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11,12,4″-Tri-*O*-methylazithromycin Monohydrate

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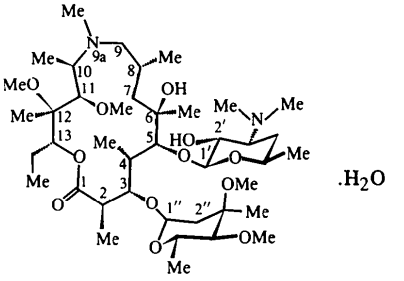
Abstract

The title compound, [2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,-11*R**,12*S**,13*S**,14*R**)]-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-4-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-10-hydroxy-3,4-dimethoxy-3,5,6,8,10,12,14-heptamethyl-11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-1-oxa-6-azacyclopentadecan-15-one monohydrate $C_{41}H_{78}N_2O_{12}.H_2O$, is an *O*-methylated derivative (in positions O11, O12 and O4″) of the 15-membered semisynthetic azalide antibiotic azithromycin. The aglycone ring adopts a 'folded-out' conformation, as found for azithromycin in the solid state, thus indicating that the introduced methyl groups do not essentially affect the molecular conformation. Both the α-L-cladinose and the β-D-desosamine sugars are in the expected chair conformations. The intramolecular hydrogen bond of 2.750 (9) Å between the methylated atom N9a and the hydroxyl O atom O61 is characteristic of this compound and the whole class of the analogous compounds. Both H atoms of the water molecule participate in hydrogen bonding with the aglycone as well as with the cladinose ring.

Comment

Azithromycin (Đokić *et al.*, 1988; Bright *et al.*, 1988) is a new semisynthetic broad-spectrum macrolide antibacterial which belongs to a recently described subclass of antibiotics called azalides. As reported in our previous paper (Kobrehel *et al.*, 1991), a new series of *O*-methylazithromycin derivatives has been synthesized and structurally characterized by two-dimensional NMR correlation spectroscopy. The title compound (I) was prepared by a synthetic route using 2′-*O*,3′-*N*-bis(benzyloxycarbonyl)-*N*-dimethylazithromycin as bisprotected intermediate (bis-CBz route). Thus, *O*-methylation with an excess of methyl iodide and sodium hydride in DMF at room temperature, the usual deprotection and reductive 3′-*N*-methylation, also afforded 11,12,4″-tri-*O*-methylazithromycin, as a by-product of the previously described 6,11,4″-tri-*O*-methyl derivative (Kobrehel *et al.*, 1991).



.H_2O

(I)

As part of our broader research on such 15-membered azalides (Đokić *et al.*, 1986, 1988, 1995; Kamenar, Mrvoš-Sermek, Vicković & Nagl, 1990; Kamenar, Mrvoš-Sermek, Banić, Nagl & Kobrehel, 1991; Kamenar, Mrvoš-Sermek, Nagl & Kobrehel, 1996; Lazarevski *et al.*, 1993), we have undertaken the X-ray structure analysis of the title compound. Up to now, the only X-ray analysis of an *O*-methylated macrolide was that of clarithromycin, the 6-*O*-methylated derivative of erithromycin A (Iwasaki, Sugawara, Adachi, Morimoto & Watanabe, 1993).

The molecular structure of 11,12,4″-tri-*O*-methylazithromycin, as of the other azalides, is characterized by a ring-expanded 15-membered macrocyclic framework which contains a methyl-substituted endocyclic N atom at position 9a of the erythromycin A aglycone ring. The α-L-cladinose and β-D-desosamine sugars are linked to the azalactone ring at positions C3 and C5, respectively. The hydrogen-bonding geometry (Vicković, 1988) is listed in Table 2 and an *ORTEP*92 (Vicković, 1994) view of the molecule is shown in Fig. 1.

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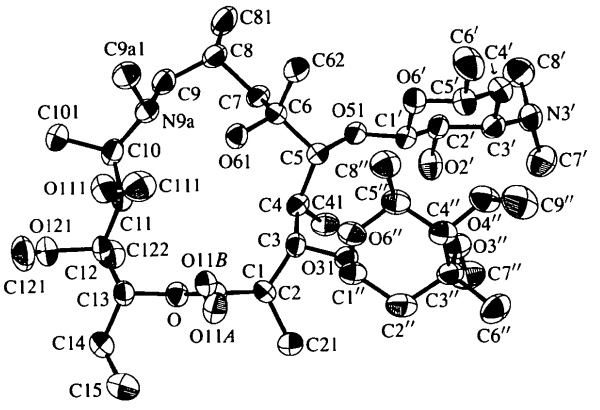

Fig. 1. *ORTEP*92 (Vicković, 1994) view of the molecule with the atom-labelling scheme. H atoms and the water molecule are omitted for clarity. Displacement ellipsoids are plotted at the 36% probability level.

