The $^{19}$F NMR spectrum showed a doublet of doublets centered at $\delta$ 120 ppm ($J = 57, 14.5$ Hz, with additional smaller couplings of 2.5 Hz). The $^1$H NMR spectrum showed a triplet of doublets centered at $\delta$ 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 was converted into its acetate, mp 193-195°C, which on smaller couplings of 2.5 Hz. The solid, mp 152-156°C, yielded after dry column chromatography of dry THF was added 2.6 mL of CF$_3$COOH followed by 1.07 g of KF, was added to 100 mL of boiling dry xylene. The product 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 compound was added to 50 mL of boiling dry xylene. The dark brown suspension of diazonium salt formed was stirred for 15 min and the solid was collected, washed with dry KF, and dried under vacuum.

The mass spectral agreed with the assigned structures for 1, 2, and 7.

References and Notes

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. 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. To date, the ionophore antibiotic A-23187 (calcimycin, 1a) appears to be unique in its divalent cation transport selectivity. 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. This communication describes the first synthesis of A-23187 (1a) and defines the absolute configuration of this natural product.

Based upon oxygen anomic effects and related stereochemical considerations, we projected that the 1,7-dioxaspiro[5.5]undecane skeleton in 1 with the requisite C$_{14}$ stereo-center would be readily attainable from the acyclic keto diol precursor via acid-catalyzed ring closure (Scheme 1). This internal ketalization process is undoubtedly a plausible step in the biosynthesis of 1a. We further assumed that stereochemical control of the C$_{14}$ methyl-bearing stereocenter need not be an issue in the enantioselective synthesis of the penultimate precursor since acid-catalyzed equilibration of this center in the target molecule should afford the desired equatorial methyl diastereoisomer. The intermediate 2, upon aldol disconnection, appeared to be readily accessible from the heterocyclic precursors $\mathbf{3} (R = H)$ and $\mathbf{5}$ 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 benzoazolone moiety 5 was developed. Methyl 5-hydroxy-N-phenylthranilate, upon trifluoroacetylation (TFAA, C$_2$H$_3$N$_2$), afforded 6a, mp 136-138°C, in 92% yield. Prior to, we had anticipated that mononitration of 6a would have revealed a greater propensity for electrophilic substitution at C$_6$ vs. C$_8$, thereby thwarting attempts to construct the requisite amino-phenol 6c. This concern was unfounded. Nitration (1 equiv of HNO$_3$, Et$_3$O, 25°C) afforded a 2:1 mixture of the desired nitrophenol 6b (mp 121-124°C) and the corresponding

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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\(_3\)I, K\(_2\)CO\(_3\), 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)-(+)-\(\beta\)-hydroxyisobutyric acid (9).\(^{13}\) In direct analogy with the procedure elaborated by Fischli,\(^{14}\) 9 was transformed without racemization to 7 ([\(\alpha\)]\(^{23}\)D +3.80° (c 0.413, CH\(_2\)Cl\(_2\))) and 8 ([\(\alpha\)]\(^{23}\)D +9.98° (c 0.239, CH\(_2\)Cl\(_2\))) of 0.239, CH\(_2\)Cl\(_3\)).

Based upon model studies and regiochemical considerations, hydrazone 11 was chosen as the 2-butanone equivalent (Scheme I). Regiospecific alkylation of 10 (K\(_2\)H) 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 \(\alpha\)-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 stereochimical 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\(_2\)CO\(_3\)) 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 metatation (sec-BuLi, THF, -78 °C)\(^ {19}\) followed by oxidation (BO\(_2\)Me\(_2\), H\(_2\)O\(_2\)). Alcohol 13a was successively oxidized\(^ {20}\) to aldehyde 13b\(^ {22}\) and condensed (110 °C, 3 min) with the lithiated benzoxazole 5b (LDA, THF, -110 °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

