present X-ray parameters. The *anti* conformer of (I) showed lower bonding energy than the eclipsed conformer of (I) with an energy difference of about 14·2 kJ mol$^{-1}$, while the two conformers of (II) gave approximately the same bonding energy. The eclipsed conformer of (II), however, showed a large dipole moment in comparison with the other conformers. Hence the unique eclipsed conformation observed in (II) is comparatively stable with respect to the molecular structure, and furthermore it must be stabilized by the intermolecular interactions such as the dipole–dipole interactions between the head groups in the bilayer structure.

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# Structure of a New Macrocyclic Antibiotic


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**Abstract.** 16-Allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.0$^{4,9}$]octacos-18-ene-2,3,10,16-tetrone–water (1/1), $C_{44}H_{69}NO_{12}.H_2O$, $M_r = 804{\cdot}0$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}939$ (1), $b = 15{\cdot}878$ (1), $c = 27{\cdot}184$ (1) Å, $V = 4721{\cdot}0$ (2) Å$^3$, $Z = 4$, $D_x = 1{\cdot}131$ Mg m$^{-3}$, $\lambda$(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}629$ mm$^{-1}$, $F(000) = 1744$, $T = 295$ K, $R(F) = 0{\cdot}071$ for 4249 observed reflections. The molecule has a 21-membered macrolide ring fused to two six-membered rings (piperidine and tetrahydropyran) and linked to another six-membered ring (cyclohexane) through a *trans*-substituted ethylene bond. A piperidinodiketone group is involved in the macrolide ring, and a specific allyl group links to the ring.


**Introduction.** A new antibiotic (FR 900506) isolated from *Streptomyces tsukubaensis* has pharmacological activities such as immunosuppressive activity and antimicrobial activity. The compound is neutral and rich in O atoms, but the crystal is insoluble in water. The structural characteristics of this compound have been studied by chemical and spectroscopic methods so far, and it was known that the molecule has a macrolide ring. The present X-ray work was undertaken in order to determine the total structure including the relative stereochemistry of the ring and its substitution groups.

**Experimental.** Single crystals obtained from methanol solution; colourless; 0·2 × 0·2 × 0·3 mm; 20 reflections for lattice parameters; intensity data collected on a Rigaku AFC5-RU diffractometer with graphite-monochromated Cu $K\alpha$ radiation; 4484 observed reflections within range $2\theta < 130°$; $h$ 0–12, $k$ 0–18, $l$ 0–31; three standard reflections monitored every 60 reflections; corrected for Lorentz and polarization factors; no absorption correction; 4249 reflections with

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$F_o > 3\sigma(F_o)$ used for structure determination; structure solved by a direct method using *RANTAN* (Yao Jia-xing, 1981); an $E$ map gave 38 true peaks for non-H atoms; the complete structure was revealed by successive Fourier syntheses and block-diagonal least-squares refinements; the absolute structure was inferred from the C(2) configuration of L-pipecolic acid; water O($W$) atom found at $R = 0{\cdot}34$; least-squares refinements based on $F$ with unit weight for all reflections; 58 non-H atoms refined with anisotropic thermal parameters; H atoms located from difference maps and theoretical calculations, and refined a few cycles with a fixed isotropic temperature factor 10 Å$^2$, but not refined during last cycles; final $R = 0{\cdot}071$, $S = 1{\cdot}56$, $(\Delta/\sigma)_{max} = 0{\cdot}78$; the final difference map was featureless with $(\Delta\rho)_{max} = 0{\cdot}32$ e Å$^{-3}$; atomic scattering factors from *International Tables for X-ray Crystallography* (1974); all computations on a FACOM M382 computer in the Data Processing Center of Kyoto University, using *KPPXRAY* programs (Taga, Higashi & Iizuka, 1985).

