$H_{30}N_4O_9$), the IR of both compounds having an ester carbonyl band (1745 cm^{-1}). Upon mild alkaline hydrolysis, **12** yielded **8** and **5**, while **13** afforded **8**, **5**, and Sar.

In the 360-MHz ^1H NMR studies,[11] the OH-bearing methine proton of the tetrahydropyridazine moiety of **1c** appeared at 4.25 ppm while that of **1a** appeared at 5.52 ppm, indicating the location of the acetyl group on the hydroxy group of the tetrahydropyridazine moiety. Thus the structures shown are assigned to BBM-928 A, B, and C.

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Supplementary Material Available: ^1H NMR, ^{13}C NMR, TLC, and amino acid analysis data of all the compounds (6 pages). Ordering information is given on any current masthead page.

Crystal and Molecular Structure of BBM-928 A, a Novel Antitumor Antibiotic from *Actinomadura luzonensis*

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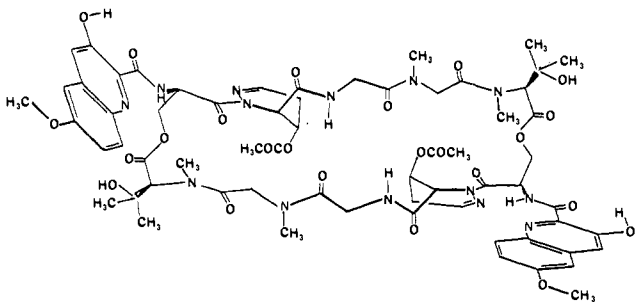
A series of potent antitumor antibiotics designated BBM-928 A, B, and C were recently isolated from *Actinomadura luzonensis*.[1,2] These compounds resembled the quinoxaline antibiotics in that they were cyclic depsipeptides containing two heteroaromatic chromophores[3-5] but differed in that they lacked the sulfur-containing bridge. Chemical[6] and crystallographic studies have now defined the structure of BBM-928 A to be that shown as **1**, and this note reports the crystallographic analysis. This is



the first crystal-structure determination of a naturally occurring[7] cyclic depsipeptide antibiotic which appears to be a bisintercalator.[8]

Early experiments indicated that BBM-928 A crystallized from toluene-containing solutions with toluenes of crystallization. We hoped to exploit this finding by replacing toluene with bromobenzene and thus facilitate the X-ray analysis by use of the heavy-atom technique. Large single crystals of BBM-928 A containing bromobenzene could be grown from CH_2Cl_2–C_6H_5Br solvent mixtures. These crystals rapidly decomposed when removed from the mother liquor, and all manipulations and data collection had to be done with the crystal surrounded by the mother liquor. Preliminary X-ray photographs revealed monoclinic symmetry, and accurate cell constants of a = 19.881 (5), b = 12.303 (2), and c = 22.919 (3) Å and β = 100.52 (2)° were obtained from a least-squares fitting of diffractometer-measured 2θ values. The space group $P2_1$ was indicated by systematic extinctions, and rough density calculations indicated that the asymmetric unit was one molecule of BBM-928 A ($C_{64}H_{78}N_{14}O_{24}$) and three to five molecules of bromobenzene.[9] All unique diffraction maxima with $2\theta \leq 100°$, nominal resolution 1 Å, were collected by using a variable-speed ω scan and graphite-monochromated Cu Kα (1.54178 Å) radiation. Of the 5995 reflections recorded, 4583 (76%) were considered observed after correction for Lorentz, polarization, and background effects ($|F_o| \geq 3\sigma(F_o)$). No corrections were made for absorption, and no decomposition was noted.

The structure was solved by a combination of Patterson and tangent formula recycling techniques.[10-12] An initial phasing model of three independent bromines was obtained from deconvolution of a sharpened ($|E_h|^2 - 1$) Patterson synthesis. Tangent formula recycling led to a chemically sensible fragment of 22 connected atoms, including what appeared to be a quinaldamide system. Further tangent formula recycling and various Fourier syntheses based on these coordinates were attempted but led to no new information. After heavily damped refinement of the fragment positions in an unconstrained block-diagonal least-squares program and tangent formula recycling in which the initial phases were not allowed to vary lest they return to the purely heavy atom phases,[12] an E synthesis clearly showed both the input fragment and a chemically identical portion. These two fragments were related by a noncrystallographic twofold axis which was suggested by our earlier analysis of the Patterson. After inclusion of both fragments in the phasing model, the majority of the remaining nonhydrogen atoms were revealed in successive cycles of tangent formula phase extension with invariant input phases and refinement. On the last cycle of tangent formula recycling, which used all E's > 1.2 (1378), 101 of the 102 atoms in BBM-928 A were clearly visible. The BBM-928 A structure was completed by a Fourier synthesis following partial least-squares refinement. We still do not have a completely satisfactory picture of the partially disordered and complex array of solvent molecules. Our current model includes 4 relatively well-behaved bromobenzene molecules and 11 other solvent atoms in the asymmetric unit. The standard crystallographic residual has converged to 0.15 for this 141 nonhydrogen atom model with anisotropic bromines, and we are attempting to improve this. The absolute configuration il-

