The ^{19}F NMR spectrum[12,13] showed a doublet of doublets centered at δ 120 ppm (J = 57, 14.5 Hz, with additional smaller couplings of 2.5 Hz). The ^1H NMR spectrum showed a triplet of doublets centered at δ 5.9 ppm (1 proton, CHF_2, J_{HF} = 57, J_{HH} = 5 Hz).

The oxime of 7-keto-7,8,9,10-tetrahydrobenzo[*a*]pyrene[4] was converted into its acetate, mp 193-195 °C, which on heating with Pd/C in naphthalene at 200-205 °C for 2 h yielded after dry column chromatography[15] 36% **1**, mp 203-204 °C; NMR showed two exchangeable protons at δ 4.66. Anal.[11] ($C_{20}H_{13}N$) C, H, N.

To a stirred mixture under N_2 of 2.18 g of $NaBF_4$ in 50 mL of dry THF was added 2.6 mL of CF_3COOH followed by 1.07 g of **1**. After 15 min at 25 °C, the mixture was cooled to −20 to −15 °C and 500 mg of $NaNO_2$ was added in small portions. The dark brown suspension of diazonium salt formed was stirred for 15 min and the solid was collected, washed with dry THF, and dried under vacuum. This solid had an IR peak at 2200 cm^{-1} (RN_2^+). The dry salt, mixed with powdered dry KF, was added to 100 mL of boiling dry xylene. The product was chromatographed over basic alumina to give 290 mg of solid, mp 152-156 °C. Analysis showed this to be a mixture of **2** and benzo[*a*]pyrene.[2,3]

The mass spectra[16] agreed with the assigned structures for **1**, **2**, and **7**.

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(2) We thank Dr. Don Jerina, NCI, Bethesda, Md., for purifying by high-pressure liquid chromatography a reaction product from diazotization that we supplied.
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(17) Postdoctoral Research Associate.

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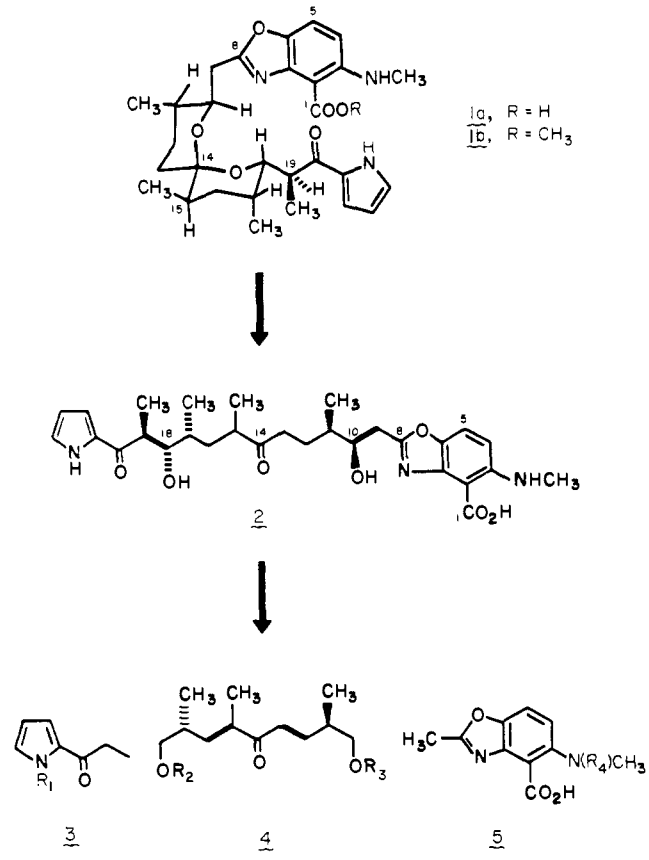
Polyether Antibiotics Synthesis. Total Synthesis and Absolute Configuration of the Ionophore A-23187

Sir:

Over the last few years the general interest in polyether antibiotics has risen dramatically.[1] This rapidly growing class of compounds, produced mainly by *Streptomyces* organisms, characteristically form lipophilic metal ion complexes which are effective in ion transport across lipid barriers.[2] To date, the ionophore antibiotic A-23187 (calcimycin, **1a**)[3] appears to be unique in its divalent cation transport selectivity.[4] Extensive literature is now rapidly accumulating on the application of this ionophore as an effective probe for the involvement of metal ions in the control of numerous physiological processes.[5] This communication describes the first synthesis of A-23187 (**1a**) and defines the absolute configuration of this natural product.

