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Stereochemistry of a Novel Macrodiolide Antibiotic IKD-8344

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The X-ray crystal structure analysis of a novel macrodiolide antibiotic, IKD-8344, has shown a cylindrically curved molecular conformation, together with its relative configuration.

In the research for new antitumor antibiotics from microbial origin, a novel macrocyclic antibiotic named IKD-8344 (**1**,Fig.1) was recently isolated from an unidentified alkalophilic *Actinomycete*. IKD-8344 (**1**), a *C*2-symmetric dilactone macrolide,1) exhibits potent cytotoxic and anthelmintic activity.2) Since the knowledge of the chemical configuration and the stable molecular conformation of **1** would be essential for the elucidation of its bioactive form that is indispensable for designing the clinically usable drug, we report here the X-ray crystal structure of **1** and describe the conformational feature.

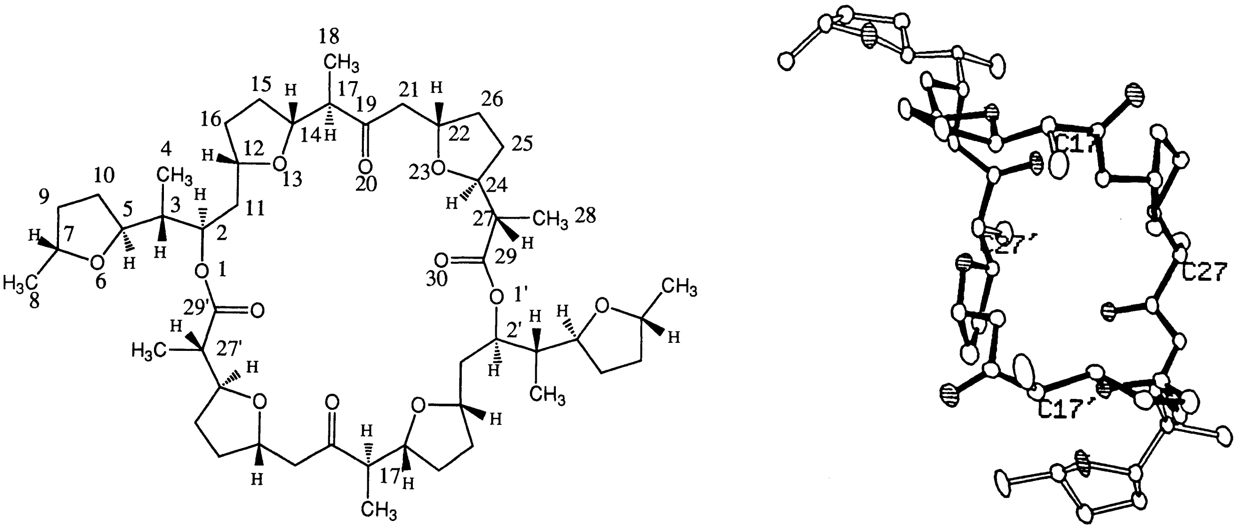

Fig.1. Chemical structures (left side) and X-ray conformation (right side) of IKD-8344 (**1**).

IKD-8344 (**1**) was crystallized as needles from an aqueous methanol solution at room temperature (20 °C) by slow evaporation of the solvents, and subjected to X-ray diffraction.3) The relative configuration4) of **1**, determined by the X-ray analysis, is shown in Fig.1. Two crystallographically independent molecules (named mol-A and mol-B) existed in the crystal lattice. Since these conformations are nearly the same, the molecular conformation of mol-A is shown in Fig.1. It is quite interesting to investigate whether **1** exists as a symmetric conformation or not. The ^{1}H-NMR spectra$^{1)}$ showed that the dominant form of **1** has $C2$ symmetry on the NMR time scale. In the crystalline form, the symmetric conformation of the backbone ring structure was essentially maintained, although some conformational flexibility was observed; the deviation of each torsion angle from$C2$ symmetry is within 30°. The reason why **1** does not crystallize in a $C2$ symmetric form is ascribed to the different puckering between the $C2$-symmetric tetrahydrofuran rings and to the different orientation of their rings with respect to the backbone ring structure .

The present X-ray analysis elucidated some conformational features of **1**. The 28-membered ring takes a rectangular conformation, and is cylindrically curved parallel to the line joining the $C2$-symmetric C27 atoms; the breadth (=C17-C17') and depth (= the length between the midpoints of C17-C17' and C27-C27' bonds) of the cylinder are about 6.27 Å and 5.73 Å for mol-A and 6.13 Å and 5.83 Å for mol-B, respectively. The C2 and C2' atoms are located at the corner of the rectangular ring, and the tetrahydrofuran side chains are protruding from it. It appears important to note that such a saddle-shaped conformation has also been observed in the 24-membered ascidiacyclamide and related cyclic peptides isolated from marine *Ascidian*,$^{5)}$ which exhibit potent antineoplastic/cytotoxic activity.$^{6)}$ The polar oxygen atoms are located along the ring structure with nearly the same interval.

References

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3) Crystal data: $C_{48}H_{76}O_{12}$, Mr=845.12, triclinic, space group $P1$, a=14.180(2) Å, b=19.940(3) Å, c=9.331(2) Å, α=102.62(2)°, β=97.22(2)°, γ=71.90(1)°, V=2442.5(8) Å^3, Z=2, Dc=1.149 g cm^{-3}, λ(Cu Kα)=1.5418 Å, μ(Cu Kα)=6.23 cm^{-1}, F(000)=920. A single crystal of dimensions 0.1 × 0.1× 0.4 mm was used for X-ray diffraction data collection employing graphite-monochromated Cu Kα radiation. The structure was determined by direct method and refined by least-squares method with use of the anisotropic temperature factors for non-H atoms and isotropic ones for H atoms. The present discrepancy indexes R and Rw are 0.093 and 0.096, respectively, using 6573 independent reflections of $|Fo|>2\sigma(Fo)$. The atomic coordinates, anisotropic thermal parameters, bond lengths and angles, and conformational torsion angles have been deposited at the Cambridge Crystallographic Data Center.
4) Concerning the absolute configuration of **1**, no definite conclusion was obtained by the careful measurement of Bijvoet pairs. Thus, its mirror image is also probable as the absolute configuration.
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