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CRYSTALLINE FURANOSE DERIVATIVES OF 3-DEOXY-D-*arabino*-HEXOSE: CONFORMATIONAL STUDIES BY N.M.R. SPECTROSCOPY

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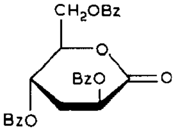
ABSTRACT

Debenzoylation of 2,4,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexono-1,5-lactone (**1**) followed by heating *in vacuo* and rebenzoylation afforded 2,5,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexono-1,4-lactone (**2**). Reduction of **2** with disiamylborane gave 2,5,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexofuranose (**3**), a convenient furanose derivative for the synthesis of glycosides. Acetylation of **3** with acetic anhydride–pyridine afforded 1-*O*-acetyl-2,5,6-tri-*O*-benzoyl-3-deoxy-α-D-*arabino*-hexofuranose (**4**). Compound **4** was converted into methyl 2,4,6-tri-*O*-benzoyl-3-deoxy-α-D-*arabino*-hexofuranoside (**5**) through the bromide obtained by treatment of **4** with bromotrimethylsilane, followed by methanol. Debenzoylation of **5** gave methyl 3-deoxy-α-D-*arabino*-hexofuranoside (**6**). All compounds mentioned were obtained crystalline. Conformational studies of **4, 5,** and **6** were made by ^{1}H-n.m.r. spectroscopy (DAERM method), and the ^{13}C-n.m.r. spectral data are correlated. The structures of compounds **2, 4** and **5** were also confirmed by mass spectrometry.



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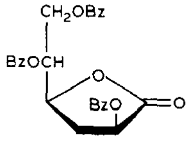

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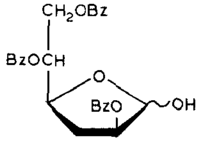

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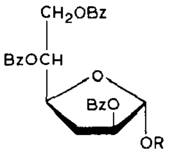
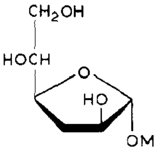


4 R = Ac
5 R = CH$_3$



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INTRODUCTION

We have used aldonolactones for synthesis of deoxy sugars *via* β-elimination reactions and stereoselective catalytic hydrogenation[1–4]. Thus, 3-deoxy-D-*arabino*-hexose was obtained in four steps from D-glucono-1,5-lactone[4] in 70% overall yield. Benzoylation of aldono-1,4-lactones caused multiple elimination[5,6] and the simple route of β-elimination–hydrogenation would not yield a derivative of 3-deoxy-D-glucono-1,4-lactone useful for the synthesis of furanoid derivatives. An indirect route from D-glucono-1,5-lactone is now described for the synthesis of methyl 3-deoxy-α-D-*arabino*-hexofuranoside (**6**). Conformational studies of the furanose derivatives by the DAERM method[7] are also reported. This method has been previously used to study the conformation of 3-deoxy-1,2;5,6-di-*O*-isopropylidene-D-hexofuranoses[8] and of derivatives of 3,6-dideoxy-α-L-*arabino*-hexofuranose[9].