Scheme I



Based upon oxygen anomeric effects and related stereochemical considerations,[6] we projected that the 1,7-dioxaspiro[5.5]undecane skeleton in **1** with the requisite C_{14} stereocenter would be readily attainable from the acyclic keto diol precursor **2** via acid-catalyzed ring closure (Scheme I).[7] This internal ketalization process is undoubtedly a plausible step in the biosynthesis of **1a**. We further assumed that stereochemical control of the C_{15} methyl-bearing stereocenter need *not* be an issue in the enantioselective synthesis of the penultimate precursor **2** since acid-catalyzed equilibration of this center in the target molecule should afford the desired equatorial methyl diastereoisomer.[8] The intermediate **2**, upon aldol disconnection, appeared to be readily accessible from the heterocyclic precursors **3** (R = H)[9] and **5** and the ketone **4** which possesses a C_2 axis of symmetry with respect to skeletal carbons C_{10}-C_{12} and C_{16}-C_{18}.

After several abortive attempts, a practical synthesis of the benzoxazole moiety **5** was developed. Methyl 5-hydroxyanthranilate,[10] upon trifluoroacylation (TFAA, C_5H_5N), afforded **6a**, mp 136-138 °C, in 92% yield.[11] A priori, we had anticipated that mononitration of **6a** would have revealed a greater propensity for electrophilic substitution at C_4 vs. C_6, thereby thwarting attempts to construct the requisite aminophenol **6c**. This concern was unfounded. Nitration (1 equiv of HNO_3, Et_2O, 25 °C) afforded a 2:1 mixture of the desired nitrophenol **6b**[11] (mp 121-124 °C) and the corresponding

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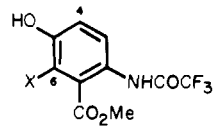
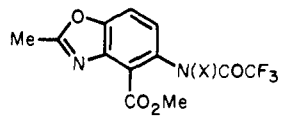


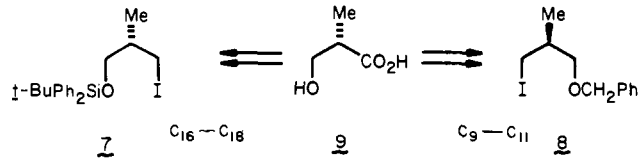
6a, X = H
b, X = NO_2
c, X = NH_2



5a, X = H
b, X = Me

4-nitro isomer which was readily separated by silica gel chromatography. Catalytic reduction of **6b** (10% Pd/C) to **6c**[11] (mp 157–158 °C), ring closure of **6c** with acetyl chloride (140 °C, xylene) to the 2-methylbenzoxazole **5a**[11] (mp 150–151.5 °C), and subsequent methylation (CH_3I, K_2CO_3, acetone) afforded the requisite protected benzoxazole **5b** (mp 97–98 °C) in a 60% overall yield from **6b**.[11,12]

Based upon the previously elaborated symmetry elements inherent in chiral ketone **4**, its construction via common chiral subunits and enolate technology was straightforward. The absolute configurations at methyl-bearing stereocenters C_{11} and C_{17} were secured in the chiral four-carbon iodides **7** and **8**, each of which was derived from (*S*)-(+)-β-hydroxyisobutyric acid (**9**).[13] In direct analogy with the procedure elab-



