Carbohydrate Research, 200 (1990) 1–7
Elsevier Science Publishers B.V., Amsterdam Printed in The Netherlands

X-Ray and conformational investigation of 6-deoxy-7-*C*-(2-furyl)-1,2:3,4-di-*O*-isopropylidene-L-*glycero-a*-D-*galacto*-heptopyranose

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(Received March 21st, 1989; accepted for publication, June 14th, 1989)

ABSTRACT

The crystals of the title compound are orthorhombic, space group $P2_12_12_1$ (Z = 4) with cell dimensions a = 9.791(1), b = 10.235(1), c = 17.703(2) Å. The pyranoid ring has a hybrid twist + screw ($^0T_2 + {}^0S_5$) conformation, and the configuration at C-7 is (*R*).

INTRODUCTION

X-Ray structural determinations of compounds containing the 1,2:3,4-di-*O*-isopropylidene-*a*-D-galactopyranose system[1-6] have revealed variations in the conformation of the dioxolane rings and, to a lesser extent, of the tetrahydropyran ring, although in solution these compounds seem to adopt almost the same conformation[7]. We now report on the structure of 6-deoxy-7-*C*-(2-furyl)-1,2:3,4-di-*O*-isopropylidene-*glycero-a*-D-*galacto*-heptopyranose (**5**), an intermediate in the synthesis of tunicamine[8], for which knowledge of the configuration at C-7 is essential.

EXPERIMENTAL

General methods. — T.l.c. was performed on Silica Gel G (Merck) and column chromatography on silica gel (40–63 μm, Merck). ^{1}H-N.m.r. spectra were recorded with a Bruker AM-500 (500 MHz) spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter.

*6-Deoxy-7-C-(2-furyl)-1,2:3,4-di-O-isopropylidene-a-*D-galacto-*hept-7-ulopyranose* (**4**). — To a solution of lithium di-isopropylamide (3.2 g, 30 mmol) in oxolane (100 mL) at −78° was added diethyl (2-furyl)methoxymethylphosphonate (7.44 g, 30 mmol), and the mixture was stirred for 1 h. A solution of **1** (6.94 g, 27 mmol) in oxolane (50 mL) was added, the mixture was stirred at −78° for an additional 30 min, then allowed to attain room temperature, and ether (200 mL) followed by saturated aqueous ammonium chloride (200 mL) were added. The mixture was shaken, and the organic layer was dried ($MgSO_4$) and concentrated to dryness, to yield crude enol ether **3** (6.45 g)

0008-6215/90/$03.50

[^{1}H-n.m.r.: *inter alia*, δ 3.7 (s, 3 H, OMe)], which was hydrolysed (2 h, reflux) in 5:1 oxolane–water (120 mL) containing pyridinium toluene-*p*-sulfonate (0.5 g). The hydrolysate was cooled, water (50 mL) was added, the solution was extracted with ether (~ 200 mL), and the extract was dried and concentrated. Column chromatography (hexane–ether, 4:1) of the residue gave **4** (5.46 g, 60%), isolated as a colourless oil, $[\alpha]_D^{20}$ $-51°$ (*c* 0.6, chloroform); ν_{max} 1690 cm^{-1}. ^{1}H-N.m.r. data: δ 7.76 (d, 1 H, $J_{4,5}$ 1.8 Hz, furan H-5), 7.25 (d, 1 H, $J_{3,4}$ 3.5 Hz, furan H-3), 6.58 (q, 1 H, furan H-4), 5.50 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.60 (q, 1 H, $J_{3,4}$ 7.9 Hz, H-3), 4.30 (q, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.15 (q, 1 H, $J_{4,5}$ 1.9 Hz, H-4), 4.10 (m, 1 H, H-5), 3.30 (q, 1 H, $J_{6,6'}$ 16.5, $J_{6,5}$ 6.5 Hz, H-6), 3.10 (q, 1 H, $J_{6',5}$ 6.5 Hz, H-6'), 1.65, 1.50, 1.30 (3 s, 12 H, 2 CMe$_2$).