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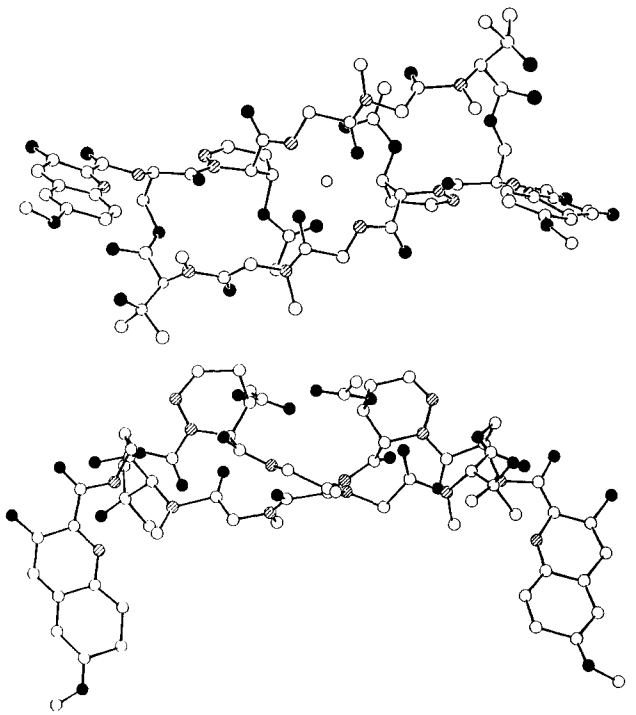

Figure 1. A computer-generated perspective drawing of two views of the current X-ray model of BBM-928 A. The top illustration is a view down the molecular twofold axis which is marked by the open circle at the center. The bottom illustration is at right angles to the first. Carbons are designated by open circles, oxygens by black circles, and nitrogens by stripes.

lustrated is based on the hydrolysis data.[6]

Two different views of the crystallographic model of BBM-928 A are given in Figure 1. The overall shape of the molecule is rectangular, with a molecular but noncrystallographic twofold axis. The long sides of the rectangle consist of twisted, antiparallel β-extended chains, and the short sides are lactone linkages from the hydroxyl group of serine to the carboxyl group of *N*-methylhydroxyvaline. The two unsubstituted amide nitrogens in the cycle are involved in weak (2.96 Å) hydrogen bonds of the 5→1 type that bridge the ring between the glycine amide hydrogen and the sarcosine carbonyl oxygen. This feature is also found in uncomplexed valinomycin.[13] There are two other intramolecular hydrogen bonds, one between the hydroxyl of *N*-methylhydroxyvaline and its own carbonyl (2.82 Å) and one between the aromatic 3-hydroxyl of the quinoline and its carbonyl (2.60 Å). There are no intermolecular hydrogen bonds. The serine residue at the corner is of the *R*(D) configuration, and this use of an "unnatural" amino acid to turn the corner is precedented in the cyclic peptide antibiotic gramicidin S.[14]

The unusual cyclic imino acid *trans*-(3*S*,4*S*)-4-acetoxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid is noteworthy. To the best of our knowledge, the only other report of a naturally occurring pyridazine ring system is the fully saturated hexahydropyridazine-3-carboxylic acid found in the monomycin series of antibiotics.[15] In the crystal the conformation of the tetrahydropyridazine ring is best described as a half-chair. β-Hydroxy-*S*(L)-valine has been previously reported,[16] but this is the first report of the *N*-methyl derivative.

One plausible model for the bisintercalation of BBM-928 A into double-helical DNA in the B form[17,18] may be constructed as follows. The geometry and symmetry are most plausible if we assume a bisintercalating mode where the quinoline rings are separated by two "sandwiched" base pairs. The simplifying assumptions we make are the following: (1) in the complex the twofold axis of BBM-928 A is coincident with that of DNA; (2) the conformation of the decadepsipeptide ring in the crystal is similar to that in the complex; (3) stacking distances are approximately 3.4 Å in both B DNA and the modification in which both quinoline systems have intercalated; (4) the quinoline systems from carboxamide to methoxy (9 Å) essentially overlap with their adjacent included base pair. It is reasonable to expect that most of the unwiding of the double helix that accompanies intercalation[19] occurs between the sets of base pairs that are being separated and that the twist angle of 36° between the two included base pairs is nearly maintained in the complex. On the basis of this model, one may calculate a serine-N to serine-N distance which ranges from 12 to 14.5 Å, depending on the exact quinoline-included base pair overlap; the observed distance in the crystal is 14.7 Å. The twisted conformation of the decadepsipeptide (see Figure 1) appears to be precisely complementary with the twisting nature of the included base pairs in a right-handed DNA double helix. Alternatively, if one relaxes the restriction in this model that the crystal conformation is conserved in the complex, at least one other bisintercalating mode is possible in which the β-extended chains are more nearly parallel to the Watson-Crick base pairs. In this second formulation, the twist angle between the included base pairs would probably be significantly less than 36°.

Further studies will explore the relevance of this crystalline conformation to the mode of action of BBM-928 A.

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Cyclopropylidene Radical Anion and 1,4-Elimination-Type Remote Ionization Effect in the Reduction of Bi(*gem*-dihalocyclopropane) Systems

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It has commonly been held that the electron-transfer reduction of *gem*-dihaloalkanes (**1**) in protic media proceeds via halocarbanion **2** and its protonated product **3** according to eq 1.[1] If

$$\underset{\mathbf{1}}{R_2CX_2} \xrightarrow[-X^-]{e,\,e} \underset{\mathbf{2}}{R_2C(X)^-:} \xrightarrow{SH} \underset{\mathbf{3}}{R_2CHX} \xrightarrow[-X^-]{e,\,e} \xrightarrow{SH} \underset{\mathbf{4}}{R_2CH_2} \quad (1)$$

this is indeed the case, then in the reduction with a deficient amount of reductant, the intermediate **3** should remain as a product until **1** is consumed, since polarographic half-wave potentials specify that the ease of reduction of haloalkanes decreases in the order RCX_3, $RCHX_2$, RCH_2X.[2] We have found, however, that the reduction of bi(*gem*-dihalocyclopropane) compounds (**5**)

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