7 $C_{16}-C_{18}$ 9 C_9-C_{11} 8

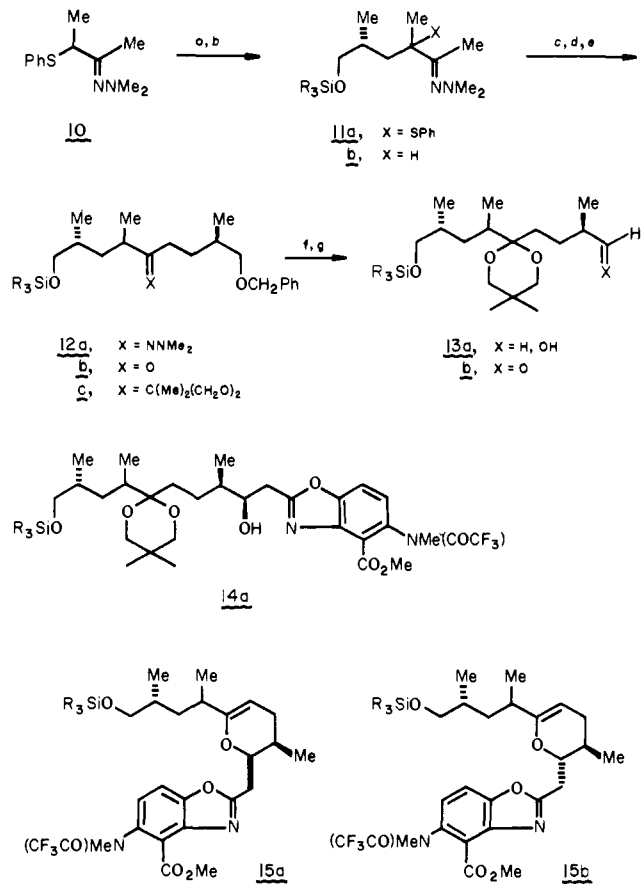
orated by Fischli,[14] **9** was transformed without racemization to **7** ($[\alpha]^{23}_D$ +3.80° (*c* 0.413, $CHCl_3$)) and **8** ($[\alpha]^{23}_D$ +9.98° (*c* 0.239, $CHCl_3$)).[11,12]

Based upon model studies and regiochemical considerations, hydrazone **10**[15] was chosen as the 2-butanone equivalent (Scheme II). Regiospecific alkylation of **10** (KH) with chiral iodide **7** afforded a 91% yield of **11a** which was desulfurized (Li, NH_3) in 91% yield to the hydrazone **11b**.[11,12] Alkylation of **11b** (LDA) with chiral iodobenzyl ether **8** regiospecifically afforded hydrazone **12a** (80%) as a 1:1 mixture of α-methyl diastereoisomers.[11] As previously discussed, this stereochemical ambiguity will be corrected in conjunction with the ultimate spiroketalization step (vide supra). Hydrolysis[17] and ketalization of **12a** (77%) completed the synthesis of the chiral fragment **12c**[11] corresponding to the dioxaspirane subunit of the target structure.

In the successive assemblage of subunits (Scheme I) via carbonyl addition, two new hydroxyl-bearing stereocenters are created (cf. **2**, C_{10} and C_{18}). Again, based upon substructural C_2 symmetry elements in **2**, the proper stereochemical relationships at both C_{10} and C_{18} can be projected from the resident stereocenters at C_{11} and C_{17} via a Cram's rule argument.[18]

Catalytic hydrogenolysis (Pd/C, EtOH, 0.2 equiv of Na_2CO_3) of benzyl ether **12c** proved to be sluggish under conditions which suppressed the interplay of hydroxyl and ketal functionalities in **13a**. Traces of acid were found to irretrievably transform **13a** to pyran byproducts. However, efficient debenzylation of **12c** to **13a** was accomplished by benzylic metalation (*sec*-BuLi, THF, −78 °C)[19] followed by oxidation ($B(OMe)_3$, H_2O_2). Alcohol **13a** was successively oxidized[20] to aldehyde **13b**[12] and condensed (−100 °C, 3 min) with the lithiated benzoxazole **5b** (LDA, THF, −100 °C) to give an 88:12 mixture of the desired alcohol **14a** along with the diastereoisomeric alcohol **14b** (33% from **12c**) which was separated by high-pressure liquid chromatography (HPLC).[21] The stereochemistry of the major isomer **14a** was assigned in accordance with Cram's rule.[18] Acid-catalyzed cyclization

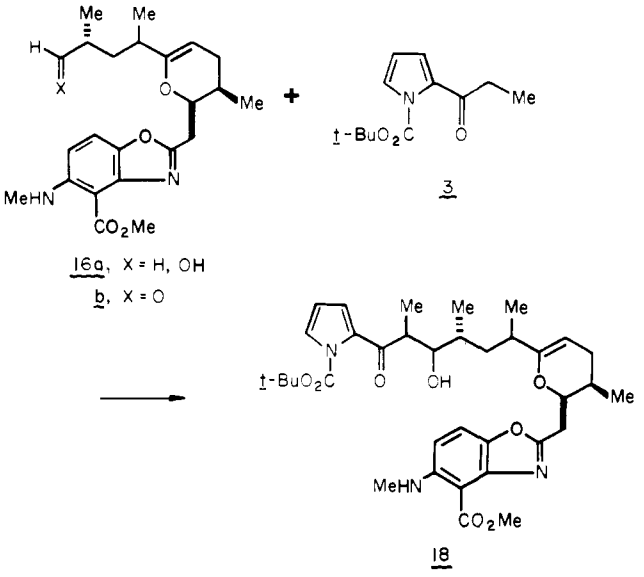
Scheme II[a]



