the slow addition of 2.5 mL of a 50 mM solution of BHAO in methanol to 5.0 mL of a 50 mM solution of $Cu(ClO_4)_2 \cdot 6H_2O$ in methanol yielded a deep blue solution characterized by electronic absorptions at 282 and 630 nm (ϵ = 9700 and 100 L mol^{-1} cm^{-1}, respectively). Upon the addition of a trace of aqueous NaOH, a new electronic absorption spectrum was observed with three bands, at 292, 465, and 630 nm (ϵ = 12,700, 270, and 300). A deep blue-violet precipitate was isolated either by allowing the solution to stand for several days or by slow infusion of $CHCl_3$ into the Cu-containing solution. The analytical data[21] were consistent with the formulation of this compound as a monohydrated[22] hydroxy-bridged perchlorate complex, $[Cu_2(OH)\subset BHAO](ClO_4)_3 \cdot H_2O$. The IR spectrum (Fluorolube mull) had a weak OH stretch at 3580 cm^{-1} (superimposed on a broad OH absorption), which is close to the OH band positions observed[23,24] for some recently reported monohydroxy-bridged dicopper(II) complexes. Preliminary magnetic susceptibility data with the solid compound indicate a strong antiferromagnetic exchange interaction.[25] This magnetic behavior is consistent with a hydroxide bridge between the copper centers as has been recently found for structurally characterized monohydroxy-bridged dicopper(II) compounds.[24,26,27]

Addition of other anions such as N_3^-, NO_2^-, SCN^-, acetate, and phenolate to the methanolic solution of $[Cu_2\subset BHAO]^{4+}$ resulted in changes in the electronic absorption spectrum indicative of interactions with the Cu centers. For example, addition of N_3^- gave a new spectrum with absorptions at 282, 390, and 582 nm (ϵ = 9500, 3200, and 200); addition of phenolate gave bands at 267, 300, and 675 nm (ϵ = 10,000, 4000, and 80). Preliminary examination of X-band EPR spectra (frozen glasses of 1:1 CH_3OH:toluene) of the dicopper complex in the presence of potentially bridging anions such as those listed above provided axial spectra with equivalent Cu's. The values found for the dicopper complex and added phenolate are typical with $g_\parallel \approx 2.21$, $g_\perp \approx 2.01$, and $A_\parallel$ = 184 G.

In summary, these new "open-face" macrobicycles offer promise for systematically studying substrate interactions at binuclear sites. The unique structural aspects of these systems may be particularly useful for enforcing unusual bridging modes (e.g., a single terminal N of N_3^- bridging two Cu's) which are relevant to elucidation of the nature of substrate interactions with bimetallic metalloproteins[28] and the design of new catalysts.[29] Future efforts will be directed toward structural characterization of such species and relating the structures to their physical and chemical properties.

Acknowledgment. This work was partially supported by the Center for Catalytic Science and Technology at the University of Delaware. We also acknowledge the National Science Foundation (Grant CHE 7803312) for funds used to purchase the Varian E-109E EPR spectrometer.

Registry No. 9 ($n = m = 4$), 80631-47-6; **11** ($n = m = 4$), 80631-48-7; $[Cu_2(OH)\subset BHAO](ClO_4)_3$, 80642-28-0; $[Cu_2(N_3)\subset BHAO]^{3+}$, 80642-29-1; $[Cu_2OPh)\subset BHAO]^{3+}$, 80642-30-4; $[Cu_2\subset BHAO]^{4+}$, 80642-31-5.

(21) Elemental analysis: (a) Anal. Calcd for $Cu_2C_{22}H_{51}N_6Cl_3O_{14}$ (from CH_3OH upon standing): C, 30.83; H, 6.00; N, 9.80. Found: C, 30.85; H, 5.91; N, 9.71. (b) Anal. Calcd for $Cu_2C_{22}H_{51}N_6Cl_3O_{14} \cdot CHCl_3$ (from CH_3OH with infusion of $CHCl_3$): C, 28.29; H, 5.37; Cu, 13.01. Found: C, 28.40; H, 5.42; Cu, 13.01.

