Carbohydrate Research, 252 (1994) 97–105
Elsevier Science B.V., Amsterdam

Synthesis, crystal structure, and conformation of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*manno*-heptofuranoside

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(Received November 13th, 1992; accepted June 22nd, 1993)

ABSTRACT

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*manno*-heptofuranoside (**9**) has been synthesised from the acetyliron complex **2** by a sequence of reactions involving deprotonation of **2**, its reaction with aldehyde **5**, decomplexation, isolation of **7**, and reduction to **9**. Compound **9** crystallises in the orthorhombic system, space group $P2_12_12_1$, with cell dimensions: $a = 6.097(1)$, $b = 7.942(1)$, $c = 26.862(3)$ Å. The intensity data were collected with a Syntex $P2_1$ diffractometer. The structure was solved by direct methods and refined by the full-matrix, least-squares procedure, resulting in $R = 0.049$. The furanoside and 2,3-*O*-isopropylidene rings are characterised by envelope conformations ^5E and E_3, respectively. Relatively strong intermolecular hydrogen bonds were observed in the crystal structure.

INTRODUCTION

6-Deoxy-D-*manno*-heptopyranose (**1**) is a component of the lipopolysaccharide (LPS) isolated from *Yersinia* (*Pasteurella*) *pseudotuberculosis* type IIA[1a]. Recently, **1** was found also in the LPS of *Pseudomonas pseudomallei*[1b]. A synthesis of **1** was performed by Boren et al.[2], starting from D-mannose; the key step (chain elongation by Wittig reaction) of this multi-stage synthesis was low-yelding.

We are interested in the application of the acetyliron complex $[(\eta^5\text{-}C_5H_5)\text{-}Fe(CO)(PPh_3)(COCH_3)]$[3,4] (**2**) in sugar synthesis[5]. Reaction of **2** with aldehydes leads to stereoisomeric aldols **3**. Decomplexation and reduction affords the CH_2CH_2OH-elongated structure **4**.

Thus, for the synthesis of **1**, a pentose derivative, methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside (**5**), was used. Condensation of the anion generated from **2** with **5** yielded a mixture of diastereoisomeric complexes **6** which was decomplexed with *N*-bromosuccinimide (NBS) in methanol to yield the

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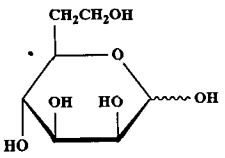

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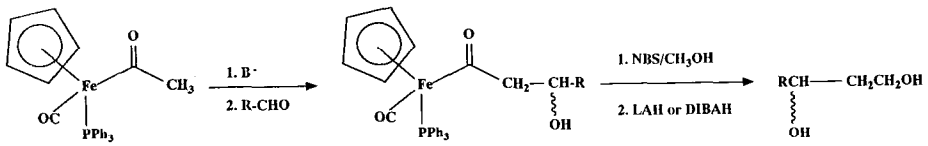

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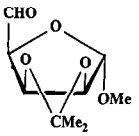
stereoisomeric methyl 6-deoxyhepturonates (**7** and **8**). The mixture was readily separated by chromatography to yield the pure D-*manno* (**7**, 50%) and L-*gulo* (**8**, 25%) stereoisomers. Reductions of **7** with diisobutylaluminium hydride (DIBAH) gave crystalline methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*manno*-heptofuranoside (**9**). The configuration of **7** was determined by conversion into peracetylated **1**[6], and of **7**–**9** by the CD method[7]. X-ray structural determination of **7** served as an additional proof of configuration. We were also interested in the solid-state conformational features of the heptofuranoside system.

EXPERIMENTAL

General methods.—All manipulations on organometallic complexes were performed under Ar. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ under a stream of Ar prior to use. Other solvents were purified and dried according to literature methods. Butyllithium was used as a 1.6 M solution in hexane and DIBAH as a 1.2 M solution in toluene. Optical rotations were measured with a Jasco DIP 360 automatic polarimeter. TLC was performed on Silica Gel HF-254 and column chromatography on Silica Gel 230–400 mesh (Merck). ^1H NMR spectra were recorded with Bruker AM-500 (500 MHz) and Varian AC-200 (200 MHz) spectrometers with Me_4Si as internal standard. High resolution mass spectra (HRMS) were measured with an AMD-604 mass spectrometer.

Methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside was obtained from D-mannose[8]. The acetyliron complex **2** was prepared according to the literature method[9].

*Methyl 2,3-*O*-isopropylidene-α-D-*lyxo*-pentodialdo-1,4-furanoside* (**5**).—To a suspension of silica gel (230–400 mesh, 50 g) in CH_2Cl_2 (400 mL) was added $NaIO_4$ (6.95 g, 32.5 mmol) in water (50 mL), and the mixture was stirred for 10 min. Then, methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (5.86 g, 25.0 mmol) in CH_2Cl_2 (50 mL) was added and the mixture was stirred at room temperature. After 30 min,



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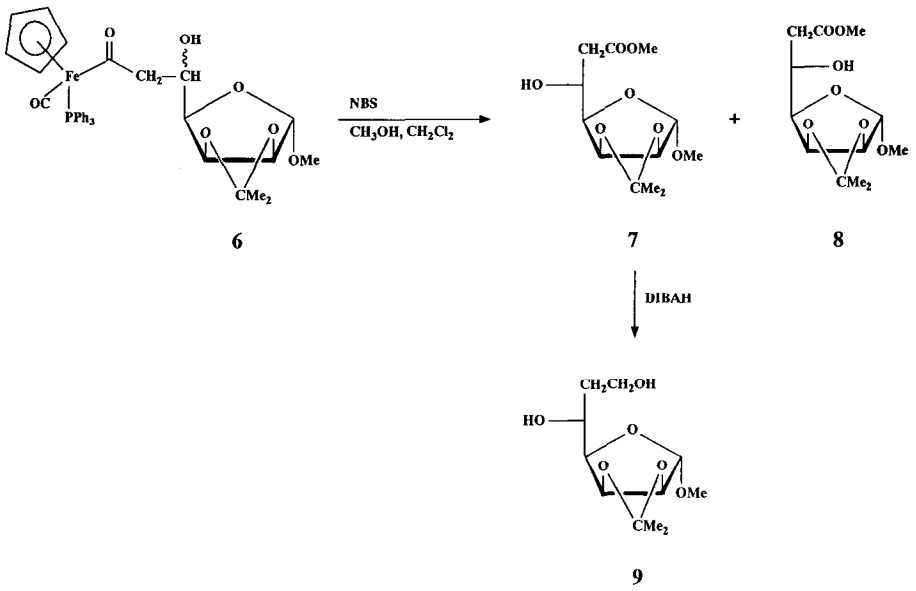

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the suspension was filtered through a Celite pad, the silica gel was washed three times with CH_2Cl_2 (100 mL each), and the combined filtrates were concentrated to dryness. Column chromatography (1:1 hexane–EtOAc) of the residue gave **5** (4.80 g, 95%).

[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH(OH)C_8H_{13}O_4$] (**6**).—A solution of the acetyliron complex **2** (6.81 g, 15.0 mmol) in THF (50 mL) was cooled to −78°C and butyllithium (11.2 mL, 18.0 mmol) was added. After 15 min, a solution of **5** (3.64 g, 18.0 mmol) in THF (10 mL) was added and the mixture was stirred at −78°C for 45 min. Methanol (15 mL) was added to the mixture which was then allowed to attain room temperature. The solution was filtered through silica gel and concentrated to dryness. The mixture (8.6 g) of starting complex and diastereomeric products (**6**) was used for the next step without further purification. An analytical sample of the mixture was separated by preparative HPLC (8:3 hexane–EtOAc) to give starting complex **2** (40.0 mg, 40%) and **6** (86.6 mg, 60%); **6**: MS (LSIMS, NBA): *m/z* 679 ($M + Na^+$), 657 ($M + H^+$), 600 ($M^+ - 2CO$). HRMS: Calcd for $C_{35}H_{38}O_7FeP$: *m/z* 657.17045. Found: *m/z* 657.17046.

