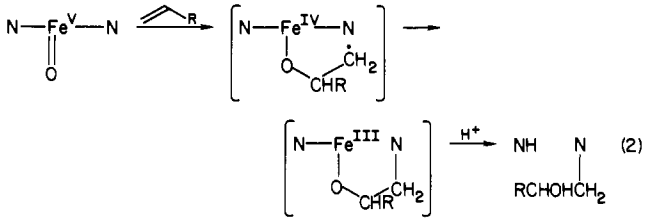
(*N*-(2-hydroxyalkyl)porphyrins) upon oxidation of monosubstituted alkenes (or alkynes) by cytochrome P-450[21] (eq 2).



(2)

Reaction of compound **1** analogues with iron porphyrins could be a good method for the preparation of model complexes containing this novel metallocyclic structure and to study their properties.

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Registry No. 1, 35024-12-5; **2**, 91759-17-0; Fe^{II}(TPP), 16591-56-3.

Supplementary Material Available: Atomic positional and thermal equivalent parameters for all non-hydrogen atoms (Table I), thermal parameters for anisotropic atoms (Table II), listing of observed and calculated structure factors amplitudes (×10) (Table III) (21 pages). Ordering information is given on any current masthead page.

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"Quantamycin": A Computer-Simulated New-Generation Inhibitor of Bacterial Ribosomal Binding

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In spite of the enormous advances in biotechnology[1,2] we still rely, by and large, on traditional methods for antibiotic discovery, and the need for conceptually novel approaches to drug development is omnipresent. A large group of clinically important antibiotics such as lincomycin, clindamycin, and erythromycin arrest bacterial infections in man by inhibition of protein biosynthesis at the ribosomal level.[3] Since lincomycin is known to bind in the region of the peptidyl transferase catalytic activity,[4] and in view of certain structural similarities with the peptidyl tRNA unit on the P site, it occurred to us that the incorporation

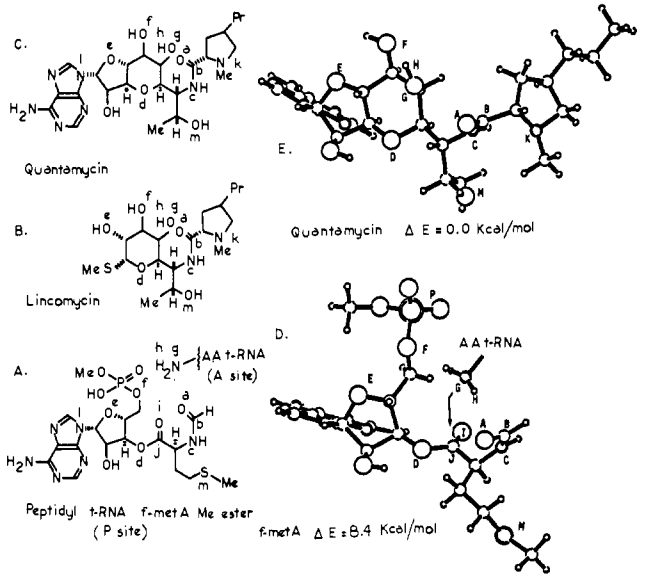

Figure 1. (A) (Left) Natural substrate (peptidyl tRNA) represented by *N*-formyl methionine terminal nucleotide. Letters a-m indicate possible foci for binding interactions at the ribosome. The LUMO in the conformation conducive to attack by the amino group (site g) of the aminoacyl tRNA (upper right) is an antibonding π orbital localized in the region of the ester unit (site j). The HOMO is associated with the amide oxygen atom (site a). (B) Corresponding foci for possible binding interactions of lincomycin at the P site of the ribosome. Site g may be a surrogate for the amino group of AA-tRNA. (C) Structure of quantamycin and convergent functional groups with the natural substrate. (D) (*N*-Formylmethionyl)adenylic acid methyl ester (model substrate for P site on ribosome) in the proposed binding conformation showing location of amino group of AA-tRNA. By means of the Duchamp molecular mechanics procedure,[6b] we have calculated the energy of this conformation to be 8.4 kcal/mol above the minimum energy conformation of the model compound. (E) Minimum energy conformation of quantamycin showing virtual convergence of sites a-h and l.