Table 1. *Atomic parameters for non-hydrogen atoms*

$B_{eq} = \frac{4}{3}\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

| | $x$ | $y$ | $z$ | $B_{eq}$(Å$^2$) |
|---|---|---|---|---|
| C(1) | 0·5477 (5) | 0·8945 (3) | 0·4312 (2) | 5·44 |
| C(2) | 0·4271 (5) | 0·8575 (3) | 0·4129 (2) | 5·60 |
| C(3) | 0·3474 (5) | 0·8331 (4) | 0·4564 (2) | 8·13 |
| C(4) | 0·3885 (7) | 0·7516 (5) | 0·4815 (3) | 11·32 |
| C(5) | 0·4019 (8) | 0·6819 (4) | 0·4434 (3) | 12·21 |
| C(6) | 0·4866 (7) | 0·7042 (3) | 0·4024 (3) | 10·35 |
| N(7) | 0·4497 (4) | 0·7846 (2) | 0·3806 (2) | 7·04 |
| C(8) | 0·4521 (5) | 0·7918 (3) | 0·3315 (2) | 7·00 |
| C(9) | 0·4330 (5) | 0·8769 (3) | 0·3077 (2) | 6·20 |
| C(10) | 0·3051 (4) | 0·9045 (3) | 0·2894 (2) | 5·23 |
| C(11) | 0·2226 (4) | 0·8307 (3) | 0·2741 (2) | 5·22 |
| C(12) | 0·0916 (4) | 0·8616 (3) | 0·2709 (2) | 5·73 |
| C(13) | 0·0519 (4) | 0·9026 (3) | 0·3179 (2) | 5·22 |
| C(14) | 0·1365 (4) | 0·9755 (3) | 0·3303 (2) | 4·74 |
| C(15) | 0·1097 (4) | 1·0173 (3) | 0·3798 (2) | 5·30 |
| C(16) | 0·1795 (4) | 1·0985 (3) | 0·3891 (2) | 5·34 |
| C(17) | 0·1441 (4) | 1·1721 (3) | 0·3564 (2) | 4·96 |
| C(18) | 0·2051 (5) | 1·2541 (3) | 0·3728 (2) | 6·02 |
| C(19) | 0·3421 (5) | 1·2613 (3) | 0·3691 (2) | 6·09 |
| C(20) | 0·4069 (4) | 1·2900 (3) | 0·4061 (2) | 5·48 |
| C(21) | 0·5403 (4) | 1·3158 (3) | 0·4059 (2) | 5·98 |
| C(22) | 0·6038 (4) | 1·2893 (3) | 0·4522 (2) | 5·23 |
| C(23) | 0·7316 (4) | 1·2513 (3) | 0·4485 (2) | 5·70 |
| C(24) | 0·7288 (4) | 1·1602 (3) | 0·4679 (2) | 4·83 |
| C(25) | 0·6405 (4) | 1·1037 (3) | 0·4401 (2) | 4·87 |
| C(26) | 0·6251 (4) | 1·0206 (3) | 0·4686 (2) | 4·95 |
| C(27) | 0·5844 (4) | 1·0302 (3) | 0·5218 (2) | 5·34 |
| C(28) | 0·6475 (5) | 0·9932 (3) | 0·5563 (2) | 5·59 |
| C(29) | 0·6212 (5) | 0·9954 (3) | 0·6114 (2) | 6·18 |
| C(30) | 0·5564 (6) | 0·9142 (3) | 0·6282 (2) | 8·21 |
| C(31) | 0·5410 (7) | 0·9147 (3) | 0·6850 (3) | 10·23 |
| C(32) | 0·6625 (9) | 0·9251 (5) | 0·7090 (2) | 11·52 |
| C(33) | 0·7183 (7) | 1·0059 (4) | 0·6956 (2) | 9·40 |
| C(34) | 0·7402 (6) | 1·0071 (4) | 0·6393 (2) | 6·90 |
| C(35) | 0·2632 (6) | 0·7904 (4) | 0·2254 (2) | 7·11 |
| C(36) | 0·0065 (5) | 1·1879 (3) | 0·3552 (2) | 6·70 |
| C(37) | 0·3909 (6) | 1·2452 (6) | 0·3191 (3) | 12·55 |
| C(38) | 0·5450 (6) | 1·4155 (4) | 0·4030 (3) | 10·58 |
| C(39) | 0·6584 (8) | 1·4547 (5) | 0·4072 (4) | 13·46 |
| C(40) | 0·7086 (9) | 1·5023 (8) | 0·3861 (6) | 23·41 |
| C(41) | 0·6786 (5) | 1·0864 (3) | 0·3870 (2) | 6·70 |
| C(42) | 0·4676 (5) | 1·0823 (4) | 0·5299 (2) | 7·12 |
| C(43) | −0·1637 (6) | 0·8851 (5) | 0·3288 (4) | 12·59 |
| C(44) | 0·0533 (10) | 0·9582 (5) | 0·4570 (3) | 14·26 |
| C(45) | 0·3628 (9) | 0·8407 (5) | 0·7061 (3) | 12·24 |
| O(1) | 0·5275 (3) | 0·9740 (2) | 0·4434 (1) | 5·66 |
| O(2) | 0·6425 (3) | 0·8592 (2) | 0·4347 (2) | 8·44 |
| O(3) | 0·4735 (5) | 0·7340 (3) | 0·3037 (2) | 11·54 |
| O(4) | 0·5208 (3) | 0·9207 (3) | 0·3014 (2) | 8·45 |
| O(5) | 0·2605 (3) | 0·9441 (2) | 0·3333 (1) | 4·89 |
| O(6) | 0·3155 (3) | 0·9609 (2) | 0·2505 (1) | 6·27 |
| O(7) | −0·0682 (3) | 0·9385 (2) | 0·3138 (2) | 7·43 |
| O(8) | 0·1356 (4) | 0·9565 (2) | 0·4172 (1) | 6·88 |
| O(9) | 0·5581 (3) | 1·2979 (2) | 0·4922 (1) | 6·44 |
| O(10) | 0·8469 (3) | 1·1223 (2) | 0·4648 (1) | 5·98 |
| O(11) | 0·4823 (6) | 0·8389 (3) | 0·6980 (3) | 17·72 |
| O(12) | 0·6488 (8) | 0·9197 (3) | 0·7633 (2) | 16·98 |
| O($W$) | 0·4995 (7) | 1·0808 (3) | 0·2435 (3) | 14·17 |

