1] based on



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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