Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1243). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1996). C**52**, 2563–2566

A [3.1.0]-Fused 2′,3′-Modified β-D-Pyrazolo[3,4-*d*]pyrimidine Nucleoside†

GOUTAM BISWAS,[a]‡ TILAK CHANDRA,[b] NEERAJ GARG,[b] DIWAN S. BHAKUNI,[b] AMITAVA PRAMANIK,[c] KAMLAKAR AVASTHI[b]* AND PRAKAS R. MAULIK[a]*

[a]*Division of Membrane Biology, Central Drug Research Institute, Chattar Manzil Palace, Post Box No. 173, Lucknow 226 001, India,* [b]*Medicinal Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Post Box No. 173, Lucknow 226 001, India, and* [c]*Inorganic Chemistry Department, Indian Association for the Cultivation of Sciences, Calcutta 700 032, India*

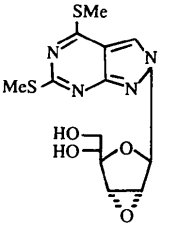
(*Received 27 November 1995; accepted 20 March 1996*)

Abstract

The furanose ring in 4,6-bis(methylthio)-2-(2,3-anhydro-1-deoxy-β-D-allofuranosyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine, $C_{13}H_{16}N_4O_4S_2$, is almost planar with the epoxide ring in an *exo* orientation.

Comment

3′-Deoxy and 2′,3′-dideoxy nucleosides are important in the treatment of AIDS (Connolly & Hammer, 1992; Huryn & Okabe, 1992). The potent antileishmanial activity of allopurinol riboside has generated considerable interest in pyrazolo[3,4-*d*]pyrimidine nucleosides (Hupe, 1986). Other pyrazolo[3,4-*d*]-pyrimidine nucleosides with important biological properties have been reported (Rideout *et al.*, 1983; Cottam, 1994). Our continued interest in pyrazolo[3,4-*d*]-pyrimidines (Garg, Avasthi & Bhakuni, 1989; Avasthi *et al.*, 1993; Biswas, Chandra, Avasthi & Maulik, 1995) and their nucleosides (Misra, Jain, Avasthi & Bhakuni, 1990) has led us to report the first synthesis of 'hexofuranosyl nucleosides' of pyrazolo[3,4-*d*]-pyrimidines (Avasthi, Dev, Garg & Bhakuni, 1991). Some 2′,3′-modified nucleosides effectively inhibit the action of several DNA polymerases including virus reverse transcriptase (Kraevskii *et al.*, 1988; Chiggeavadze *et al.*, 1989). This, together with the X-ray crystallographic studies on several [3.1.0]-fused 2′,3′-modified β-D nucleosides of various natural bases (Koole *et al.*, 1991), has prompted us to report the synthesis and X-ray structure of the [3.1.0]-fused 2′,3′-modified nucleoside of pyrazolo[3,4-*d*]pyrimidine, (2). To the best of our knowledge this is the first report describing the synthesis and X-ray study of a novel [3.1.0]-fused 2′,3′-modified nucleoside comprising a six-carbon furanose sugar and a pyrazolo[3,4-*d*]pyrimidine ring system, which is isomeric with the biologically important purine system.



(2)

The X-ray diffraction study of the nucleoside (2) showed three molecules (*A*, *B* and *C*) of similar conformation in one asymmetric unit, connected by intermolecular hydrogen bonding (Fig. 1). The pyrazolo-[3,4-*d*]pyrimidine bases together with the exocyclic methylthio groups attached at the 4 and 6 positions are planar. The furanose ring of the six-carbon sugar moiety of each molecule is flattened compared with 2′-deoxy-nucleosides, presumably due to fusion of the epoxide ring with the C(2′)—C(3′) bond. This result is similar to that observed in many [3.1.0]-fused 2′,3′-modified nucleosides where the furanose ring is derived from a five-carbon sugar (Koole *et al.*, 1991).

The C(2′) and C(3′) atoms deviate [average value of −0.49 (2) Å in each case] in the same direction from the planes through atoms C(1′), O(1′) and C(4′). The epoxy O(23) atoms are further away from these planes [by −1.74 (2), −1.72 (2) and −1.72 (2) Å for *A*, *B* and *C*, respectively], while atoms O(5′) and O(6′) of the ethylene glycol moiety deviate in the opposite direction.