**Discussion.** The atomic coordinates and thermal parameters for non-H atoms are listed in Table 1.* A perspective drawing of the molecule is shown in Fig. 1. Atomic numbering and bond parameters are given in Fig. 2. The atoms in the peripheral part of the molecule have unusually large thermal parameters, and the structure may be inaccurate around these atoms, giving the large $R$ value. However, bond distances and bond angles are normal if the short bond distances of the terminal groups are considered to be due to their extremely large thermal motions. The molecule has a 21-membered macrolide ring fused to piperidine and tetrahydropyran rings. A hydroxy- and methoxy-substituted cyclohexane ring links to the macrolide ring through a *trans*-substituted ethylene bond. All the six-membered rings have a chair form. All the bonds attached to the six-membered rings are equatorial except for C(1)–C(2) to the piperidine ring and O(6)–C(10) to the tetrahydropyran ring. The six atoms N(7), C(2), C(6), C(8), C(9) and O(3) of the piperidinoketone group are coplanar within 0·06 Å. The two planes of the ketone groups are approximately perpendicular to each other with the O(3)–C(8)–C(9)–O(4)

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43563 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

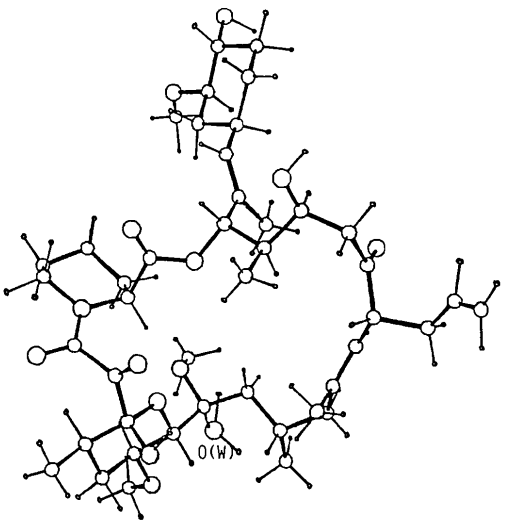
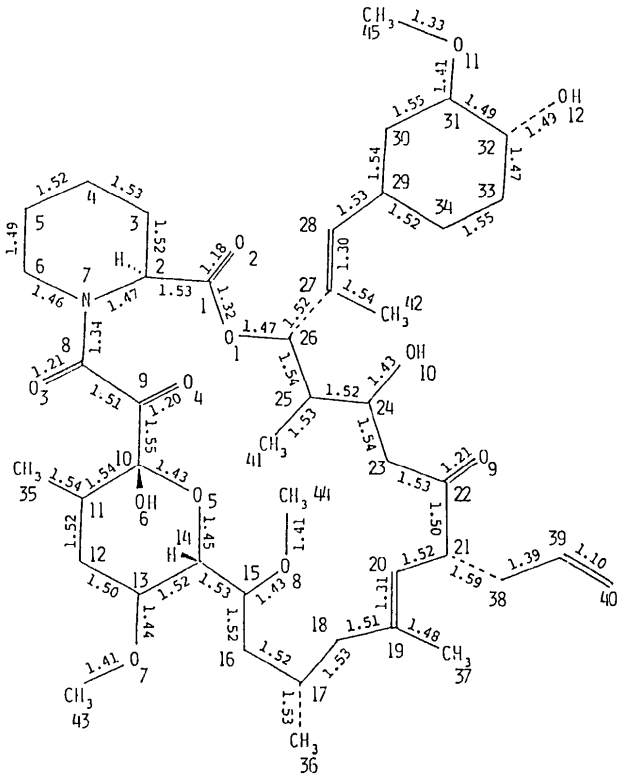
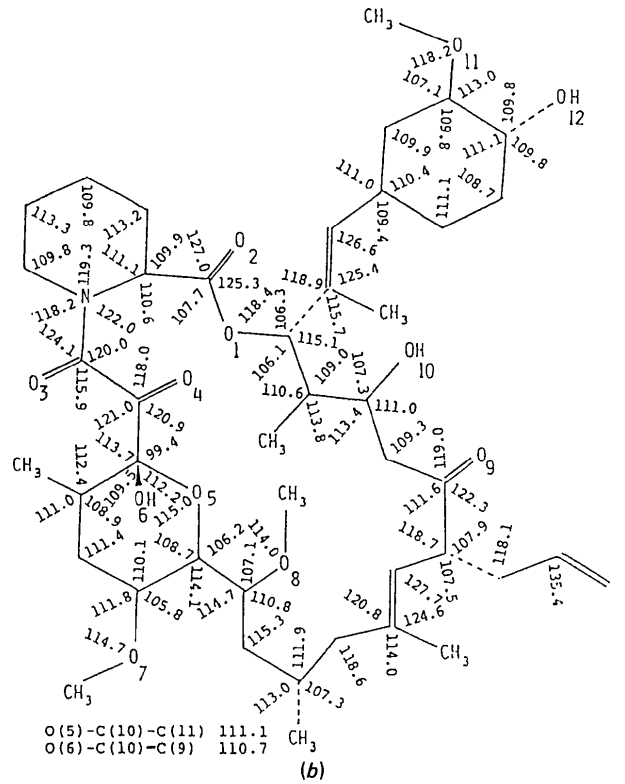