*Methyl (methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*manno*-heptofuranosid)uronate* (**7**) *and methyl (methyl 6-deoxy-2,3-*O*-isopropylidene-β-L-*gulo*-heptofuranosid)-*

uronate (**8**).—A solution of the crude product **6** (8.6 g) in CH_2Cl_2 (80 mL) and MeOH (80 mL) was cooled to −78°C and NBS (2.9 g, 16.5 mmol) in CH_2Cl_2 (80 mL) was added. The mixture was stirred at this temperature for 15 min and then allowed to attain room temperature slowly. The solvents were evaporated. The residue was extracted with ether (5 × 50 mL), and the combined extracts were concentrated. Column chromatography (7:3 hexane–EtOAc) of the residue gave **7** (1.24 g, 50%) and **8** (0.62 g, 25%).

Compound **7**: syrup; $[\alpha]_D^{20}$ +64.4° (*c* 1.4, $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 4.89 (s, 1 H, H-1), 4.83 (dd, 1 H, $J_{3,2}$ 5.9, $J_{3,4}$ 3.7 Hz, H-3), 4.57 (d, 1 H, H-2), 4.37 (m, 1 H, H-5), 3.82 (dd, 1 H, $J_{4,5}$ 8.3 Hz, H-4), 3.73 (s, 3 H, $COOCH_3$), 3.30 (s, 3 H, OCH_3), 2.82 (dd, 1 H, $J_{6a,5}$ 3.2, $J_{6a,6b}$ 16.3 Hz, H-6a), 2.60 (dd, 1 H, $J_{6b,5}$ 9.0 Hz. H-6b), 1.48 and 1.33 (2 s, 6 H, CMe_2). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.50; H, 7.56.

Compound **8**: syrup; $[\alpha]_D^{20}$ +54.4° (*c* 1.3, $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 4.96 (s, 1 H, H-1), 4.74 (dd, 1 H, $J_{3,2}$ 5.9, $J_{3,4}$ 3.6 Hz, H-3), 4.58 (d, 1 H, H-2), 4.45 (m, 1 H, H-5), 3.90 (dd, 1 H, $J_{4,5}$ 5.7 Hz, H-4), 3.73 (s, 3 H, $COOCH_3$), 3.34 (s, 3 H, OCH_3), 2.71 (dd, 1 H, $J_{6a,5}$ 4.5, $J_{6a,6b}$ 15.8 Hz, H-6a), 2.66 (dd, 1 H, $J_{6b,5}$ 8.1 Hz, H-6b), 1.47 and 1.30 (2 s, 6 H, CMe_2). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.30; H, 7.48.

Methyl 6-deoxy-2,3-O-isopropylidene-α-D-manno-heptofuranoside (**9**). — To a solution of **7** (510 mg, 1.84 mmol) in CH_2Cl_2 (10 mL) was added DIBAH (10 mL, 12.0 mmol) at 0°C, and the mixture was stirred for 1.5 h. Then MeOH (10 mL) and water (1 mL) were slowly added, and stirring was continued for 1 h. To the mixture was added silica gel (5 g) and the solvents were evaporated. Column chromatography (2:1 hexane–acetone) of the residue gave **9** (295 mg, 67%). Crystals of suitable quality for an X-ray analysis were obtained from a $CHCl_3$ solution.

Compound **9**: mp 94–95°C; $[\alpha]_D^{20}$ +58.8° (*c* 1.1, $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 4.92 (s, 1 H, H-1), 4.85 (dd, 1 H, $J_{3,2}$ 5.9, $J_{3,4}$ 3.8 Hz, H-3). 4.58 (d, 1 H, H-2), 4.15 (m, 1 H, H-5), 3.91 (m, 2 H, H-7a,7b), 3.83 (dd, 1 H, $J_{4,5}$ 7.8 Hz, H-4), 3.32 (s, 3 H, OCH_3), 1.97 and 1.87 (2 m, 2 H, H-6a,6b), 1.49 and 1.33 (2 s, 6 H, CMe_2). HRMS: Calcd for $C_{10}H_{17}O_6$ ($M^+ - CH_3$): *m/z* 233.10251. Found: *m/z* 233.10240.

X-ray structural investigations.—A colourless crystal of **9** (0.25 × 0.30 × 0.50 mm) was obtained as above. The reflection intensities were collected on a Syntex $P2_1$ diffractometer, using graphite-monochromated Mo$K\alpha$ radiation (0.71069 Å). The cell constants were obtained from a least-squares refinement on the setting angles of 25 reflections. The data were collected with the $\theta/2\theta$ scan technique up to $2\theta_{max} = 52°$.