† CDRI communication No. 5401. ‡ Present address: Ramananda College, Department of Physics, PO Bishnupur, Bankura, West Bengal, India.

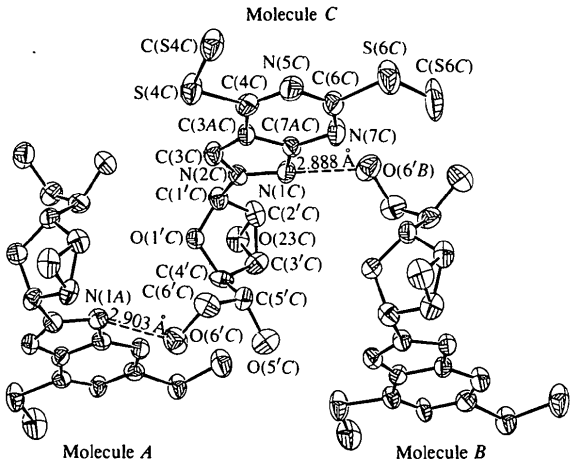


Fig. 1. *ORTEP* (Johnson, 1965) diagram showing displacement ellipsoids at 50% probability for the non-H atoms of the three molecules (*A*, *B* and *C*) in one asymmetric unit. H atoms have been omitted for clarity. Intermolecular hydrogen bonding is shown by broken lines.

Least-squares planes through the atoms of the equilateral triangles formed by the epoxy O(23) atom with C(2′) and C(3′) are inclined at angles of 82.5 (4), 82.3 (4) and 80.7 (4)° to the mean planes through the atoms of the sugar moieties for *A*, *B* and *C*, respectively. Thus, the epoxy O atoms are *exo* oriented.

The epoxide ring has virtually the same impact on the furanoid conformation as has been observed with other [3.1.0]-fused 2′,3′-modified nucleosides (Koole *et al.*, 1991). In the almost planar furanoid rings, the C(1′)—C(2′) and C(2′)—C(3′) bonds are shortened by 0.02–0.07 Å, and the C(1′)—C(2′)—C(3′) and C(2′)—C(3′)—C(4′) bond angles are widened by 5–6° compared with compounds having no epoxide ring fused to the sugar moiety. The conformation about the glycoside bond [O(1′)—C(1′)—N(2)—N(1)] is *anti*, with values of 91.8 (8), 101.5 (8) and 114.2 (8)° for *A*, *B* and *C*, respectively. The most common conformation around the C(4′)—C(5′) bond in normal nucleosides derived from five-carbon sugars is *gauche–gauche* (Sundaralingam, 1965). In the title nucleoside (2), however, the *gauche–trans* conformation was observed for *A*, *B* and *C*, whereas in the closely related 2′,3′-*O*-anhydroadenosine, the *gauche–gauche* conformation (Koole *et al.*, 1991) was observed. This difference is presumably due to the presence of an extra hydroxymethyl group at the C(5′) position. The molecules are packed in such a way that they form alternate columns, each consisting of stacked sugar and base moieties running along the *c* axis of the unit cell (Fig. 2).

The unusual formation of the N-2 product, 4,6-bis(methylthio)-2-(2′-*O*-acetyl-5′,6-di-*O*-methylsulfonyl-β-D-glucofuranosyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine, (1), as a major product during *N*-glycosidation (Avasthi *et al.*, 1991) is further confirmed as a result of the structure determination of the epoxide derivative (2).

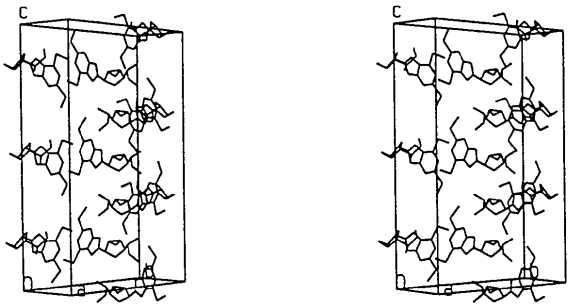


Fig. 2. Stereoview of the crystal-packing diagram.