(22) Dicopper(II) complexes of perchlorate salts typically form monohydrates upon crystallization in the presence of H_2O.[3a,23]

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Stereocontrolled Total Synthesis of Antibiotic A-23187 (Calcimycin)†

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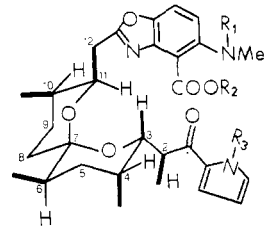
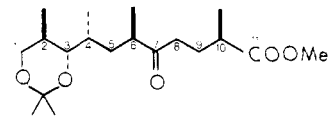
Received November 2, 1981

Considerable attention remains focused on antibiotics such as A-23187 (**1**)[1] and X-537A (lasalocid A)[2] because these ionophores



1 $R_1 = R_2 = R_3 = H$



2

17 $R_1 = CF_3CO$, $R_2 = Me$, $R_3 = NMe_2$

represent useful biochemical tools for probing the phenomenon of ion transport.[3] A-23187 (calcimycin), which was isolated from the cultures of *Streptomyces chartreusensis*, is a unique divalent cation ionophore.[1a] Intrigued by the presence of the 1,7-dioxaspiro[5.5]undecane ring system and the accompanying seven centers of chirality, we embarked, a few years ago, on a stereocontrolled total synthesis of **1**. We record below the successful realization of our goal.[4]

Careful analysis of the dioxaspiro[5.5]undecane ring system reveals that each ring oxygen atom bears an axial relationship to the six-membered ring to which it is attached. This arrangement of atoms clearly implies, based on the well-known anomeric effect,[5] that the dioxaspirane unit in A-23187 is in its most stable arrangement. Thus the acyclic keto diol derived from **1**, or its equivalent, emerges as the logical precursor to A-23187 via a thermodynamically controlled acid-catalyzed ring closure. Synthetic efforts reported to date[1b,c] have concentrated on an aldol approach for the elaboration of the chirality at C(2)-C(4). However, the stereochemical problems associated with such an approach led us to pursue an alternate pathway to A-23187 that centered around the stereospecific construction of the C(1)-C(11) segment **2**.

The basic plan for the synthesis of the C(1)-C(11) acyclic portion of A-23187 was performed in two stages (Scheme I): (1) preparation of the C(1)-C(7) segment **7** of **1** from the known bicyclo[2.2.1]heptenone **3**[1c] and (2) elaboration of the remaining C(8)-C(11) carbon atoms bearing the additional chiral center at C(10) onto the C(1)-C(7) segment via the application of the Ireland ester enolate Claisen rearrangement[6] to the propionate

†Dedicated to Professor Gilbert Stork on the occasion of his 60th birthday.

(1) (a) Chaney, M. D.; Demarco, P. V.; Jones, N. D.; Occolowitz, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1932. (b) The first total synthesis of A-23187 was recently reported: Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *Ibid.* **1979**, *101*, 6798. (c) For a formal total synthesis of **1**, see: Grieco, P. A.; Williams, E.; Tanaka, H.; Gilman, S. *J. Org. Chem.* **1980**, *45*, 3537.