Crystal data: $C_{11}H_{20}O_6$, $M_r = 248.27$; orthorhombic, space group $P2_12_12_1$; $a = 6.097(1)$, $b = 7.942(1)$, $c = 26.862(3)$ Å; $V = 1300.7(3)$ Å^3, $Z = 4$, $F(000) = 536$, $D_x = 1.27$ g cm^{-3}, $\mu(MoK_\alpha) = 0.96$ cm^{-1}.

A total of 1527 reflections were collected, of which 1345 were unique; 1228 reflections were found to be $I > 2\sigma_I$. Lorentz and polarisation corrections were

TABLE I

Atomic fractional co-ordinates ($\times 10^4$) [a] and equivalent, isotropic temperature factors (Å^2) for **9**

Atom	x/a	y/b	z/c	B_{eq} [b]
O-1	1131(4)	791(3)	9598(1)	4.20(7)
O-2	3162(4)	−3338(2)	9413(1)	4.28(7)
O-3	3713(4)	−3020(2)	8589(1)	3.57(6)
O-5	−73(3)	−844(2)	8930(1)	3.34(6)
O-6	2664(3)	−642(2)	7722(1)	3.43(7)
O-7	−3236(3)	−2180(2)	7497(1)	4.17(7)
C-1	888(5)	−860(4)	9404(1)	3.49(9)
C-2	3173(6)	−1549(4)	9332(1)	3.66(10)
C-3	3651(5)	−1331(3)	8777(1)	3.12(9)
C-4	1630(5)	−419(3)	8579(1)	2.87(9)
C-5	887(4)	−887(3)	8061(1)	2.61(9)
C-6	−1141(5)	57(3)	7893(1)	3.04(9)
C-7	−2175(5)	−604(4)	7424(1)	3.47(9)
C-8	−934(7)	1582(5)	9659(1)	5.98(13)
C-9	4200(5)	−4106(4)	8997(1)	3.50(9)
C-10	3130(6)	−5778(4)	8902(1)	4.82(11)
C-11	6635(6)	−4239(5)	9075(1)	5.78(12)

[a] In this and subsequent Tables, the values in parentheses are estimated standard deviations. [b] Calculated from anisotropic thermal parameters as $B_{eq} = 8\pi^2 \cdot D_u^{1/3}$ where D_u is the determinant of the U_{ij} matrix.

applied to the data. No absorption correction was applied at the measurement stage. The phase problem was solved by direct methods using the SHELXS-86 program[10]. A total of 16 atoms were found in an E-map. Initially, the positional parameters and individual isotropic temperature factors of all nonhydrogen atoms were refined to $R = 0.115$.

The positions of the hydrogen atoms bonded to carbon atoms were generated from assumed geometries, and those of the hydroxyl hydrogen atoms were found from a difference Fourier map and added with isotropic temperature factors to the set of atomic parameters. The refinement of atomic positional and thermal anisotropic parameters (isotropic for H) was performed by the least-squares, full-matrix procedure using program SHELX-76[11]. The final R was 0.049, $R_w = 0.034$, $w = 1.1/(\sigma_F^2)$. The highest peak in the final difference map was 0.19 e/Å^3.

The refined positional parameters * for the non-H atoms of **9**, together with their B_{eq} values, are given in Table I.

RESULTS AND DISCUSSION

The bonding interatomic distances, and valence angles for **9** are given in Table II. Fig. 1 presents a stereoview of **9**.

* Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

TABLE II

Bond distances (Å) and bond angles (°) for **9**

C-1–O-1	1.419(4)	C-7–O-7	1.423(4)
C-8–O-1	1.417(5)	C-2–C-1	1.509(5)
C-2–O-2	1.437(4)	C-3–C-2	1.529(4)
C-9–O-2	1.422(4)	C-4–C-3	1.525(4)
C-3–O-3	1.434(3)	C-5–C-4	1.510(4)
C-9–O-3	1.426(4)	C-6–C-5	1.515(4)
C-1–O-5	1.402(4)	C-7–C-6	1.503(4)
C-4–O-5	1.443(4)	C-10–C-9	1.501(5)
C-5–O-6	1.429(3)	C-11–C-9	1.503(5)
O-1–C-1–O-5	111.7(2)	O-5–C-1–C-2	105.8(2)
O-1–C-1–C-2	106.6(3)	C-1–O-5–C-4	107.2(2)
C-1–O-1–C-8	111.1(3)	O-5–C-4–C-3	104.0(2)
O-2–C-2–C-1	109.6(3)	O-5–C-4–C-5	109.2(2)
O-2–C-2–C-3	105.1(2)	O-6–C-5–C-4	109.0(2)
C-2–O-2–C-9	107.6(2)	O-6–C-5–C-6	111.2(2)
O-2–C-9–O-3	104.6(2)	O-7–C-7–C-6	112.5(2)
O-2–C-9–C-10	108.6(2)	C-1–C-2–C-3	105.1(2)
O-2–C-9–C-11	111.1(2)	C-2–C-3–C-4	103.9(2)
O-3–C-3–C-2	104.0(2)	C-3–C-4–C-5	116.5(2)
O-3–C-3–C-4	110.0(2)	C-4–C-5–C-6	113.4(2)
C-3–O-3–C-9	107.5(2)	C-5–C-6–C-7	114.8(2)
O-3–C-9–C-10	108.3(2)	C-10–C-9–C-11	113.0(3)
O-3–C-9–C-11	110.8(2)		

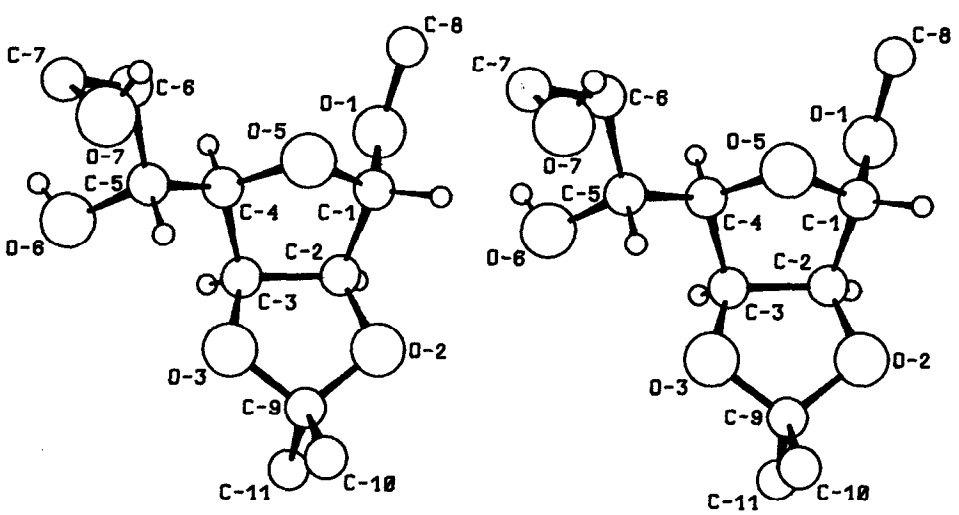

Fig. 1. A stereo-view of the arbitrarily oriented molecule of **9** with the crystallographic labeling of atoms. For clarity reasons, the only hydrogen atoms shown are those at asymmetry centers and of hydroxyl groups.

TABLE III

A comparison of selected torsion angles (°) from the X-ray structure and obtained by molecular mechanics calculations

	X-ray	MMX [a]
C-1–C-2–C-3–C-4	3.5(3)	3.8
C-2–C-3–C-4–O-5	−24.2(3)	−25.5
C-3–C-4–O-5–C-1	38.0(2)	39.3
C-4–O-5–C-1–C-2	−36.0(3)	−36.6
O-5–C-1–C-2–C-3	19.1(3)	19.0
O-5–C-1–O-1–C-8	62.3(3)	71.1
C-2–C-1–O-1–C-8	177.4(2)	−172.4
C-2–O-2–C-9–O-3	−31.1(3)	−35.3
O-2–C-9–O-3–C-3	33.9(3)	37.3
C-9–O-3–C-3–C-2	−23.1(3)	−24.0
O-3–C-3–C-2–O-2	3.9(3)	2.8
C-3–C-2–O-2–C-9	16.6(3)	19.4
C-4–C-5–C-6–C-7	−168.9(2)	172.5
O-6–C-5–C-4–C-3	−56.1(3)	−58.0
C-7–C-6–C-5–O-6	67.8(3)	52.5
C-6–C-5–C-4–C-3	179.4(2)	−179.4
O-7–C-7–C-6–C-5	71.5(3)	52.4

[a] MMXE = 24.6 kcal.