Experimental

A mixture of 4,6-bis(methylthio)-2-(2′-*O*-acetyl-5′,6-di-*O*-methylsulfonyl-β-D-glucofuranosyl)-2*H*-pyrazolo[3,4-*d*]pyrimidine [(1), 0.801 g, 1.14 mmol; Avasthi *et al.*, 1991] and methanolic ammonia (70 ml) was kept at 278 K in a steel bomb for 48 h. Standard work-up followed by column chromatography gave epoxide (2) in 85% yield; m.p. 433 K (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (*s*, 3H, SCH_3), 2.70 (*s*, 3H, SCH_3), 3.70 [*dd*, *J* = 4, 12 Hz, H(6′)], 3.83 [*dd*, *J* = 3, 12 Hz, H(6″)], 4.08 [*m*, 1H, H(5′)], 4.14 [*d*, 1H, *J* = 3 Hz, H(3′)], 4.43 [*m*, 2H, H(2′) and H(4′)], 6.02 [*s*, 1H, H(1′)], 8.15 [*s*, 1H, H(3)]; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.7, 13.4, 58.1 [C(2′) and C(3′)], 62.6 [C(6′)], 70.5 [C(5′)], 81.1, 108.2, 126.8 [C(3)], 157.9, 167.5, 168.2; correct elemental analysis was obtained for $C_{13}H_{16}N_4O_4S_2$. Diffraction quality crystals were obtained by slow evaporation from 2-propanol at room temperature.

Crystal data

$C_{13}H_{16}N_4O_4S_2$	Mo $K\alpha$ radiation
M_r = 356.42	λ = 0.71073 Å
Orthorhombic	Cell parameters from 40 reflections
$P2_12_12_1$	θ = 7.2–12.5°
a = 7.529 (4) Å	μ = 0.362 mm^{-1}
b = 20.689 (12) Å	*T* = 293 K
c = 30.469 (16) Å	Prismatic
V = 4746 (5) Å^3	0.44 × 0.36 × 0.28 mm
Z = 12	Colourless
D_x = 1.496 Mg m^{-3}	
D_m not measured	

Data collection

Nicolet *R3m/V* diffractometer	θ_{max} = 25°
ω scans	*h* = 0 → 8
Absorption correction: none	*k* = 0 → 24
4742 measured reflections	*l* = 0 → 36
4742 independent reflections	2 standard reflections monitored every 98 reflections
2850 observed reflections [$I > 2\sigma(I)$]	intensity decay: none

Refinement

Refinement on F^2	$(\Delta/\sigma)_{max}$ = 0.027
$R(F)$ = 0.052	$\Delta\rho_{max}$ = 0.313 e Å^{-3}
$wR(F^2)$ = 0.087	$\Delta\rho_{min}$ = −0.268 e Å^{-3}

$S = 1.106$
4705 reflections
683 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.0217P)^2 + 5.02P]$
where $P = [\max(F_o^2,0) + 2F_c^2]/3$
Extinction correction: *SHELXL93* (Sheldrick, 1993)
Extinction coefficient: 0.00011 (6)
Atomic scattering factors from *SHELXL93*