Anal. Calc. for $C_{17}H_{22}O_7 \cdot H_2O$: C, 57.3; H, 6.8. Found: C, 57.0; H, 6.6.

*6-Deoxy-7-C-(2-furyl)-1,2:3,4-di-O-isopropylidene-*L- (**5**) *and* -D-glycero-*α*-D-galacto-*heptopyranose* (**6**). — To a solution of **4** (4.75 g, 14 mmol) in oxolane (100 mL) at $-78°$ was added L-Selectride (M solution in oxolane, 19 mmol), and the mixture was stirred at $-78°$ until **4** had disappeared (t.l.c.; hexane–ether, 4:1). The mixture was then poured into saturated aqueous sodium potassium tartrate (200 mL) and extracted with ether, and the extract was dried and concentrated. Column chromatography (hexane–ether, 9:1) of the residue gave, first, **5** (2.89 g, 60.7%), m.p. 146–148° (from hexane–ether), $[\alpha]_D^{20}$ $-51°$ (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 7.35 (q, 1 H, $J_{4,5}$ 1.8 Hz, furan H-5), 6.31 (q, 1 H, $J_{3,4}$ 3.2 Hz, furan H-4), 6.28 (q, 1 H, $J_{3,5}$ 0.9 Hz, furan H-3), 5.54 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 4.99 (m, 1 H, H-7), 4.61 (q, 1 H, $J_{3,4}$ 7.9 Hz, H-3), 4.31 (q, 1 H, $J_{2,3}$ 2.4 Hz, H-2), 4.14 (q, 1 H, $J_{4,5}$ 1.8 Hz, H-4), 4.11 (dq, 1 H, $J_{5,6}$ 10.5, $J_{5,6'}$ 2.7 Hz, H-5), 2.22 (dq, 1 H, $J_{6,6'}$ 14.5, $J_{6,7}$ 3.2 Hz, H-6), 2.02 (dq, 1 H, $J_{7,6'}$ 9.2 Hz, H-6'), 1.48, 1.46, 1.35, 1.31 (4 s, 12 H, 2 CMe$_2$).

Anal. Calc. for $C_{17}H_{24}O_7$: C, 60.0; H, 7.1. Found: C, 59.7; H, 7.5.

Eluted second was **6** (1.06 g, 22.3%), m.p. 137–139°, $[\alpha]_D^{20}$ $-77°$ (*c* 0.1, chloroform). ^{1}H-N.m.r. data: δ 7.36 (q, 1 H, $J_{4,5}$ 1.8 Hz, furan H-5), 6.31 (q, 1 H, $J_{3,4}$ 3.2 Hz, furan H-4), 6.29 (q, 1 H, $J_{3,5}$ 0.9 Hz, furan H-3), 5.50 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 4.94 (m, 1 H, H-7), 4.59 (q, 1 H, $J_{3,4}$ 7.9 Hz, H-3), 4.30 (q, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.15 (q, 1 H, $J_{4,5}$ 1.8 Hz, H-4), 3.80 (dq, 1 H, $J_{5,6}$ 9.5, $J_{5,6'}$ 3.8 Hz, H-5), 2.30 (dq, 1 H, $J_{6,6'}$ 14.3, $J_{6,7}$ 8.0 Hz, H-6), 2.10 (dq, 1 H, $J_{7,6'}$ 5.6 Hz, H-6'), 1.49, 1.46, 1.34, 1.30 (4 s, 12 H, 2 CMe$_2$).

Anal. Calc. for $C_{17}H_{24}O_7 \cdot H_2O$: C, 57.0; H, 7.3. Found: C, 56.6; H, 7.5.

X-Ray diffractometry. — A colourless crystal of **5** (0.32 × 0.26 × 0.19 mm) was obtained from ether–hexane. The reflection intensities were collected on an Enraf–Nonius CAD-4 diffractometer, using graphite-monochromated Cu-K_α radiation (1.54178 Å). The cell constants were obtained from a least-squares refinement on the setting angles of 25 reflections. The data were collected with the $\omega/2\theta$ scan technique up to $2\theta_{max} = 140°$.