RESULTS AND DISCUSSION

When 2,4,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexono-1,5-lactone (**1**) was debenzoylated with sodium methoxide and then heated *in vacuo* in a boiling water-bath, the more-stable 1,4-lactone was obtained as a syrup. The product was rebenzoylated to give crystalline 2,5,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexono-1,4-lactone (**2**), characterized by its spectroscopic data. The i.r. spectrum showed absorption at 1800 cm^{-1} characteristic of a 1,4-lactone. The ^{13}C-n.m.r. spectrum showed C-1 at 171.05 p.p.m., whereas C-1 in compound **1** resonated at 167.2 (see Table II). This is in accord with the previous observation[10] that the carbonyl carbon atom in 1,4-lactones resonates at lower field than C-1 in the corresponding 1,5-lactones. Another difference between both types of acylated aldonolactone is that C-6 in the latter resonates at lower field than C-6 in 1,4-lactones. This is not the case with free aldonolactones[11]. The C-2 signal (δ_c 68.41) of **2** was assigned by comparison with C-2 (δ_c 68.57) in the configurationally related 2,5-di-*O*-benzoyl-3,6-dideoxy-L-*arabino*-hexono-1,4-lactone, which was assigned by single-frequency decoupling[10]. The most deshielded carbon atom was assigned to C-4 (δ_c 74.46 p.p.m.). The mass spectrum showed the ion at *m/z* 205 (M − 269, 8% of the base peak), which corresponds to cleavage between C-4 and C-5, characteristic of 1,4-ring structures. The loss of benzoic acid (122 m.u.) from the molecular ion accounts for the cation at *m/z* 352, with the highest mass of the spectrum. The most abundant ions correspond to the aromatic series 105 → 77 → 51. Reduction of **2** with disiamylborane[12] gave crystalline 2,5,6-tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexofuranose (**3**) in >90% yield. Its i.r. spectrum showed disappearance of the carbonyl absorption and the anomeric hydroxyl group gave a band at 3300 cm^{-1}. In the ^{1}H-n.m.r. spectrum (Table I) the hydroxyl resonance appeared as a doublet at δ 2.98 (*J* 3 Hz), which disappeared on deuteration. The assignment was confirmed by irradiation at the anomeric-proton frequency, which made the doublet collapse to a singlet. Only one anomeric proton was evident and gave a doublet at δ 5.55

TABLE I

^{1}H-N.M.R DATA FOR COMPOUNDS **2**–**6**

Compound	*Chemical shifts in δ values*											*Coupling constants in Hz*							
	H-1	*H-2*	*H-3*	*H-3'*	*H-4*	*H-5*	*H-6*	*H-6'*	*OBz*	*CH$_3$*	$J_{2,3}$	$J_{2,3'}$	$J_{3,3'}$	$J_{3,4}$	$J_{3',4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
2		5.80m	3.06m	3.54m	4.92m	5.80m	4.88dd	4.64dd	7.50m 8.10m		[a]	[a]	13	[a]	[a]	[a]	4	6	12
3	5.56s	5.32dd	2.09m	2.74m	4.68m	5.62m	4.78dd	4.54dd	7.35m 7.90m		2	6	15	4	8	[a]	3	5	12
4	6.38s	5.42dd	2.30m	2.75m	4.68m	5.76m	4.82dd	4.54dd	7.35m 7.90m	2.10s	2	6	14	6	7	10	3	6	12
5	5.13s	5.35dd	2.19m	2.70m	4.60m	5.72m	4.85dd	4.62dd	7.42m 8.20m	3.40s	3	6	13	6	8	10	3	4	11
6	4.94s	4.28dd	1.88m	2.40m	3.72m	4.26m	3.86m	3.60m		3.34s	2	6	13	5	7	[a]	[a]	[a]	[a]

[a] Unresolved.

TABLE II

^{13}C-N M R CHEMICAL SHIFTS FOR COMPOUNDS **1–7**

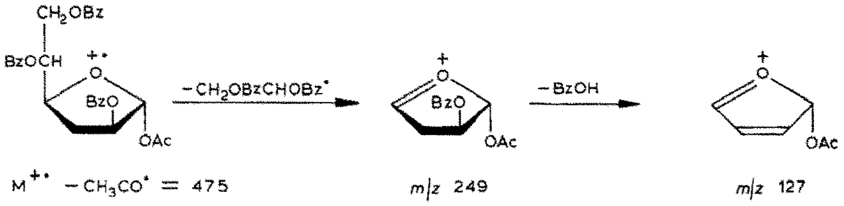
Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C=O benzoate*	*C=O acetate*	*CH$_3$*
1[a]	167.20	64 73	30.95	66.78	77 70	63.46	165.72 165.09		
2	171.05	68.41	31.28	74.46	71.79	62.31	165.83 161.21		
3	101.11	76.78	31.78	78.38	72.82	63.45	166.01 165.80 165.40		
4	99.94	77.32	32.08	78.41	72.56	63.34	165.57	169.04	21.17
5	107.20	76.42	32.24	77.70	72.85	63.63	165.47 165.68 165.99		54.78
6	109.73	75.04	33.43	79.31	73.51	63.68			55.45
7[a]	102.89	76.14	33.12	79.00	73.70	63.70			

[a] The data for compound **1** and for 3-deoxy-α-D-*arabino*-hexofuranose (**7**) are taken from ref. 4.