of additional features in its structure could result in a new-generation-type compound that might mimick the natural substrate.[5] By a combination of quantum and molecular mechanical calculations,[6] computer simulated superimpositions of energy-minimized structures, and considerations of frontier orbital theory,[7] we were able to generate a hybrid structure to which we have coined the name "quantamycin" (Figure 1). This model combines features present in lincomycin[8] and the terminal unit of peptidyl tRNA (represented as fMet-5'-adenylic acid methyl ester) and in its energy-minimized conformation shows a HOMO associated with the oxygen atom of the amide carbonyl group.[5] The purpose of this paper is to describe the total synthesis of quantamycin and to report on its biological activity.

Examination of the structure of our intended target reveals several potential difficulties associated with the construction of the strained, highly functionalized trans-fused perhydrofuropyran motif.[9-11] These challenges were overcome by a judicious choice of protecting groups and the development of novel manipulations

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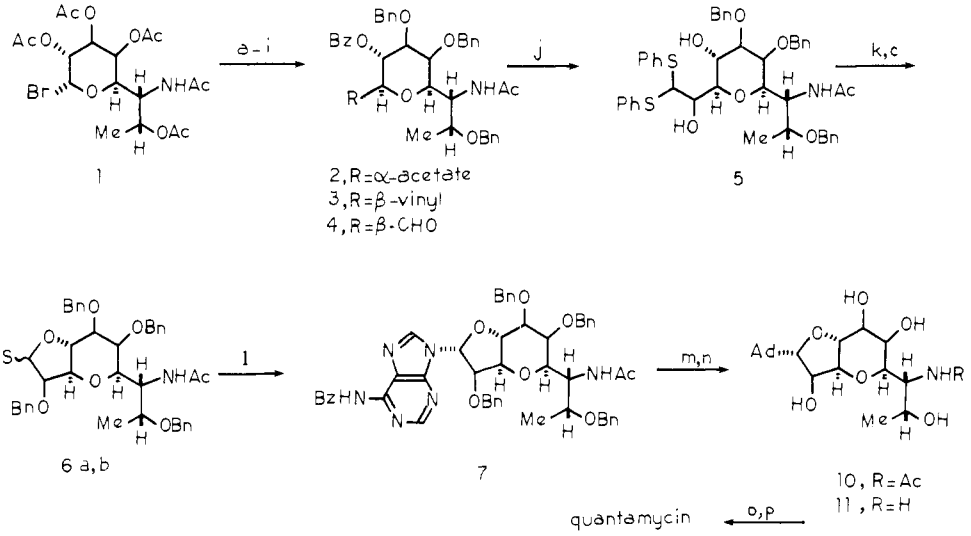
Scheme I[a]



[a] (a) Bu_3SnOMe, Bu_4NBr, $CHCl_3$, 98%; (b) NaOMe, MeOH; (c) BnBr, NaH, DMF; (d) aqueous HCl; (e) Ac_2O, pyr, 67% (4 steps); (f) HBr, AcOH; (g) vinyl MgBr, THF; (h) Bz_2O, DMAP, pyr, 66.8% (3 steps); (i) OsO_4–$NaIO_4$, aqueous acetone; (j) $(PhS)_2CH_2$, *n*-BuLi, −78 °C, 70% 7:1 ratio (2 steps); (k) $Me_2S^+Br\ Br^-$, CH_2Cl_2, 0 °C, 80% (2 steps); (l) *N*-benzoyladenine, Br_2, DMF, 62%; (m) 20% $Pd(OH)_2/C$, H_2, MeOH, 88% (2 steps); (n) aqueous 0.5 N $Ba(OH)_2$, reflux 30 min; (o) hexamethyldisilazane, DMF, 120 °C, 2 h, then add mixed anhydride from isobutyl chloroformate and *N*-propylhygric acid in the presence of *N*-methylmorpholine, −20 °C, 45 min; (p) chromatography, then Bu_4NF, THF.