Crystal data: $C_{17}H_{24}O_7$, $M_r = 340.4$, $F(000) = 728$, orthorhombic, space group $P2_12_12_1$, $a = 9.791(1)$, $b = 10.235(1)$, $c = 17.703(2)$ Å, $V = 1774.0(3)$ Å^3, $Z = 4$, $D_x = 1.27$ Mg.m^{-3}, $\mu(\text{Cu-}K_\alpha) = 0.79$ mm^{-1}.

Of a total of 2024 collected reflections, 1524 were of $I > 2\sigma(I)$. Lorentz and polarisation corrections were applied to the data. No absorption correction was applied.

The phase problem was solved by direct methods using the SHELXS-86 program[9]. The positions of the hydrogen atoms were found from ΔF maps.

The refinement of atomic positional and thermal parameters, initially isotropic and then anisotropic, was performed by the least-squares, full matrix procedure, using the SHELX-76 program[10]. The final refinement step involved all of the positional and thermal parameters except the H-atomic temperature factors (set invariant as B_{eq} of the adjacent atom + 1Å^2). The final R value was 0.0413 (unit weights). The highest peak in the final difference map was 0.21 e/Å^3.

The refined positional parameters for the non-H atoms of **5**, together with their B_{eq} values, are given in Table I*.

TABLE I

Fractional co-ordinates (× 10^4)[a] and equivalent, isotropic temperature factors (Å^2) for **5**

Atom	x/a	y/b	z/c	B_{eq}[b]
C-1	8642(5)	3552(5)	−459(3)	3.4(1)
C-2	7558(5)	3256(5)	141(2)	3.2(1)
C-3	6841(5)	4452(5)	458(2)	3.2(1)
C-4	6519(5)	5512(5)	−125(3)	3.5(1)
C-5	7190(5)	5268(5)	−885(3)	3.2(1)
C-6	7275(6)	6508(5)	−1353(3)	3.7(1)
C-7	7617(6)	6262(5)	−2167(3)	3.7(1)
C-8	7241(6)	1806(5)	−829(3)	4.0(1)
C-9	7704(7)	491(6)	−528(4)	6.0(2)
C-10	6344(7)	1705(7)	−1502(3)	6.0(2)
C-11	7435(6)	6455(5)	944(3)	4.0(1)
C-12	6299(7)	6775(6)	1497(3)	5.2(1)
C-13	8727(7)	7190(6)	1105(4)	6.0(2)
C-14	7703(6)	7497(6)	−2613(2)	3.8(1)
C-15	8686(6)	8052(6)	−3029(3)	4.5(1)
C-16	8103(8)	9229(6)	−3323(3)	4.9(1)
C-17	6839(8)	9303(6)	−3063(3)	5.2(1)
O-1	8417(4)	2574(4)	−1014(2)	4.4(1)
O-2	6558(4)	2527(3)	−257(2)	3.6(1)
O-3	7752(4)	5079(3)	973(2)	3.7(1)
O-4	7030(5)	6683(3)	201(2)	4.6(1)
O-5	8564(3)	4811(3)	−773(2)	3.4(1)
O-6	6568(5)	5413(3)	−2459(2)	4.4(1)
O-7	6546(4)	8248(4)	−2618(2)	4.7(1)

[a] In this and subsequent Tables, the values in parentheses are estimated standard deviations. [b] $B_{eq} = 8\pi^2 \cdot D_u^{1/3}$, where D_u is the determinant of the U matrix in orthogonal space.

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*Fractional co-ordinates and isotropic temperature factors of the hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, and Tables of bond lengths, bond angles, and torsion angles are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/430/*Carbohydr. Res.*, 200 (1990) 1-7.