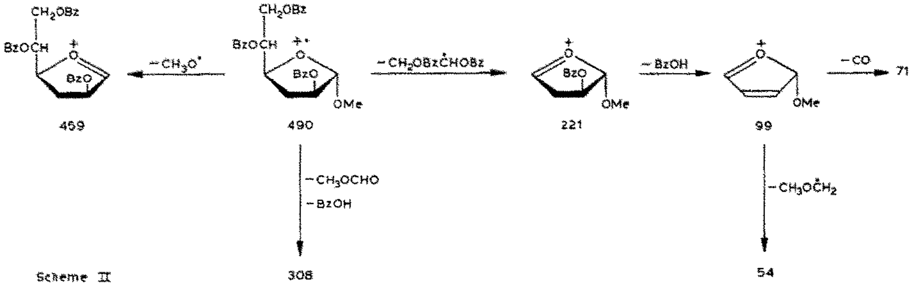
($J_{1,OH}$ 3 Hz). No coupling with H-2 could be observed, which is indicative of the α-anomeric configuration[13]. As expected the ^{13}C-n.m.r. spectrum (see Table II) shows the α-anomeric carbon resonance at lower field (δ_c 101.1) than in the corresponding pyranose derivative (δ_c 90.9). A small signal at δ_c 95.1 was assigned to the β anomer. A ratio of 8:1 for the α_F/β_F tautomers was estimated from the integrated intensities of the resonances of C-1. The C-4 atom (δ_c 78.4) was more deshielded than the other ring carbon atoms, followed[4] by C-2. Compound **3** is a convenient furanose derivative for the synthesis of disaccharides and glycosides. By acetylation with acetic anhydride–pyridine, crystalline 1-*O*-acetyl-2,5,6-tri-*O*-benzoyl-3-deoxy-α-D-*arabino*-hexofuranose (**4**) was obtained in 82% yield. The ^{1}H-n.m.r. spectrum (Table I) showed a singlet at δ 6.38, indicating no change in the anomeric configuration. The ^{13}C-n.m.r. spectrum (Table II) showed C-1 at δ_c 99.9, shifted upfield (+1.2) with respect to C-1 in compound **3** with a free 1-OH group. The other carbon signals showed only slight variation.

The furanoic structure of **4** was confirmed by mass spectroscopy as shown in Scheme I. Compound **4** was converted into the methyl glycoside through the corresponding bromide. Bromotrimethylsilane was used as the anomeric brominating agent[14]. After 2 h, the volatile excess reagent and trimethylsilyl acetate were removed and treatment with methanol afforded crystalline methyl 2,4,6-tri-*O*-benzoyl-3-deoxy-α-D-*arabino*-hexofuranoside (**5**) in 85% yield.

The ^{1}H-n.m.r. spectrum (Table I) showed only one singlet (δ 5.13) in the anomeric region, which is consistent with the α configuration. The ^{13}C-signal for C-1 appeared at δ_c 107.20. The downfield shift (6.09 p.p.m.) caused by methyl glycosidation is similar to the value encountered for other monosaccharides[15]. The other resonances were only slightly modified by glycosidation. In the mass spectrum



Scheme I



Scheme II

(Scheme II), the ion at *m/z* 221 formed by cleavage between C-4 and C-5, characteristic of furanose structures, is present with an abundance of 99% from the base peak. Further elimination of benzoic acid gave the ion at *m/z* 99 (98%). The loss of OCH_3 from the molecular ion gave the peak with the highest mass ($M - OCH_3$, 459, 6%). Debenzoylation of **5** afforded crystalline methyl 3-deoxy-α-D-*arabino*-hexofuranoside (**6**). Only the α anomer was evident from examination of the ^1H- and ^{13}C-n.m.r. spectra. The C-1 signal appeared at δ_c 109.73, which is in accord with the shift observed for other 1,2-*trans* methyl aldofuranosides[16]. Conformational studies on 3-deoxy derivatives may be made by the DAERM method[7] (dihedral angle estimation by the ratio method). Analysis of the 3-deoxy-α-D-*arabino* hexofuranoside derivatives **4**, **5**, and **6** was achieved from the ^1H-n.m.r. data (Table I) and the diehedral angles between H-2, H-3, H-3′, and H-4 were estimated by DAERM. The results are listed in Table III. Only calculations with a logical value for the Karplus constants are included. For compounds **4** and **5**, the solution *a/c*, which indicates a ${}^{O}T_1$ conformation that minimizes interaction between the benzoyl substituents is the most probable. Stevens and Fletcher[13] reported a ${}^{O}T_1$ conformation for benzoylated derivatives of α-D-arabinofuranoses. In this conformation the H-1–H-2 dihedral angle would be close to 90°, which explains that no coupling was observable for the anomeric proton. For compound **6**, in which there is no interaction between substituents, the DAERM solutions would favor a ${}^{O}T_1 \rightleftharpoons {}^{O}E$ equilibrium.