[a] (a) (1) KH, KO-*t*-Bu (0.03 equiv), THF, reflux; (2) 7, 0 °C to room temperature, 5 min. (b) Li, NH_3. (c) (1) LDA, THF, 0 °C; (2) 8. (d) $CuCl_2$, THF–H_2O. (e) $C(Me)_2(CH_2OH)_2$, *p*-TsOH. (f) (1) *sec*-BuLi, THF, −78 °C; (2) $B(OMe)_3$, −78 °C to room temperature; (3) H_2O_2, NaOH. (g) CrO_3, pyridine.

(HO_2CCO_2H, CH_3OH, 25 °C) of alcohols **14a** and **14b** to the dihydropyrans **15a** and **15b** proceeded in 87% yield, while the cyclization of **14a** cleanly afforded **15a**. In practice, it was found that chromatographic diastereoisomer resolution was more *expedient* prior to, rather than after, dihydropyran formation. Desilylation with tetra-*n*-butylammonium fluoride (8 equiv, THF, 25 °C) conveniently liberated *both* the primary alcohol and secondary amine functions to afford alcohol **16a** (60%) which was oxidized to the corresponding aldehyde **16b** with Collins reagent (80%).[20]

The final aldol condensation between aldehyde **16b** and the zinc enolate derived from ketone 3 (R = *t*-BOC)[22] was executed in analogy with conditions (1:1 Et_2O-DME, 10 °C, 5 min) established by House.[23] In model studies with benzaldehyde, the above zinc enolate afforded predominately the threo-aldol adduct (threo:erythro, 70:30) under the reported equilibrating conditions. The resultant aldol condensation adduct **18**,[24] without purification, was treated with acidic ion-exchange resin (Bio Rad AG 50W-X8, $PhCH_3$, 100 °C, 10 h) to sequentially induce the following events: (a) spiroketal formation; (b) equilibration of the diastereoisomeric C_{15} methyl epimers; (c) deletion of the pyrrole protecting group. The major product (23% from aldehyde **16b**), isolated by flash chromatography on silica gel, was the methyl ester derived from A-23187 (**1b**), $[\alpha]^{23}_D$ −10° (*c* 0.011, $CHCl_3$).[12] A sample of **1b**[25] prepared from the natural product was identical in all respects (IR, NMR, $[\alpha]_D$, HPLC) with the synthetic material. Hydrolysis of **1b** to the free acid **1a** was carried out in quantitative yield with lithium *n*-propylmercaptide in



HMPA.[26] Synthetic **1a**,[11] mp 184.5–186 °C, $[\alpha]^{24}_D$ −56° (*c* 0.010, $CHCl_3$),[27] was identical in all respects (IR, UV, MS, ^1H NMR, ^{13}C NMR, $[\alpha]_D$, mixture melting point) with an authentic sample of A-23187. This study establishes the absolute configuration of A-23187 as that depicted in structure **1a.**

Further studies are in progress to enhance the aldol diastereoselection (**3** + **16** → **18**) via the use of boron enolates,[28]

Acknowledgment. Support from the National Institutes of Health and the Eli Lilly Company is greatly appreciated.

