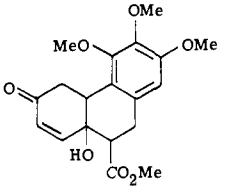
extraction in 75–95% yield. Representative ketal **7** (Table I) was conveniently chromatographed on neutral alumina (Activity III) and recrystallized, mp 77–78 °C (87%). The *p*-quinols of general structure **6** are prepared in an analogous fashion employing the quinone silyl cyanohydrins **2a** and **2b**.[4,6] Alternatively, we have found that ketals **5** can be hydrolyzed to the *p*-quinols **6** in good yield with oxalic acid (4 mg/mmol) in THF–water (5:1, 25 °C, 1 h). In the preparation of the sulfone ketals (cf. **17**, Table I), the requisite sulfone **4** (G = SO_2Ph) was metalated with *n*-butyllithium (−78 °C, 10 min; −10 °C, 1 h).

The results of the acid-catalyzed cyclization reactions of a series of *p*-quinols and *p*-quinol ketals are summarized in Table I.[8] In general we have found it unnecessary to purify the quinol derivatives prior to acid-catalyzed cyclization. Accordingly, the yields reported in Table I represent the combined yields for the condensation and cyclization steps (Scheme I). The structural assignments for the substitution patterns of the 9,10-dihydrophenanthrenes listed in Table I rest upon ^1H and ^{13}C NMR analysis and, in selected cases, correlation with known structures. The physical properties of phenanthrene **18** are identical with those reported.[9] The dihydrophenanthrene **14** (entry 4) was correlated with the corresponding phenanthrene via DDQ oxidation,[10] mp 202–205 °C (lit.[11] 202–204 °C). The ring substitution patterns in dihydrophenanthrenes **8, 10, 12,** and **16** may be conveniently analyzed by ^1H NMR spectroscopy. It is well documented that 9,10-dihydrophenanthrenes bearing oxygen substituents at C_4 exhibit a characteristic deshielded C_5 aromatic proton.[12] Analysis of the spin multiplicity of this signal facilitates the assignment of the substitution pattern of the mono- or disubstituted aromatic rings in the above-mentioned derivatives.

It was observed that the choice of Lewis acid catalyst in certain instances was critical to the success of the cyclization process (entries 1, 2, Table I). As an example, treatment of **7** and **9** with either $SnCl_4$, CF_3CO_2H, or $BF_3{\cdot}Et_2O$ in solvents such as CH_2Cl_2, C_6H_6, or CH_3NO_2 afforded, in addition to the expected adducts **8** and **10,** respectively, the tricyclic enone **23**[13] in nearly equal amounts. Since **23** was stable to the above



23

cyclization conditions, and since **10** is not a contaminant in the cyclization of **7, 23** is neither a penultimate intermediate in the cyclization of quinol **9** nor is **7** converted to **9** under these conditions.

Efforts to carry out related cyclizations on substrates lacking methoxy-activated aromatic rings have failed to date (entry 7). The products derived from these reactions result from dienone–phenol rearrangements rather than ring closure. The scope of these and related annelation reactions will be reported in due course.

Acknowledgements. Support from the National Institutes of Health is gratefully acknowledged.

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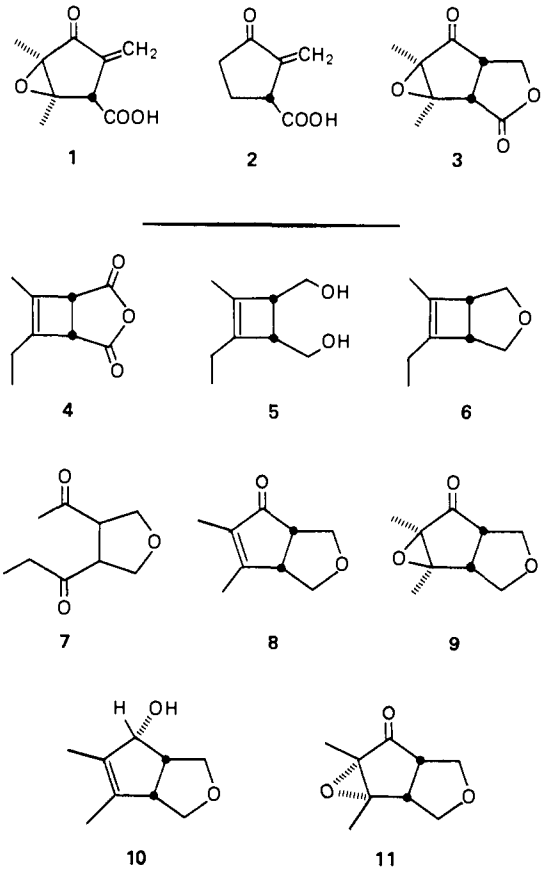
A Stereospecific Total Synthesis of (±)-Methylenomycin A. A Novel Antibiotic Possessing an α-Methylene Ketone Functionality