TABLE III

DAERM ANALYSIS[a] OF COUPLINGS IN COMPOUNDS **4**–**6**

Compound	*Protons coupled*	*Case*	J_1	J_2	$Ø_1$	$Ø_2$	k_1	k_2
4	H-2;H-3;H-3′	*a*	2	6	51	176	5.7	6.3
		b	6	2	1	126	6.3	6.9
	H-4;H-3;H-3′	*c*	3	7	46	171	6.8	7.5
		d	7	3	5	130	7.3	8.2
5	H-2;H-3;H-3′	*a*	3	6	44	169	6.0	6.7
		b	6	3	7	132	6.5	7.2
	H-4;H-3;H-3′	*c*	6	8	34	159	8.9	9.9
		d	8	6	17	142	9.3	10.3
6	H-2;H-3;H-3′	*a*	2	6	51	176	5.7	6.3
		b	6	2	1	126	6.3	6.9
	H-4;H-3;H-3′	*c*	5	7	34	159	7.6	8.5
		d	7	5	17	142	7.9	8 8

[a] w = 124°; k_1/k_2 = 0.9, typical values for furanoid systems[8].

EXPERIMENTAL

General methods. — The instrumentation used has been described previously[6]. N.m.r. spectra were recorded at ~30° with a Varian XL-100 spectrometer operating in the f.t. mode with a 620 L-100 computer interfaced to a Sykes 7000 dual disk-drive. Solutions were made in chloroform-*d* with tetramethylsilane as internal standard, except for compound **6** which was recorded in D_2O with 1,4-dioxane as the external standard (δ_c 67.4 p.p.m. downfield from tetramethylsilane). Mass spectra were performed with a Varian MAT Ch-7A mass spectrometer at 70 eV, coupled to a Varian MAT data system 166. T.l.c. was performed on Silica Gel G (Merck) with 19:1 benzene–ethyl acetate. Detection was effected with iodine vapor. Paper chromatography was conducted by the descending method on Whatman No. 1 paper with 6:4:3 1-butanol–pyridine–water. G.l.c. was performed with glass columns (180 × 0.2 cm) packed with 3% ECNSS-M on Gas-chrom Q with nitrogen at a flow rate of 29 mL/min, T_i 210°, T_d 210°, T_c 170°.

*2,5,6-Tri-O-benzoyl-3-deoxy-*D-arabino*-hexono-1,4-lactone* (**2**). — 2,4,6-Tri-*O*-benzoyl-3-deoxy-D-*arabino*-hexono-1,5-lactone (**1**; 2 g) was debenzoylated by treatment with 0.1M sodium methoxide in methanol (40 mL), for 2 h at room temperature. The solution was decationized with Amberlite IR-120 (H^+) resin and evaporated to a syrup that was dissolved in water and extracted with benzene in order to remove methyl benzoate.

The water phase was evaporated and the resulting syrup heated under diminished pressure for 4 h in a boiling water-bath. The lactone was dissolved in anhydrous pyridine (5 mL) and benzoyl chloride added with stirring. After shaking for 2 h at room temperature, the mixture was poured into ice–water. The syrup that was separated by decantation crystallized on addition of ethanol; yield 1.65 g (82.5%).

Recrystallization from the same solvent gave pure **2**; m.p. 113–115°, $[\alpha]_D^{20}$ −26.2° (*c* 0.7, chloroform); R_F 0.46; ν_{max}^{Nujol} 1800 (1,4-lactone C=O); 1720 cm^{-1} (benzoate C=O); ^{1}H-n.m.r. see Table I, ^{13}C-n.m.r. see Table II; *m/z* 352 (9%), 268 (9%), 229 (21%), 205 (8%), 135 (6%), 122 (6%), 105 (100%), 96 (6%), 77 (45%), 71 (7%), 54 (13%), 51 (5%), and 43 (14%).