The presence of the 2,3-*O*-isopropylidene grouping and the α-glycosidic methyl group imposes some conformational rigidity on **9**. The torsion angles O-4–C-1–O-1–CH_3 and C-2–C-1–O-1–CH_3 are 62.3 and 177.4°, respectively, corresponding rather favorably to the glycosidic system exhibiting the anomeric effect.

The furanoside and 2,3-*O*-isopropylidene rings are in envelope forms, ^5E and E_3, respectively. In the furanose ring, atoms C-1–C-2–C-3–C-4 and, in the 1,3-dioxolane ring, atoms O-2–C-2–C-3–O-3 lie in single planes. This shape resembles strongly the X-ray structure determined for methyl 6,6,7,7-tetradehydro-6,7-dideoxy-2,3-*O*-isopropylidene-β-D-*allo*-heptofuranoside[12]. The side chain C-5–C-6–C-7 is in an extended zigzag conformation. The torsion angle C-4 · · · C-7 corresponds to ca. 170° (Table III).

In Table III, a comparison of selected torsion angles from the X-ray structure and those obtained by molecular mechanics calculations[13] is presented. The calculated structure fits rather well to the experimentally determined shape.

TABLE IV

Intermolecular hydrogen bonds

H-bond D–H · · · A	D · · · A (Å)	D–H (Å)	H · · · A (Å)	D–H · · · A (°)	Acceptor symmetry
O-7–H-7O · · · O-6	2.847(4)	0.81(3)	2.10(3)	153(2)	$-1+x, y, z$
O-6–H-6O · · · O-7	2.833(4)	0.82(3)	2.04(3)	165(2)	$-x, 1/2+y, 3/2-z$

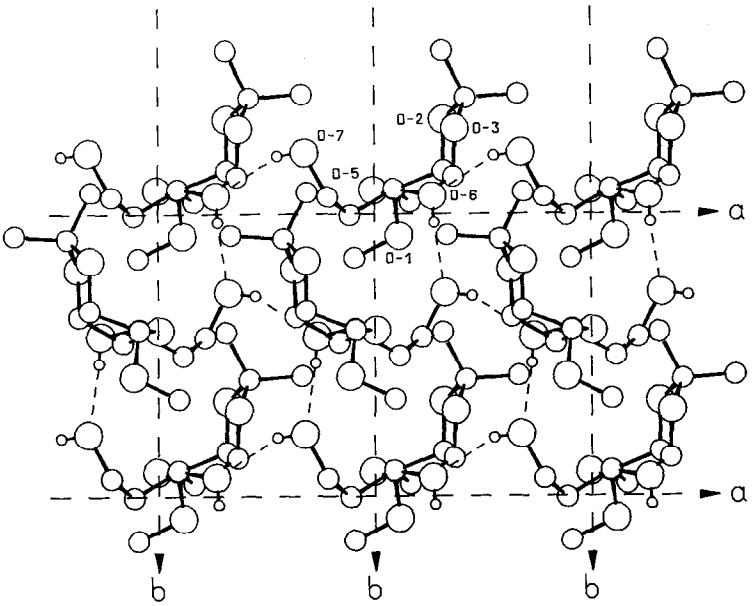

Fig. 2. A parallel projection of hydrogen-bonded molecules onto the *ab* plane of the crystal. Hydrogen bonds are represented by short-dashed lines. Long-dashed axes of the crystal show the outline of the cell units. The oxygen atoms of the original molecule are labeled.

Compound **9** forms two kinds of intermolecular hydrogen bonds (Table IV) involving both hydroxyl groups occurring in the side chain of the molecule. Considering the O-H $\cdots$ acceptor distances, the bonds are relatively strong in nature. They form a system of planes, all found to be parallel to the *ab* plane of the crystal (Fig. 2). Probably, the existence of these hydrogen bonds in the crystal lattice is responsible for some discrepancies, involving torsion angles in the side chain, between the MM and X-ray model (Table III).

The X-ray structural determination of **9** definitely confirms its *manno* configuration.

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