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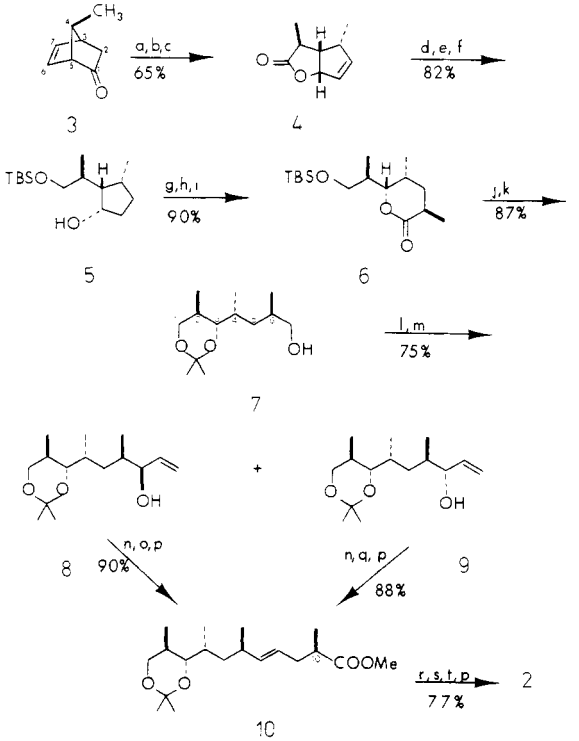
Scheme I. Construction of the C(1)–C(11) Segment 2[a]



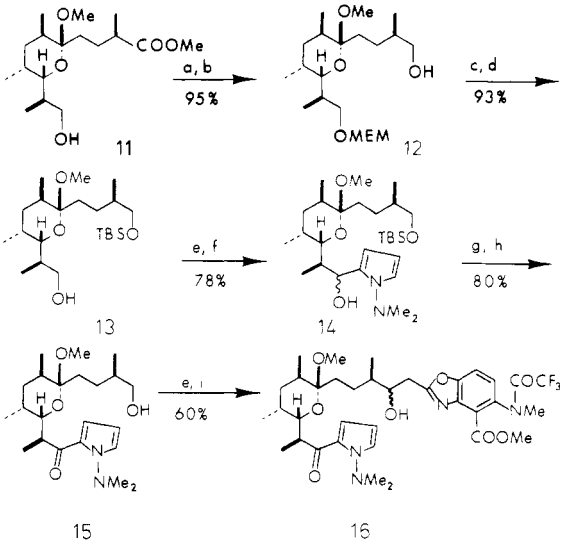
[a] (a) H_2O_2, OH^-, MeOH. (b) $BF_3 \cdot Et_2O$, C_6H_6. (c) LDA, THF, HMPA, MeI, −78 °C. (d) $LiAlH_4$, Et_2O. (e) H_2, PtO_2, EtOAc. (f) *t*-Bu(Me)$_2$SiCl, CH_2Cl_2, DMAP, Et_3N. (g) $CrO_3 \cdot 2pyr$, CH_2Cl_2, 0 °C, 20 min. (h) MCPBA, $NaHCO_3$, CH_2Cl_2, 0–5 °C. (i) LDA, THF, HMPA, −78 °C, MeI. (j) $LiAlH_4$, Et_2O. (k) Acetone, $CuSO_4$, TsOH. (l) $CrO_3 \cdot 2Pyr$, CH_2Cl_2, 30 min, 0 °C. (m) CH_2=CHMgBr, THF, −78 °C. (n) C_2H_5COCl, pyr. (o) LDA, THF, −78 °C; TBSCl, HMPA; reflux, 1.5 h; Bu_4NF. (p) CH_2N_2. (q) LDA, THF, HMPA, −78 °C; TBSCl, HMPA, reflux, 1.5 h, Bu_4NF. (r) OsO_4, pyr; $NaHSO_3$; CSA, C_6H_6. (s) Me_2SO, $(COCl)_2$, CH_2Cl_2, Et_3N, −65 °C → room temperature. (t) Al(Hg), THF, HOH, EtOH, $NaHCO_3$, 0 °C.

ester derived from vinylcarbinol **8**.

Baeyer–Villiger oxidation of **3** followed by Lewis acid catalyzed rearrangement and subsequent methylation of the resultant γ-lactone provided exclusively bicyclic lactone **4**. In a straightforward fashion **4** was transformed into **5**, which set the stage for the elaboration of **6** via a three-step stereospecific process: oxidation, Baeyer–Villiger oxidation, and methylation. Reduction of δ-lactone **6** with lithium aluminum hydride was accompanied by loss of the *tert*-butyldimethylsilyl group, giving rise to the corresponding triol, which was directly converted into acetonide alcohol **7**, which represents the intact C(1)–C(7) fragment of A-23187.