Fig. 1. Perspective drawing of the molecule.



(a)



O(5)-C(10)-C(11) 111.1
O(6)-C(10)-C(9) 110.7

(b)

Fig. 2. (*a*) Bond distances (Å) and (*b*) bond angles (°). The e.s.d.'s are 0·01–0·02 Å for bond distances and 0·4–1·2° for bond angles.

torsion angle 89·4 (7)°. The 21-membered ring is a macrolide lactone ring. Similar lactone rings have been found in several antibiotics, *e.g.* rapamycin (White & Swindells, 1981), venturicidin (Brufani, Cerrini, Fedeli, Musu, Cellai & Keller-Schierlein, 1971), oligomycin (Glehn, Norrestam, Kierkegaard, Maron & Ernster, 1972), milbemycin (Mishima, Kurabayashi, Tamura, Sato, Kuwano, Saito & Aoki, 1975), avermectin (Albers-Schonberg, Arison, Chabala, Douglas, Eskola, Fisher, Lusi, Mrozik, Smith & Tolman, 1981), cytovaricin (Sakurai, Kihara & Isono, 1983), and rhizoxin (Iwasaki, Namikoshi, Kobayashi, Furukawa, Okuda, Itai, Kasuya, Iitaka & Sato, 1986). Among these neutral antibiotics, rapamycin has the most similar molecular skeleton to the present compound. It has three six-membered rings in the same configuration, and the piperidinoketone–tetrahydropyran linkage is also the same. Its macrolide ring is, however, a 29-membered ring including four unsaturated C=C bonds, and the C(27)–C(28) bond is saturated. The present molecule has an allyl group attached to C(21) of the macrolide ring. Rapamycin and other antibiotics lack such an allyl group, and the existence of this group is specific for the present antibiotic. All hydrophilic groups bonded to the macrolide ring point outwards from the ring. There are no intramolecular hydrogen bonds, but intermolecular hydrogen bonds O(10)H···O(9) $(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$ and O(12H···O(7) $(\frac{1}{2}-x, 2-y, \frac{1}{2}+z)$ occur. The water molecule forms three hydrogen bonds: O(4)–C(9)–C(10)–O(6) chelates to O(*W*) with two hydrogen bonds, O(*W*)H···O(4) and O(*W*)···HO(6); the other hydrogen bond is O(*W*)H···O(3) $(1-x, \frac{1}{2}+y, \frac{1}{2}-z)$.

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