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

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

	x	y	z	U_{eq}
S(4A)	1.0064 (4)	0.7870 (1)	0.6012 (1)	0.055 (1)
S(6A)	0.8500 (4)	0.7992 (1)	0.7669 (1)	0.052 (1)
N(7A)	0.8891 (9)	0.6827 (3)	0.7294 (2)	0.040 (2)
O(1′A)	0.8670 (7)	0.4856 (2)	0.6117 (2)	0.040 (1)
O(23A)	1.0668 (8)	0.3974 (3)	0.6532 (2)	0.048 (2)
C(3AA)	0.9717 (11)	0.6789 (4)	0.6517 (2)	0.035 (2)
N(5A)	0.9229 (9)	0.7798 (3)	0.6858 (2)	0.041 (2)
C(4A)	0.9612 (11)	0.7474 (3)	0.6499 (3)	0.035 (2)
O(5′A)	0.5102 (9)	0.4309 (3)	0.6860 (2)	0.057 (2)
N(1A)	0.9453 (9)	0.5853 (3)	0.6904 (2)	0.037 (2)
C(3′A)	0.9069 (11)	0.4223 (4)	0.6741 (3)	0.041 (2)
C(4′A)	0.7716 (10)	0.4429 (3)	0.6416 (2)	0.038 (2)
C(7AA)	0.9308 (11)	0.6495 (4)	0.6919 (3)	0.036 (2)
C(5′A)	0.6172 (11)	0.4774 (4)	0.6630 (3)	0.040 (2)
C(S6A)	0.8059 (16)	0.7457 (4)	0.8116 (3)	0.063 (3)
C(2′A)	1.0631 (11)	0.4624 (4)	0.6696 (3)	0.039 (2)
O(6′A)	0.4169 (8)	0.4720 (3)	0.6011 (2)	0.056 (2)
N(2A)	1.0001 (9)	0.5746 (3)	0.6484 (2)	0.037 (2)
C(1′A)	1.0240 (11)	0.5088 (3)	0.6319 (3)	0.037 (2)
C(3A)	1.0160 (11)	0.6283 (3)	0.6241 (2)	0.039 (2)
C(6A)	0.8893 (12)	0.7461 (4)	0.7229 (3)	0.040 (2)
C(6′A)	0.5056 (13)	0.5144 (4)	0.6305 (3)	0.048 (2)
C(S4A)	0.9881 (9)	0.8695 (4)	0.6181 (4)	0.072 (3)
S(6B)	0.8346 (4)	0.7965 (1)	1.1033 (1)	0.057 (1)
S(4B)	0.8822 (4)	0.7812 (1)	0.9336 (1)	0.058 (1)
N(7B)	0.8611 (9)	0.6803 (3)	1.0662 (2)	0.042 (2)
C(3AB)	0.8932 (11)	0.6748 (3)	0.9859 (2)	0.035 (2)
C(3B)	0.9212 (11)	0.6236 (4)	0.9577 (3)	0.041 (2)
C(S6B)	0.8067 (18)	0.7423 (4)	1.1486 (2)	0.072 (4)
C(4′B)	0.6757 (11)	0.4438 (3)	0.9746 (2)	0.040 (2)
N(2B)	0.9208 (8)	0.5707 (3)	0.9822 (2)	0.035 (2)
N(5B)	0.8631 (9)	0.7764 (3)	1.0200 (2)	0.040 (2)
N(1B)	0.8967 (8)	0.5819 (3)	1.0262 (2)	0.035 (2)
O(1′B)	0.7740 (7)	0.4847 (2)	0.9454 (2)	0.037 (1)
C(4B)	0.8818 (11)	0.7430 (4)	0.9842 (3)	0.039 (2)
O(23B)	0.9616 (7)	0.3920 (2)	0.9856 (2)	0.051 (2)
O(6′B)	0.3217 (8)	0.4742 (3)	0.9351 (2)	0.056 (2)
C(6′B)	0.4105 (12)	0.5169 (4)	0.9636 (3)	0.053 (3)
C(3′B)	0.8080 (11)	0.4196 (3)	1.0076 (2)	0.042 (2)
C(2′B)	0.9685 (11)	0.4576 (3)	1.0014 (3)	0.042 (2)
C(1′B)	0.9350 (11)	0.5047 (4)	0.9648 (3)	0.038 (2)
C(7AB)	0.8811 (11)	0.6469 (3)	1.0281 (2)	0.034 (2)
C(6B)	0.8562 (12)	0.7433 (4)	1.0591 (3)	0.042 (2)
C(5′B)	0.5220 (11)	0.4800 (4)	0.9965 (3)	0.047 (2)
O(5′B)	0.4165 (9)	0.4348 (3)	1.0201 (2)	0.063 (2)
C(S4B)	0.8738 (18)	0.8645 (4)	0.9487 (3)	0.068 (3)
S(4C)	0.6048 (4)	0.2224 (1)	0.7695 (1)	0.053 (1)
S(6C)	0.5082 (4)	0.2086 (1)	0.9376 (1)	0.069 (1)
O(1′C)	0.6463 (7)	0.5206 (2)	0.7773 (2)	0.038 (1)
N(5C)	0.5486 (9)	0.2279 (3)	0.8554 (2)	0.045 (2)
C(6C)	0.5188 (13)	0.2620 (4)	0.8930 (3)	0.043 (2)
C(7AC)	0.5155 (11)	0.3576 (3)	0.8605 (2)	0.033 (2)
C(4C)	0.5620 (11)	0.2610 (4)	0.8189 (3)	0.038 (2)
N(2C)	0.5058 (9)	0.4329 (3)	0.8139 (2)	0.035 (2)
C(4′C)	0.7402 (10)	0.5629 (3)	0.8068 (3)	0.038 (2)
N(1C)	0.4934 (9)	0.4221 (3)	0.8581 (2)	0.037 (2)
N(7C)	0.5052 (10)	0.3241 (3)	0.8991 (2)	0.044 (2)
C(3C)	0.5325 (11)	0.3796 (3)	0.7901 (2)	0.040 (2)
C(5′C)	0.8899 (11)	0.5274 (4)	0.8307 (3)	0.042 (2)
O(5′C)	0.9901 (10)	0.5731 (4)	0.8549 (2)	0.065 (2)
O(23C)	0.4459 (8)	0.6108 (2)	0.8167 (2)	0.048 (2)
O(6′C)	1.0983 (8)	0.5347 (3)	0.7708 (2)	0.056 (2)
C(3′C)	0.6026 (11)	0.5869 (4)	0.8385 (3)	0.042 (2)
C(S4C)	0.5998 (14)	0.1393 (4)	0.7860 (3)	0.052 (3)
C(3AC)	0.5408 (11)	0.3298 (3)	0.8195 (2)	0.032 (2)
C(1′C)	0.4865 (12)	0.4991 (4)	0.7961 (3)	0.039 (2)
C(6′C)	1.0055 (13)	0.4913 (4)	0.7982 (3)	0.049 (2)
C(2′C)	0.4444 (11)	0.5467 (4)	0.8322 (3)	0.044 (2)
C(S6C)	0.459 (2)	0.2629 (5)	0.9815 (3)	0.102 (5)