Sir:

We wish to report here the first total synthesis of methylenomycin A, an antibiotic recently isolated from a strain of *Streptomyces violaceoruber,*[1] and shown by x-ray crystallographic analysis[2] to possess structure **1**.[3] Our interest in this synthetic target was prompted both by its demonstrated in vitro activity[1] against gram-positive and gram-negative bacteria as



well as its similarity to the pharmacologically important α-methylene lactones[4] and to sarkomycin (**2**),[5] a known antitumor agent. Our synthetic route is particularly attractive in that it is short, stereospecific, highly efficient (i.e., proceeds in 12% overall) and requires no chromatographic separations.

The structure of methylenomycin A placed two constraints on our synthetic strategy. First, it appeared desirable to introduce the highly reactive α-methylene ketone functionality in the latter stages of our synthetic scheme.[1] Second, to ensure the requisite stereochemistry of methylenomycin A, a method was required which would allow introduction of the epoxide trans to the carboxyl group. With these constraints in mind, lactone **3**, an isomer of methylenomycin A, appeared to be a most suitable penultimate precursor.[6] Final conversion to **1** would then simply require an overall retrolactonization process.

Our approach to methylenomycin A begins with the readily available cyclobutene **4**. Irradiation of a mixture of maleic anhydride (0.5 M) and 2-pentyne (0.6 M) in acetonitrile employing benzophenone (0.06 M) as sensitizer afforded **4**[7] in 79% yield[8] as a colorless oil, bp 115 °C (1.0 Torr). This photochemical [2 + 2] cycloaddition was conveniently carried out on a 10–20-g scale employing the standard Hanovia 450-W mercury arc fitted with Corex filter.[9] Subsequent reduction of **4** ($LiAlH_4$/THF, 40 h at reflux) led to a 96% yield of diol **5**,[7] which in turn was converted to tetrahydrofuran **6**,[7] (bp 75 °C (20 Torr), 86%) via treatment at 0 °C with 1.1 equiv of tosyl chloride in dry pyridine for 18 h, followed by heating at reflux for 2 h.[10]

Next tetrahydrofuran **6** was converted to epoxy ketone **9**. To this end ozonolysis of **6** at −76 °C in methanol followed by reductive workup with triphenylphosphine afforded diketone **7**[7] (bp 110 °C (2.0 Torr)) in 75% yield. Cyclization of this diketone (**7**), employing the aldol conditions of McCurry and Singh[11] (i.e., 2% NaOH in 90% (v/v) aqueous MeOH) led efficiently (85%) to crystalline cyclopentenone **8**[7] (mp 75 °C). Consistent with structure **8** were the infrared absorption bands at 1700 (s), 1655 (m), and 920 (m) cm^{-1}, as well as the two three-proton singlets at δ 1.66 and 2.03 in the high field (220 MHz) NMR spectrum. Subsequent epoxidation of cyclopentenone **8** at −20 °C with basic hydrogen peroxide[12] (30% H_2O_2/NaOH/MeOH, 18 h) afforded **9**[7] in 90% yield, IR 1745 cm^{-1}.