of functional groups. The synthesis shown in Scheme I starts with **1**, which is readily available from lincomycin,[12] and proceeds to install a glycol aldehyde equivalent as in **5**, $[\alpha]_D$ +7.4°,[10] in a highly stereocontrolled manner. Treatment with bromodimethylsulfonium bromide, followed by benzylation led to a 3:1 mixture of anomeric α- and β-phenyl thioglycosides, **6a**, $[\alpha]_D$ +87.9°, *m/e* 561 ($M^+ - PhCH_2OH$), and **6b**, $[\alpha]_D$ −2°, respectively. In a unique ring-closure reaction, the mixture of glycosides **6a,b** was transformed into a 2:1 mixture of **7**, $[\alpha]_D$ +31.3°, *m/e* 797 ($M^+ - PhCH_2\cdot$), and the unwanted anomeric α-nucleoside, which could be recycled to the desired **7** by mercaptolysis to the diphenyl dithioacetal, $[\alpha]_D$ +30.93°, *m/e* 760 ($M^+ - PhS\cdot$), and subjecting it to cyclization as for **6**. It should be remarked that not only does this method produce the delicately balanced functionality in the intended target, but it also constitutes a novel way of forming cyclic nucleosides from acyclic dithioacetals and thioglycosides.[10,13] With the ring structure established, we proceeded to complete the synthesis of quantamycin. Deprotection of benzyl ethers gave the *N*-acetyl derivative **10** as an amorphous solid, $[\alpha]_D$ +23.1°. De-N-acetylation to quantamine **11** and coupling with *n*-propylhygric acid[14] gave quantamycin as a microcrystalline solid: mp 205–207 °C dec; $[\alpha]_D$ +4.5° (*c* 0.7, $CHCl_3$); M^+ 535.2721 (measured), 535.2754 (calcd).

Although quantamycin was found to have no antibacterial activity, *it exhibited anti-ribosomal activity in competitive binding tests of* ^{14}C *lincomycin to ribosomes from Streptomyces.*[15-17] Although somewhat weaker than anticipated,[18] the ribosomal binding activity of quantamycin constitutes an encouraging lead considering its mode of conception and genesis. The results could pave the way to designing potentially bioactive, new-generation drugs through further fine tuning of the original quantamycin model, or others based on the same concept.

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Registry No. **1**, 6991-36-2; **2**, 91899-81-9; **3**, 91899-82-0; **4**, 91899-83-1; **5**, 91899-84-2; **6a**, 91899-85-3; **6b**, 91899-86-4; **7**, 91899-87-5; **10**, 91899-88-6; **11**, 91899-89-7; quantamycin, 91899-90-0; *N*-benzoyladenine, 4005-49-6; *N*-propylhygric acid, 20488-28-2.

Supplementary Material Available: NMR spectra of **4**, **5**, **6** (α and β anomers), **7**, **10**, and quantamycin and IR spectrum of **4** (10 pages). Ordering information is given on any current masthead page.

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(17) While the observed activity with quantamycin may be partly due to "residual" lincomycin-like features, the drastic alteration of the aglycone portion producing a novel structural entity should not be overlooked. This feature is presently under active study.
(18) The extent of inhibition of binding was 8–10% that of unlabeled lincomycin or erythromycin and 15–20% that of chloramphenicol at the same concentration. The lack of in vitro antibacterial activity and the weak inhibition of protein biosynthesis in cell-free systems (*Streptomyces lividans*)[16] may be due to a pharmacodynamic (e.g., partitioning) behavior.

Anomalous Rearrangement in the Hydrolysis of Diazotized *syn*-4-Amino[2.2](1,4)naphthalenoparacyclophane

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The anomalous rates and products of electrophilic substitutions of layered aromatics such as [2.2]paracyclophanes have been generally accepted as being due to transannular electronic in-

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