The two methoxy groups attached to C11 and C12 of the aglycone ring do not change its conformation which is essentially the same as that found in the crystalline state of azithromycin itself (Đokić *et al.*, 1988). The short proton–proton distance C11—H11···H4—C4 of 2.99 (2) Å indicates a 'folded-out' conformation as is also found in the crystal structures of azithromycin (2.65 Å; Lazarevski *et al.*, 1993) and erythromycin derivatives (Everet, Hatton, Tyler & Williams, 1989). The lactone O atom O11 exhibits positional disorder from an ideal sp^2 hybridization (Keller, Neeland, Rettig, Trotter & Weiler, 1988) being split between two positions O11*A* and O11*B*, both with an occupancy factor of 0.5. According to the values of the torsion angles C2—C3—O31—C1″ [−88.5 (7)°], C3—O31—C1″—O6″ [−75.0 (7)°], C4—C5—O51—C1′ [−103.2 (7)°] and C5—O51—C1′—O6′ [−76.4 (7)°], the conformation about the glycoside bonds is between (−)-anticlinal and (−)-synclinal. The orientation of the sugars with respect to the aglycone ring does not differ significantly from that in azalide and erythromycin derivatives (Sheldrick, Kojić-Prodić, Banić, Kobrehel & Kujundžić, 1995; Everet *et al.*, 1989). Both the α-L-cladinose and the β-D-desosamine sugar rings are in chair conformations. All bond lengths and angles in the aglycone ring as well as in the sugar components are within expected values. The intramolecular hydrogen bond O61—H61···N9a of 2.750 (9) Å is characteristic of this class of compounds with the atom N9a sp^3 hybridized (Đokić *et al.*, 1988; Kamenar *et al.*, 1991; Sheldrick *et al.*, 1995). The water molecule is hydrogen bonded to both the lactone and cladinose rings [O1*W*—H1*WA*···O61 and O1*W*—H1*WB*···O6″ 2.80 (3) and 3.31 (2) Å, respectively].

Experimental

Crystals were prepared by slow evaporation of dimethyl sulfoxide–acetone solution (3:1, *v*/*v*).

Crystal data

$C_{41}H_{78}N_2O_{12}.H_2O$
M_r = 809.09
Orthorhombic
$P2_12_12_1$
a = 10.604 (5) Å
b = 13.327 (3) Å
c = 32.664 (9) Å
V = 4616 (3) Å^3
Z = 4
D_x = 1.164 Mg m^{-3}
D_m = 1.104 Mg m^{-3}
D_m measured by flotation
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 13 reflections
θ = 4–12°
μ = 0.66 mm^{-1}
T = 293 K
Prismatic
0.4 × 0.3 × 0.2 mm
Transparent

Data collection

Philips PW1100 diffractometer updated by Stoe
$\omega/2\theta$ scans
Absorption correction: none
5012 measured reflections
4261 independent reflections
1757 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.1019
θ_{max} = 63.67°
h = 0 → 12
k = 0 → 15
l = 0 → 37
2 standard reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F^2
$R(F)$ = 0.0624
$wR(F^2)$ = 0.1758
S = 1.316
4261 reflections
511 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.1389P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.434
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.36 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)
Flack parameter = 0.4 (5)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
C1	0.5381 (9)	0.1803 (6)	0.3556 (3)	0.082 (2)
C2	0.6484 (7)	0.2525 (5)	0.3543 (3)	0.080 (2)
C3	0.6192 (7)	0.3461 (5)	0.3803 (2)	0.073 (2)
C4	0.5983 (7)	0.4383 (5)	0.3532 (2)	0.071 (2)
C5	0.5395 (7)	0.5261 (5)	0.3772 (2)	0.072 (2)
C6	0.3992 (7)	0.5436 (5)	0.3677 (2)	0.070 (2)
C7	0.3854 (7)	0.5855 (5)	0.3244 (2)	0.078 (2)
C8	0.2504 (7)	0.6055 (6)	0.3075 (3)	0.085 (2)
C9	0.2043 (8)	0.5184 (6)	0.2814 (3)	0.090 (2)
C9a1	0.0573 (8)	0.4384 (8)	0.3261 (3)	0.106 (3)
C10	0.1911 (8)	0.3355 (6)	0.2813 (3)	0.090 (2)
C11	0.2482 (7)	0.2507 (6)	0.3075 (2)	0.079 (2)
C12	0.3051 (7)	0.1632 (6)	0.2827 (2)	0.080 (2)
C13	0.3876 (7)	0.0973 (6)	0.3102 (2)	0.078 (2)
C14	0.4327 (9)	0.0011 (7)	0.2928 (3)	0.099 (3)
C15	0.5063 (12)	−0.0635 (8)	0.3227 (4)	0.147 (4)
C21	0.7697 (9)	0.1953 (8)	0.3640 (4)	0.134 (3)
C41	0.7169 (8)	0.4656 (6)	0.3294 (2)	0.088 (2)
C62	0.3437 (8)	0.6129 (6)	0.3996 (2)	0.096 (2)
C81	0.2533 (9)	0.6989 (7)	0.2805 (3)	0.127 (3)