Final conversion of **9** to **3**, the required penultimate intermediate, was accomplished via oxidation with ruthenium tetroxide employing a two-phase catalytic protocol (RuO_2/$NaIO_4$ (excess)/H_2O-CCl_4).[13] Under these conditions, **3**[7] (mp 80.5–81.0 °C) was obtained in 46% yield as the *sole* product: IR 1780 (s), 1750 (s) cm^{-1}; NMR (220 MHz) δ 1.46 (s, 3 H), 1.65 (s, 3 H) 3.17 (dd, J = 9 Hz, 1 H), 3.59 (d, J = 9 Hz, 1 H), 4.42 (dd, J = 9 Hz, 1 H), 4.57 (d, J = 9 Hz, 1 H).

Three comments concerning the above transformations are in order. First, to demonstrate that the stereochemistry assigned to **9** had in fact been achieved, the following chemical interconversions were carried out. Reduction of enone **8** with the sterically encumbered reducing agent DIBAL.[14] led selectively to **10**[7] in 94% yield. Epoxidation of this allylic alcohol with *m*-chloroperbenzoic acid, a reagent known[15] to be directed by allylic hydroxyl substituents, followed by Jones oxidation,[16] afforded a 95:5 mixture of two ketones, the major component being a new epoxy ketone **11**[7] (mp 61.5 °C); the minor, identified as **9**, was identical in all respects (IR, 60- and 220-MHz NMR, and VPC) with that prepared previously. The availability of both **9** and **11**, in conjunction with their mode of synthesis and spectroscopic properties, established the relative stereochemistry assigned to these compounds. Second, concerning the apparent regiospecificity of the ruthenium tetroxide oxidation of **9**, we have demonstrated in model systems that 1,3-dicarbonyl systems capable of enolization are oxidatively destroyed by ruthenium tetroxide, while systems incapable of enolization are stable to further oxidation.[17] Finally, to confirm rigorously both the structure and stereochemistry of **3** we have completed an x-ray crystallographic analysis of this key intermediate.[18]

With an efficient route to **3** secured, there remained only the final conversion to methylenomycin A to achieve our synthetic goal. Toward this end we initially envisioned a direct retrolactonization process induced via the ketone enol or enolate. However, during the course of our study, Baldwin[19] demonstrated that such a reaction (i.e., a retro-5-endo-trigonal cyclization) was in fact a disfavored process. Indeed, all attempts to effect either an acid- or base-promoted ring opening of **3** lead only to recovered starting material or to complex mixtures.

With this approach to methylenomycin A blocked, we directed our attention to alternative modes of opening the butyrolactone functionality. An attractive possibility appeared to be nucleophilic cleavage of the alkyl–oxygen bond of the lactone induced via a nonbasic nucleophile[20] (e.g., sulfur or selenium anion[21]) which in a subsequent transformation (e.g., oxidation) would yield methylenomycin A under mild conditions.

After an exhaustive examination of a wide variety[21] of reaction conditions, success was finally achieved. Specifically, treatment of **3** with 2 equiv of lithium methyl mercaptide[22] in HMPA (r.t., 3 h, under N_2) led directly to crystalline (±)-methylenomycin A in 68% yield (mp 88.5–89 °C after filtration through a short plug of silica). That this solid was indeed methylenomycin A was apparent both from its spectroscopic properties (IR, 220-MHz NMR, UV, and mass spectrum) as well as by direct comparison with the published UV and 100-MHz NMR spectra. Presumably the final conversion (**3** → **1**) proceeds via initial nucleophilic cleavage of the lactone ring followed, in a second step, by base-induced (i.e., CH_3S^-) elimination of methyl mercaptide. Support for this reaction pathway arises from the observation that treatment of **3** with 1 equiv of lithium methyl mercaptide yields a 1:1 mixture of **1** and **3**.

Studies extending this synthetic route to the epimer of methylenomycin A as well as to analogues of this novel antibiotic are currently in progress in our laboratory.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institute of Health through Grant No. CA-19033. In addition we thank Mr. S. T. Bella of the Rockefellor University for the microanalysis and the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania where the 220-MHz NMR spectra were obtained.