\[(\text{HO}_2\text{CCO}_2\text{H}, \text{CH}_3\text{OH}, 25 ^\circ \text{C})\] of alcohols 14a and 14b to the dihydropyrans 15a and 15b proceeded at 87% yield, while the cyclization of 14a cleanly afforded 15a. In practice, it was found that chromatographic diastereisomer resolution was more expedient prior to, rather than after, dihydropyran formation. Desilylation with tetra-n-butylammonium fluoride (7 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\(_2\)O-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,\(^ {23}\) 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\(_{13}\) 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), [\(\alpha\)]\(^{22}\)D -108° (c 0.011, CHCl\(_3\)).\(^ {12}\) A sample of 1b\(^ {12}\) prepared from the natural product was identical in all respects (IR, NMR, [\(\alpha\)]\(^{22}\)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

\[\begin{align*}
\text{Scheme I} \\
\text{Scheme II}^a
\end{align*}\]
Consistent elemental analyses and spectral data were obtained on all new compounds. 

**References and Notes**


(4) (a) D. R. Pfeiffer and H. A. Lardy, Biochemistry, 15, 335 (1976); (b) D. R. Pfeiffer, W. Reid, and H. A. Lardy, ibid., 19, 4007 (1974); (c) G. D. Case, J. M. Vanderkooi, and A. Scarpa, Arch. Biochem. Biophys., 162, 174 (1974).


(8) Model studies were conducted to confirm this postulate. In addition, H+ incorporation into the aliphatic backbone occurred selectively at O-4 and O-5.

(9) These experiments were carried out in collaboration with Dr. M. Debono, Eli Lilly Co.


(12) H. R. Suga, 1715, 163S, 1570 cm\(^{-1}\); \(\text{H NMR} (CDCl}_3\) \(\delta\) 10.2 (1H, br), 7.83 (1H, br), 7.61 (1H, d, J = 9 Hz), 6.89 (2H, m), 6.65 (1H, d, J = 9 Hz), 6.20 (1H, m), 3.95 (3H, s), 2.94 (3H, d, J = 3 Hz); \(\text{IR} (725,1695, 1570 \text{cm}^{-1}); \text{H NMR} (CDCl}_3\) \(\delta\) 7.65 (1H, d, J = 9 Hz), 7.22 (1H, d, J = 9 Hz), 3.99 (3H, s), 3.33 and 3.49 (3H, s), 2.70 (3H, s); 7: \(\text{H NMR} (CDCl}_3\) \(\delta\) 7.5 (10H, m), 3.50 (1H, d, J = 9 Hz), 5.5 (5H, m), 3.49 (1H, d, J = 9 Hz). 6.39 (2H, d, J = 5 Hz), 1.69 (1H, m), 0.97 (3H, s), 0.91 (3H, s), 1.39 (8H, m), 1.78 (5H, s), 4.68 (2H, s), 3.28 (1H, d, J = 9 Hz), 9.2 (5H, m), 9.2 (2H, m), 3.19 (2H, m), 3.16 (1H, d, J = 9 Hz), 6.73 (1H, m), 1.70 (1H, m), 0.94 (3H, d, J = 6 Hz); 1.18: \(\text{H NMR} (CDCl}_3\) \(\delta\) 7.2-7.7 (4H, m), 3.2-3.7 (2H, m), 2.28 (8H, m), 1.74 (3H, m), 1.04 (9H, s), 0.97, 0.94, and 0.92 (6H, d, J = 6.8, 8.4, and 8.4Hz); 12: \(\text{IR} (1707 \text{cm}^{-1}); \text{H NMR} (CDCl}_3\) \(\delta\) 7.0-7.9 (10H, m), 7.22 (5H, s), 4.39 (2H, s), 3.41 (2H, d, J = 5.4 Hz), 3.20 (2H, d, J = 5.4 Hz), 1.09 (3H, s), 1.03 (3H, s), 0.94 (3H, s), 1.04 (9H, s), 0.92 (6H, d, J = 6.8, 8.4, and 8.4Hz).

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 hemes 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.\(^3\) Our goals are to determine precisely the geometric relationships between the chlorophyll molecular structure and (1) the orientations of translation 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 photoelectron experiments on bacterial photosynthetic reaction centers.\(^4\) \(^5\) A single crystal of this type is very well suited for studies of energy transport, since the chlorophores 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.