RESULTS AND DISCUSSION

The heptose derivative **5** was obtained from 1,2:3,4-di-*O*-isopropylidene-*α*-D-*galacto*-hexodialdo-1,5-pyranose[11] (**1**). Wittig reaction of **1** with the ylid prepared from diethyl (2-furyl)methoxymethylphosphonate[12] (**2**) gave the enol ether **3**, which was hydrolysed to the ketone **4**. Reduction of **4** with L-Selectride furnished 83% of a 2.7:1 mixture of **5** and **6**. The major alcohol **5** was isolated by chromatography in a form suitable for X-ray crystallographic investigation. Fig. 1 shows a stereoview of **5** with crystallographic labelling of selected atoms.

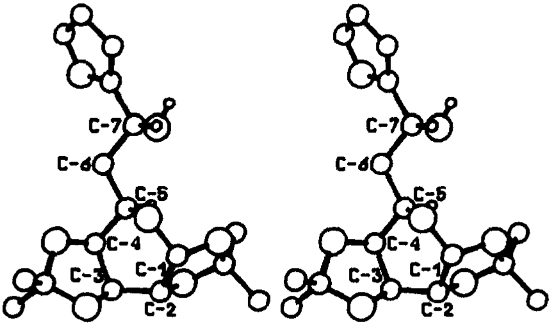
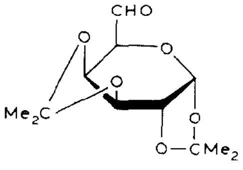


Fig. 1 A stereo-view of 5. The hydrogen atoms are omitted for clarity, except for the hydroxyl group and those attached at C-5 and C-7.



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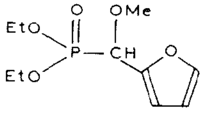

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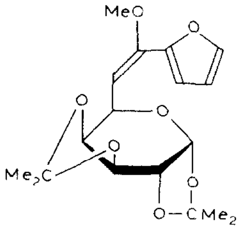

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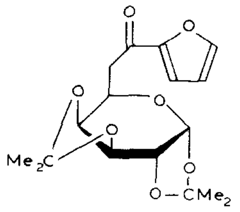

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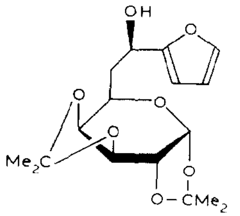

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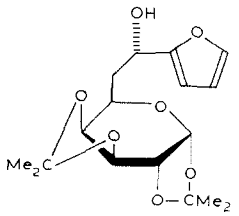
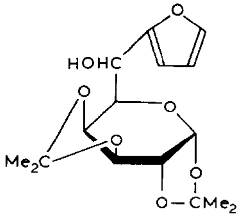


6

Contrary to earlier observations [1-6], no elongation of bonds was found for C-1/4 of the galactopyranose ring. The only peculiarities were the values of endocyclic valence angles at C-1/3, which were > 114°, indicating relatively high internal strain in the ring.



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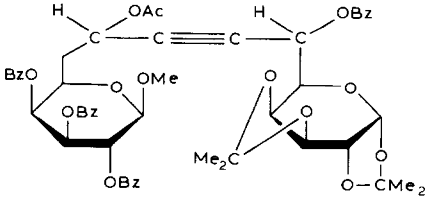

8

The absolute configuration at C-7 in **5**, based on the D-enantiomorph, was shown to be (*R*), *i.e.*, the same as at C-6.

Conformations of the pyranose rings in **5**, **7**[1], *and* **8**[2]. — The values of endocyclic torsion angles in the galactopyranose rings of **5**, **7**, and **8** (Table II) deviated much from those in a classical model of the energetically most-favoured chair form.

Previous investigations of 1,2:3,4-di-*O*-isopropylidenegalactopyranose derivatives have revealed various conformations of galactopyranose rings, including screw-twist[2], twist-boat[1], and almost "pure" twist[3].