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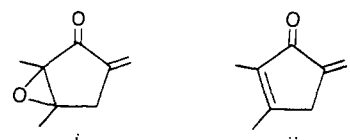

i *ii*

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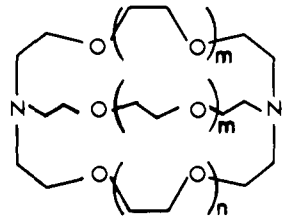
Synthesis and Chemical Properties of Lanthanide Cryptates

Sir:

Several polyoxadiazamacrobicyclic ligands[1] of the type pictured have been found by Lehn and co-workers[2] to encapsulate alkali and alkaline earth cations to form metal cryptate coordination compounds that are extremely stable in aqueous as well as in nonaqueous media. The complexes are found to attain maximum thermodynamic stability when the sizes of the bare metal ions are comparable with the dimensions of the



1 m = 1, n = 0 2:2:1
2 m = n = 1 2:2:2

cryptate cavity.[2] Further, the rate constant for dissociation of the divalent $[Ca(2:2:2)]^{2+}$ cryptate is markedly smaller than that for the monovalent $[Na(2:2:2)]^{+}$ cryptate in aqueous solution,[3,4] despite the closeness (near 1 Å) of ionic radius for Ca^{2+} and Na^{+} and the similar thermodynamic stabilities of the two complexes.[2] Such considerations suggested that the encryptation[5] of the tripositive lanthanide ions, whose ionic radii[6] vary in the range of 0.85–1.15 Å, would produce a series of systematically varied, substitutionally inert, yet thermodynamically stable, complexes which could find use in NMR, electrochemistry, synthesis, and medicine. Herein we report the preparation of these novel coordination compounds and discuss a few of their more uncommon chemical properties.

Various nonaqueous solvent syntheses were required to produce analytically pure, crystalline samples.[7] Reaction of stoichiometric quantities of anhydrous $EuCl_3$, for example, with the 2:2:1 ligand **1** in anhydrous organic solvents results in quantitative complex formation. Evaporation and precipitation with ethyl ether gave the crude product, which yielded a white, microcrystalline sample after recrystallization. Analogous procedures were used to prepare the 2:2:1 cryptate trichlorides of tripositive La, Pr, Gd, and Yb. The following analytical determinations for the europium complex are representative. Calcd for $Eu(C_{16}H_{32}N_2O_5)Cl_3$: C, 32.53; H, 5.46; N, 4.74; Eu, 25.72. Found: C, 32.45; H, 5.60; N, 4.92; Eu, 24.73. Formation of the 2:2:2 ligand **2** salts was found to be more facile. The use of lanthanum nitrate yielded $[La(C_{18}H_{36}N_2O_6)](NO_3)_3$. Calcd: C, 30.79; H, 5.13. Found: C, 30.68; H, 5.15. An x-ray crystallographic study of the latter complex is underway.

The Eu(III) and Gd(III) cryptates exhibit remarkable kinetic stability in water and appear to be the first truly substitutionally inert lanthanide complexes.[8] Neutral solutions show no metal hydroxide precipitate even after several days of aging. In strongly basic solution, pH >10, the complexes are stable for hours. Virtually no dissociation of complex is seen even after several days in 0.1 M aqueous perchloric acid, as evidenced by unchanged NMR spectra.[9] This inertness renders the $[Gd(2:2:1)]^{3+}$ ion useful as a T_1 (shiftless) relaxation reagent[10] for NMR spectroscopy in polar organic solvents or in aqueous solution. For D_2O solutions containing 10% 1,4-dioxane and 40% acetone, successive additions of that cryptate were seen, by using a Varian CFT-20 spectrometer, to reduce the T_1 relaxation times of the acetone CH_3 and CO carbons from 17.6 and 35.4 s, respectively, to 4.9 and 4.8 s at 0.0018 M Gd(III) and to 0.56 and 0.51 s at 0.018 M Gd(III). The relatively inert nature of the cryptate is proven by the exceedingly small (0.2, 1.1 Hz) paramagnetic shifts induced into these resonances, as measured vs. the dioxane signal, even at 0.18 M Gd(III) concentrations. Some very recent, soon to be reported, results of similarly decreased relaxation times from ^{15}N and metal nuclide NMR spectroscopy are even more portentous.

Although the Eu(III) cryptates do tend to act as aqueous lanthanide shift reagents, the effect of encryptation upon the electrochemical behavior of the Eu(III)/Eu(II) redox couple is more remarkable, as illustrated by the cyclic voltammograms