Table 2. *Selected torsion angles (°)*

	Molecule A	Molecule B	Molecule C
O(5′)—C(5′)—C(4′)—O(1′)	170.2 (6)	172.2 (6)	173.0 (6)
O(5′)—C(5′)—C(4′)—C(3′)	−73.1 (8)	−69.6 (9)	−69.9 (8)
O(6′)—C(6′)—C(5′)—C(4′)	66.6 (10)	66.0 (10)	66.6 (10)
O(6′)—C(6′)—C(5′)—O(5′)	−55.5 (10)	−55.7 (10)	−54.2 (10)

The title structure was solved by direct methods and refined anisotropically on non-H atoms using full-matrix least-squares methods. All H atoms were placed geometrically in idealized positions and allowed to ride on their parent atoms for the final cycles of refinement. 13 reflections [most disagreeable; $\Delta(F^2)/\sigma > 6.0$] were suppressed during the last cycles of refinement. All calculations were performed on a PC/AT 486 DX Computer.

Data collection: Nicolet program package. Cell refinement: Nicolet program package. Data reduction: Nicolet program package. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *NRCVAX* (Gabe, Le Page, Charland, Lee & White, 1989). Software used to prepare material for publication: *SHELXL93* and *NRCVAX*.

GB and TC thank CSIR (India) for financial support. Thanks are due to Professor A. Chakravorty, IACS (Calcutta), for the X-ray diffractometer facility.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and torsion angles have been deposited with the IUCr (Reference: DE1032). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1996). C**52**, 2566–2568

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

BORIS KAMENAR,[a] NADA KOŠUTIĆ HULITA,[a] IVAN VICKOVIĆ,[a] GABRIJELA KOBREHEL[b] AND GORJANA LAZAREVSKI[b]

[a]*Laboratory of General and Inorganic Chemistry, Faculty of Science, University of Zagreb, Ul. kralja Zvonimira 8, 10000 Zagreb, Croatia, and* [b]*PLIVA, Research Institute, Prilaz Baruna Filipovića 25, 10000 Zagreb, Croatia. E-mail: boris.kamenar@public.srce.hr*

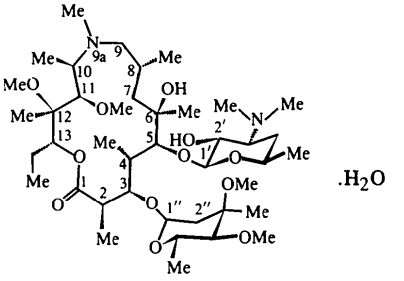
(*Received 6 February 1996; accepted 26 April 1996*)

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.