The galactopyranose ring in **5** adopted a twist-screw conformation which differed from those already known. Comparison of the puckering parameters[13], endocyclic torsion angles, and asymmetry parameters[14] for **5** and **7** (see Table II) and an analysis of the least-squares planes occurring in these rings suggest that there may be two four-atomic least-squares planes in **5** characteristic of a twist conformation (C-1,C-2,C-4,O-5

TABLE II

Conformational parameters of galactopyranose rings for **5**, **7**, and **8**

	5	**7**	**8**
Puckering parameters[13]			
Q (Å)	0.631	0.632	0.592
Φ (°)	84.9	81.4	84.3
Θ (°)	100.3	100.9	106.4
q_2(Å)[a]	0.620	0.635	0.568
Endocyclic torsion angles (degrees)			
C-1–C-2	−16.3(4)	−17.7(8)	−8.6(5)
C-2–C-3	39.3(4)	37.3(7)	29.2(5)
C-3–C-4	−9.8(4)	−5.5(7)	−2.0(5)
C-4–C-5	−41.6(4)	−45.6(6)	−45.3(5)
C-5–O-5	68.8(4)	70.6(5)	70.6(4)
O-5–C-1	−37.8(4)	−36.1(6)	−41.4(5)
Asymmetry parameters (degrees)[14]			
ΔC_2	5.4(4)	11.2(6)	5.4(5)
Conformation	${}^{0}T_2+{}^{0}S_5$	${}^{0}T_2+B_{2,5}$	${}^{0}S_5+{}^{0}T_2$

[a] q_2 = Q·sin Θ.

and C-1,C-3,C-4,C-5), and also two that indicate a screw diplanar conformation (C-1,C-2,C-3,O-5 and C-2,C-3,C-4,C-5). Therefore, the conformation of the galactopyranose ring in **5** is defined as $^{0}T_{2} + {}^{0}S_{5}$.

For the galactopyranose ring in **7**, there are the two least-squares planes of $^{0}T_{2}$, but only one plane (C-2,C-3,C-4,C-5) that indicates a boat conformation. Thus, the conformation of the galactopyranose ring in **7** should be defined as hybrid $^{0}T_{2} + B_{2,5}$.

The galactopyranose ring in **8** has mostly the energetically unfavoured conformation $^{0}S_{5} + {}^{2}T_{0}$.

Conformations of dioxolane rings in **5**, **7**[1], *and* **8**[2]. — The results of conformational calculations for the dioxolane rings of **5**, **7** and **8** are given in Table III. The variety of conformational assignments, from envelope through the hybrid forms $T + E$ and $E + T$ to the "pure" twist form, indicate a great conformational lability of these rings.

TABLE III

Conformation of dioxolane rings in **5**, **7**, and **8**

	5		**7**		**8**	
	1,2-Ring	*3,4-Ring*	*1,2-Ring*	*3,4-Ring*	*1,2-Ring*	*3,4-Ring*
Puckering parameters[13]						
q_2(Å)	0.286	0.296	0.308	0.277	0.306	0.313
Φ (°)	262.4	12.4	257.4	22.2	237.1	30.5
Asymmetry parameters[14] (°)						
ΔC_s	5.8(4)	—	2.4(7)	8.6(6)	—	3.9(4)
ΔC_2	8.2(4)	3.3(4)	—	4.4(6)	1.7(4)	—
Conformation[a]	$^{3}E + {}^{3}T_{4}$	$^{2}T_{1}$def	^{3}E	$^{2}T_{1} + {}^{2}E$	$^{3}T_{2}$	^{2}E

[a] The indexing conforms to that for cyclopentane.

Hydrogen bonds in **5**. — An intermolecular hydrogen bond of medium strength was found in the crystal lattice of **5**. As in the 6-*C*-(2-furyl) derivative **7**, the hydrogen bond formed by the hydroxyl group involves O-3 of the dioxolane ring in the neighbouring molecule as the acceptor. The distances and the angle at H-atom are O-6–H 0.84, O-6···O-3 2.899, H···O-3 2.08 Å, and O-6–H···O-3 162°. The symmetry of the O-3 acceptor is $3/2 - x$, $1 - y$, $-1/2 + z$. The bonded molecules form infinite chains parallel to the *c*-axis of the crystal. The hydrogen bond in **5** is much weaker than in the 6-*C*-(2 furyl) derivative.

ACKNOWLEDGMENTS

These investigations were supported by Projects PR.II.10 of the Ministry of Education and CPBP 01.13 of the Polish Academy of Sciences.

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