With four of the seven chiral centers in **1** defined, we focused our efforts on incorporating the four additional carbon atoms C(8)–C(11), including the chiral center at C(10), onto the existing seven-carbon fragment **7**. Addition of vinylmagnesium bromide to the aldehyde derived from alcohol **7** (Scheme I) provided as the major product vinylcarbinol **8**, in keeping with Cram's rule,[7] and the isomeric vinyl carbinol **9** in a ratio of 2:1, respectively, which could be readily separated by silica gel column chromatography. Elaboration of the stereochemical center at C(10) was efficiently realized through application of the ester enolate Claisen rearrangement to the propionate ester derived from **8**. Reaction of pure vinylcarbinol **8** with propionyl chloride followed by generation of the corresponding (*E*)-*O*-(*tert*-butyldimethylsilyl)ketene acetal gave rise exclusively to ester **10**[8] after cleavage of the silyl

Scheme II. Construction of Acyl Pyrrole 16[a]



[a] (a) MEMCl, CH_2Cl_2, *i*-Pr_2NEt. (b) $LiAlH_4$, Et_2O. (c) *tert*-Butyldimethylsilylimidazole, CH_2Cl_2. (d) BuLi, heptane; $Hg(OAc)_2$, H_2O–THF (1:1). (e) $CrO_3 \cdot 2pyr$, CH_2Cl_2, 0 °C. (f) 2-lithio-*N*(*N*,*N*-dimethylamino)pyrrole, THF, −78 °C. (g) DDQ (1.3 equiv), dioxane, 10 h. (h) Bu_4NF, THF. (i) Methyl-5-(2,2,2-trifluoro-*N*-methylacetamido)-2-lithiomethyl-4-benzoxazolecarboxylate, THF −100 °C.

ester and subsequent esterification.

*The "unwanted" vinylcarbinol **9** was also conveniently and efficiently transformed into the C(1)–C(11) ester segment **10**.* Vinylcarbinol **9** was thus converted, in comparable yield, into ester **10** by employing the same procedure as above with the exception that HMPA was present during the formation of the ester enolate to ensure formation of the (*Z*)-*O*-(*tert*-butyldimethylsilyl)ketene acetal. Transformation of **10** into **2** was carried out via a four step process: (a) glycolation, (b) oxidation, (c) reductive cleavage of the C(8)–oxygen bond, and (d) esterification (Scheme I).

Completion of the synthesis of A-23187 required introduction of both the pyrrole unit and the benzoxazole moiety onto fragment **2** (Scheme II). Toward this end ketone **2** was subjected to treatment (15 min) with methanol and *p*-toluenesulfonic acid at 0 °C, which gave rise (95% based on recovered starting material) to alcohol **11**. Protection of the hydroxyl function in **11** as a (β-methoxyethoxy)methyl (MEM) ether[9] and subsequent reduction of the ester residue provided alcohol **12**. Silylation of **12** using *tert*-butyldimethylsilylimidazole[10] in methylene chloride followed by cleavage of the MEM ether with butyllithium and exposure to $Hg(OAc)_2$ in aqueous tetrahydrofuran (1:1) provided, in 95% yield, alcohol **13**.[11]

Oxidation of **13** followed by condensation with 2-lithio-*N*-(dimethylamino)pyrrole[12] afforded adduct **14**, which when submitted to a variety of oxidation conditions (e.g., Ag_2CO_3-celite, MnO_2, $CrO_3 \cdot 2Py$, NiO_2, Me_2SO–$(COCl)_2$) led to none of the desired acyl pyrrole. Fortunately, oxidation with DDQ (1.3 equiv) in dioxane gave way to the desired acyl pyrrole, which upon desilylation (Bu_4NF, THF) generated alcohol **15**, thus setting the stage for introduction of the benzoxazole unit.