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(8) Model studies were conducted to confirm this postulate. In addition, H^+/D^+ exchange (DCl, dioxane, Δ, 18 h) on **1a** confirmed that deuterium incorporation into the aliphatic backbone occurred selectively at C_{15} and C_{13}. These experiments were carried out in collaboration with Dr. M. Debono, Eli Lilly Co.
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(12) **1b:** IR 3440, 1715, 1635, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.2 (1 H, br s), 7.83 (1 H, br s), 7.61 (1 H, d, *J* = 9 Hz), 6.89 (2 H, m), 6.65 (1 H, d, *J* = 9 Hz), 6.20 (1 H, m), 3.95 (3 H, s), 2.94 (3 H, d, *J* = 3 Hz). **5b:** IR 1725, 1695, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (1 H, d, *J* = 9 Hz), 7.22 (1 H, d, *J* = 9 Hz), 3.99 (3 H, s), 3.33 and 3.49 (3 H, s), 2.70 (3 H, s). **7:** ^1H NMR (CCl_4) δ 7.2–7.9 (10 H, m), 3.50 (1 H, d of d, *J* = 9.9, 5.0 Hz), 3.46 (1 H, d of d, *J* = 9.9, 6.3 Hz), 3.27 (2 H, d, *J* = 5.5 Hz), 1.69 (1 H, m), 1.07 (9 H, s), 0.97 (3 H, d, *J* = 6.8 Hz). **8:** ^1H NMR (CCl_4) δ 7.23 (5 H, s), 4.39 (2 H, s), 3.29 (1 H, d of d, *J* = 9.2, 5.6 Hz), 3.19 (2 H, *J* = 5.6 Hz), 3.16 (1 H, d of d, *J* = 9.2, 6.3 Hz), 1.70 (1 H, m), 0.94 (3 H, d, *J* = 6.1 Hz). **11b:** ^1H NMR (CCl_4) δ 7.2–7.8 (10 H, m), 3.2–3.7 (2 H, m), 2.28 (6 H, s), 1.74 (3 H, s), 1.04 (9 H, s), 0.97, 0.94, and 0.92 (6 H, d, *J* = 6.8, 8.4, and 8.4 Hz). **12:** IR 1707 cm^{-1}; ^1H NMR (CCl_4) δ 7.0–7.9 (10 H, m), 7.22 (5 H, s), 4.39 (2 H, s), 3.41 (2 H, d, *J* = 5.4 Hz), 3.20 (2 H, d, *J* = 5.4 Hz), 1.09 (9 H, s). **13b:** IR 1723 cm^{-1}; ^1H NMR (CCl_4) δ 9.54 and 9.58 (1 H, d, *J* = 2.0 and 2.0 Hz), 7.1–7.8 (10 H, m), 2.9–3.8 (6 H, m), 1.08 (9 H, s). **14a:** IR 3340, 1729, 1701, 1567, 1562, 1556 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.1–8.0 (12 H, m), 2.8–4.6 (10 H, m), 3.94 (3 H, s), 3.33 (3 H, s), 1.09 (9 H, s).
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(15) Hydrazone **10** (bp 93 °C (0.3 Torr)) was prepared from phenylthioacetone[16] in two steps: (a) Me_2NNH_2, 50 °C, 90%; (b) KH, MeI, THF, 85%.
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(21) HPLC conditions: column, Altex LiChrosorb Si 60, 5μ (10 mm × 25 cm); solvent, 35% ethyl acetate–hexane; flow rate, 5.0 mL/min; t_R(**14a**) = 19 min, t_R(**14b**) = 17.9 min.
(22) Ketone **3** (R = *t*-BOC), mp 57.5–58.5 °C, was prepared from **3** (R = H)[9] and KO-*t*-Bu (THF) and $(t\text{-}BuO_2C)_2O$ in 85% yield. The resultant zinc enolate was prepared by successive treatment of **3** (R = *t*-BOC) with LDA (−78 °C, Et_2O) followed by anhydrous $ZnCl_2$ (1 equiv) and dimethoxyethane (DME).
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(24) Under the stated conditions the zinc enolate derived from **3** was found to add to $OCHCH(CH_3)CH_2CH_2CO_2Me_2$ to give a 50% yield of the threo Cram aldol condensation product.
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Preparation and Properties of a Chlorophyllide–Apomyoglobin Complex

Sir:

The spectroscopy of large molecules like chlorophyll poses a number of problems because it is difficult to obtain a transparent host matrix for single-crystal optical and magnetic resonance investigations. In order to surmount this problem we have pursued the simple subterfuge of substituting chlorophyll derivatives in the place of heme in the protein apomyoglobin (apoMb). Myoglobin (Mb) is ideal because it is available in large quantities, is readily crystallizable, and has a very well-characterized crystal structure.[1,2] Our goals are to determine precisely the geometric relationships between the chlorophyll molecular structure and (1) the orientations of transition dipole moments for the lowest singlet excited states, (2) the principal axis systems of the **g** and hyperfine tensors in the radical ions, and (3) the principal axis system of the zero-field tensor in the lowest triplet excited state. Each of these relationships is required for an analysis of recent photoselection experiments on bacterial photosynthetic reaction centers.[3-7] A single crystal of this type is very well suited for studies of energy transport, since the chromophores should interact weakly and are regularly separated (in this respect the protein host is much superior to typical lattices, because of the large size of the unit cell and regular site substitution). Furthermore, a well-defined water-soluble chlorophyll-protein complex offers many interesting possibilities for electrochemical and photochemical studies. We report here the preparation and characterization of the complex in solution.

Zinc[8] or magnesium pyrochlorophyllides[9,10] (R_1 in Figure

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