C101	0.0711 (8)	0.3035 (7)	0.2586 (3)	0.119 (3)
C111	0.1842 (11)	0.2297 (9)	0.3781 (3)	0.141 (4)
C121	0.1266 (11)	0.0418 (9)	0.2897 (4)	0.139 (4)
C122	0.3779 (8)	0.1995 (7)	0.2463 (2)	0.101 (2)
C1′	0.6876 (7)	0.6534 (6)	0.3998 (2)	0.077 (2)
C2′	0.7682 (7)	0.7315 (6)	0.3800 (2)	0.078 (2)
C3′	0.8537 (8)	0.7800 (6)	0.4109 (3)	0.084 (2)
C4′	0.7757 (9)	0.8169 (6)	0.4459 (3)	0.098 (3)
C5′	0.6919 (9)	0.7344 (7)	0.4631 (3)	0.099 (2)
C6′	0.6066 (11)	0.7704 (9)	0.4968 (3)	0.143 (3)
C7′	1.0543 (9)	0.8203 (9)	0.3760 (3)	0.138 (4)
C8′	0.8801 (11)	0.9356 (7)	0.3719 (4)	0.139 (4)
C1″	0.7101 (8)	0.3195 (6)	0.4466 (2)	0.083 (2)
C2″	0.8418 (9)	0.3169 (7)	0.4661 (3)	0.102 (3)
C3″	0.8808 (8)	0.4157 (6)	0.4867 (2)	0.088 (2)
C4″	0.7730 (9)	0.4474 (7)	0.5139 (2)	0.092 (3)
C5″	0.6493 (8)	0.4528 (7)	0.4919 (3)	0.094 (2)
C6″	1.0036 (9)	0.3995 (8)	0.5104 (3)	0.121 (3)
C7″	0.9903 (10)	0.4880 (8)	0.4286 (3)	0.128 (3)
C8″	0.5379 (9)	0.4746 (8)	0.5192 (3)	0.113 (3)
C9″	0.8288 (15)	0.5479 (9)	0.5735 (3)	0.161 (5)
N9a	0.1785 (6)	0.4267 (5)	0.3061 (2)	0.085 (2)
N3′	0.9415 (7)	0.8572 (5)	0.3961 (3)	0.108 (2)
O	0.4996 (5)	0.1609 (4)	0.3177 (1)	0.076 (1)
O31	0.7199 (5)	0.3699 (3)	0.4075 (1)	0.073 (1)
O51	0.6045 (5)	0.6182 (4)	0.3695 (2)	0.078 (1)
O11*A*†	0.5239	0.1310	0.3857	0.104 (4)
O11*B*†	0.4690	0.1580	0.3848	0.070 (3)
O61	0.3388 (5)	0.4497 (4)	0.3716 (2)	0.083 (1)
O111	0.1590 (5)	0.2157 (4)	0.3361 (2)	0.100 (2)
O121	0.2074 (7)	0.1002 (4)	0.2645 (2)	0.113 (2)
O2′	0.8431 (5)	0.6889 (5)	0.3481 (2)	0.102 (2)
O6′	0.6155 (5)	0.6953 (4)	0.4318 (2)	0.087 (1)
O3″	0.8918 (6)	0.4958 (4)	0.4574 (2)	0.091 (1)
O4″	0.7970 (6)	0.5435 (5)	0.5305 (2)	0.109 (2)
O6″	0.6197 (6)	0.3590 (4)	0.4723 (2)	0.094 (2)
O1*W*	0.318 (2)	0.351 (2)	0.447 (1)	0.45 (1)

† The coordinates of O11*A* and O11*B* were not refined owing to the positional disorder.

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O61—H61···N9a	0.82 (5)	1.94 (6)	2.750 (9)	171 (5)
O1*W*—H1*WA*···O61	0.97 (3)	1.848 (6)	2.80 (3)	168 (2)
O1*W*—H1*WB*···O6″	1.14 (2)	2.179 (6)	3.31 (2)	171 (1)

The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1985) which revealed the skeleton of the molecule. The remaining atoms were found after successive Fourier syntheses, the methoxy C atoms in the difference Fourier synthesis. The atom O11 of the disordered lactone group was found disordered over two positions, each with 50% occupancy. All non-H atoms were refined with anisotropic displacement parameters using *SHELXL*93 (Sheldrick, 1993). The majority of H atoms, including those bonded to O atoms, were found *via* inspection of the difference Fourier maps. The H atoms were refined with fixed geometry, each riding on a carrier atom, with a fixed isotropic displacement parameter amounting to 1.5 (for methyl/hydroxyl/water H atoms) or 1.2 (for the other H atoms) times the value of the equivalent isotropic displacement parameter of the carrier atom. The parameters of the water H atoms were not refined.

Data collection: *DIF*4 (Stoe & Cie, 1992*a*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1992*b*). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*92 (Vicković, 1994). Software used to prepare material for publication: *CSU* (Vicković, 1988).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KA1189). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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