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(8) ^{13}C NMR analysis of ester **10** derived from the ester enolate Claisen rearrangement of the propionate ester derived from **8** revealed a single substance. Futher evidence that **10** was homogeneous was secured by comparison of the ^{13}C NMR spectra of **10** with that obtained from a sample of the C(10) epimeric compound, which were clearly different.

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Collins oxidation (CH_2Cl_2, 0 °C, 30 min) of alcohol **15** and subsequent condensation with the lithio derivative (LDA, THF, −100 °C) of the appropriately substituted 2-methylbenzoxazole[13] produced (~60%) alcohol **16** as a mixture of diastereomers, which were not separable by HPLC analysis. Exposure (10 h) of **16** to camphorsulfonic acid in methylene chloride at −15 °C led (30%) to formation of the desired dioxaspirane, **17**. Reductive cleavage ($Cr_2(OAc)_4 \cdot 2H_2O$, EtOH)[11] followed by treatment with potassium carbonate in aqueous methanol (1:1) afforded in 50% overall yield A-23187 which was identical in all respects (NMR (220 MHz) and IR spectroscopies and TLC) with a sample of natural material obtained from Lilly Research Laboratories.[14]

Acknowledgment. This research was supported by a Public Health Research Grant from the National Institute of Allergy and Infectious Diseases (Grant AI 17410) and, in part, by a grant from G. D. Searle & Co. We are grateful to Dr. Robert L. Hamill (Lilly Research Laboratories) for a generous gift of A-23187.

Registry No. 1, 52665-69-7; **2**, 80657-85-8; **3**, 80657-86-9; **4**, 80657-87-0; **5**, 80630-91-7; **6**, 80630-92-8; **7**, 80657-88-1; **8**, 80657-89-2; **9**, 80657-90-5; **10**, 80657-91-6; **11**, 80657-92-7; **12**, 80630-93-9; **13**, 80630-94-0; **14**, 80630-95-1; **15**, 80630-96-2; **16** isomer 1, 80630-97-3; **16** isomer 2, 80657-93-8; **17**, 80630-98-4; vinyl bromide, 593-60-2; 2-lithio-*N*-(dimethylamino)pyrrole, 78307-77-4; methyl 5-(2,2,2-trifluoro-*N*-methylacetamido)-2-lithiomethyl-4-benzoxazolecarboxylate, 80630-99-5.

Supplementary Material Available: Listings of IR and ^1H NMR spectral data for **1**, **2–13**, **15**, and **17** (4 pages). Ordering information is given on any current masthead page.

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(14) Assigned structures are fully supported by IR, NMR, and mass spectral measurements and combustion analysis.

Nucleophilic Displacements on Phosphoric Monoesters: Stereochemical Evidence

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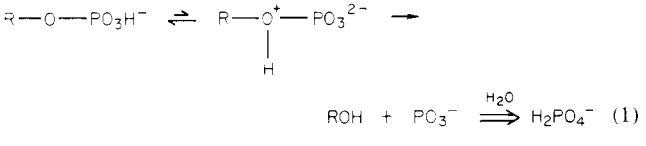
Received December 22, 1981

To account for the fact that the hydrolysis of monoesters of phosphoric acid is most rapid at around pH 4, where the monoanion predominates, the mechanistic pathway shown in eq 1



was proposed independently by Westheimer[2] and by Bunton[3] in 1955. Since that time, evidence has accumulated from a variety of sources in support of this formulation, which involves monomeric metaphosphate as an intermediate in the reaction. To provide more information about the nature of the transition state(s) for such processes, we have used chiral [^{16}O,^{17}O,^{18}O]phosphoric monoesters to examine the stereochemical consequence at phosphorus of reactions that are believed to follow the pathway of eq 1.

The view that phosphoric monoesters are hydrolyzed by a dissociative mechanism involving metaphosphate is based upon findings such as the following: (a) The values of $\Delta S^{\ddagger}$ are close to 0 eu,[4,5] which (despite the problems of interpreting activation parameters for reactions in structured solvents) is suggestive of a dissociative reaction. (b) There is an approximate correlation between the molarity of acceptor nucleophiles in mixed aqueous alcoholic solvents and the molar ratio of products formed, indicative of reaction of a highly reactive and unselective intermediate.[6,7] (c) The β_{lg} (lg = leaving group) for phenolic esters is −1.2 for dianions and −0.3 for monoanions, suggesting that bond breaking is far advanced in the rate-determining transition state,[5] the leaving group being the phenolate (from the dianion) or the phenol (on cleavage of the dipolar species of eq 1). (d) The reactivity of monoanions is often greater than that of the neutral species, indicating that rate-limiting nucleophilic attack at phosphorus is unlikely.[2,3] (e) The β_{nuc} (nuc = nucleophile) for the attack of amines on *p*-nitrophenyl phosphate is low, at 0.13.[8] (f) The ^{18}O kinetic isotope effect suggests rate-limiting cleavage of the (C)–^{18}O–P bond.[9] (g) The transfer of a phospho group from one solid phase to another in dioxane appears to involve metaphosphate as an intermediate.[10] (h) Monomeric metaphosphate has been explicitly generated in both apolar and polar solvents and shown to have the expected properties of a highly reactive electrophile.[11] There appears, in summary, to be persuasive evidence in support of the intermediacy of monomeric metaphosphate in the solvolytic reactions of phosphoric monoesters.

Table I. Predicted[a,b] and Observed[b] Peak Intensities (%) for ^{31}P NMR Spectra

peak number[c]	phenyl phosphate substrate pred[d]	phenyl phosphate substrate obsd	phenyl phosphate product pred[e]	phenyl phosphate product obsd	2,4-dinitrophenyl phosphate substrate pred[f]	2,4-dinitrophenyl phosphate substrate obsd	2,4-dinitrophenyl phosphate product pred[g]	2,4-dinitrophenyl phosphate product obsd
1	19.1	23.1	27.9	28.4	12.6	9.5	22.1	23.3
2	29.9	28.5	35.8	37.4	28.4	28.1	36.9	36.5
3	40.3	38.4	27.8	27.5	42.8	44.9	28.1	28.2
4	10.8	10.0	8.5	6.7	16.2	17.5	12.7	12.0
5	19.1	21.9	27.9	28.6	12.6	11.1	22.1	22.1
6	40.3	39.2	27.8	28.0	42.8	42.3	28.1	27.5
7	29.9	28.7	35.8	34.6	28.4	29.9	36.9	38.9
8	10.8	10.1	8.5	6.7	16.2	16.7	12.7	13.6

[a] On the basis of the measured isotopic content of the derived 1-[^{16}O,^{17}O,^{18}O]phosphopropane-1,2-diol and the measured contamination by the 2-phospho isomer. [b] The ratios of each set of four peaks are taken separately. [c] Numbering from downfield to upfield. [d] For 80% *R*. [e] For 86% *S*. [f] For 86% *R*. [g] For 87% *S*.

In a study of the hydrolysis of substituted aromatic phosphoric monoesters, Kirby and Varvoglis[5] found that esters whose leaving groups had $pK_a > 6$ were hydrolyzed most rapidly at pH 4 as the monoanion and that esters with leaving groups of $pK_a < 5.5$ were hydrolyzed most rapidly as the dianion. These results suggested that prior proton transfer (eq 1) was necessary to facilitate the heterolysis with relatively poor leaving groups, but as the pK_a of the leaving group was lowered, expulsion from the dianion became the preferred path. Guided by this[5] and earlier[4,12] work on the solvolysis of phosphoric monoesters, we chose to investigate the stereochemical course of the methanolysis of phenyl phosphate monoanion (leaving group pK_a 9.9) and 2,4-dinitrophenyl phosphate dianion (leaving group pK_a 4.1). For each of these reactions,

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