Anal. Calc. for $C_{27}H_{22}O_8$: C, 68.36; H, 4.64. Found: C, 68.39; H, 4.81.

*2,5,6-Tri-*O*-benzoyl-3-deoxy-*D-arabino-*hexofuranose* (**3**). — A solution of compound **2** (500 mg) was reduced with disiamylborane as previously described[2]. Compound **3** (R_F 0.30) crystallized spontaneously and was recrystallized from ethanol–water; yield 445 mg (89%), m.p. 132–134°, $[\alpha]_D^{20}$ −53.2° (*c* 0.5, chloroform); ν_{max}^{Nujol} 3.300 (OH) and 1700 cm^{-1} (benzoate C=O); ^{1}H-n.m.r. see Table I, ^{13}C-n.m.r. see Table II. For estimation of the $\alpha F/\beta F$ ratio, a 2.5% solution of **3** in chloroform-*d* was used, number of scans 15000, acquisition time 0.8 s, pulse width 31 μs, pulse delay 1.3 s.

Anal. Calc. for $C_{27}H_{24}O_8$: C, 68.05; H, 5.09. Found: C, 67.84; H, 5.01.

Debenzoylation of **3** as previously reported for the pyranose derivative[4] gave 3-deoxy-D-*arabino*-hexose having the same m.p., m.m.p. (140–142°), and chromatographic properties as an authentic sample. Gas–liquid chromatography of the alditol acetate gave *T* 0.57 (relative to glucitol hexaacetate).

*1-*O*-Acetyl-2,5,6-tri-*O*-benzoyl-3-deoxy-α-*D-arabino-*hexofuranose* (**4**). — Compound **3** (120 mg) was acetylated according to Wolfrom and Wood[17] to give crystalline 1-*O*-acetyl-2,5,6-tri-*O*-benzoyl-3-deoxy-α-D-*arabino*-hexofuranose (**4**); yield 98.5 mg (75%). Upon recrystallization from 3:2 ethanol–water it had m.p. 74–76°, R_F 0.5, $[\alpha]_D^{20}$ −14.7 (*c* 0.5, chloroform); ν_{max}^{Nujol} 1740 (acetate C=O) and 1720 cm^{-1} (benzoate C=O); *m/z* 475 (0.3%), 249 (24%), 127 (6.5%), 105 (100%), 77 (16%), 43 (18%); ^{1}H-n.m.r. see Table I, and ^{13}C-n.m.r. see Table II.

Anal. Calc. for $C_{29}H_{26}O_9$: C, 67.18; H, 5.02. Found: C, 67.46; H, 5.27.

*Methyl 2,5,6-tri-*O*-benzoyl-3-deoxy-α-*D-arabino-*hexofuranoside* (**5**). — Compound **4** (185 mg) was dissolved in dichloromethane (1.5 mL) and treated with bromotrimethylsilane (0.3 mL) at 0°. The reaction was complete in 1 h as monitored by t.l.c. Only one spot with R_F 0.35 was shown. After drying *in vacuo,* the bromide was treated with an excess of anhydrous methanol for 24 h at room temperature. The solution was evaporated and the residue crystallized on addition of 2-propanol. Recrystallization from the same solvent afforded compound **5** (160 mg, 85%). It showed R_F 0.62, m.p. 69–71°, $[\alpha]_D^{20}$ −29.15 (*c* 0.8, chloroform); *m/z* 459 (6%), 308 (7%), 221 (99%), 205 (18%), 106 (48%), 105 (100%), 99 (98%), 81 (15%), 77 (85%), 71 (15%), 54 (50%), and 51 (10%); ^{1}H-n.m.r. see Table I and ^{13}C-n.m.r. see Table II.

Anal. Calc. for $C_{28}H_{26}O_8$: C, 68.57; H, 5.33. Found: C, 68.28; H, 5.61.

*Methyl 3-deoxy-α-*D-arabino-*hexofuranoside* (**6**). — The benzoate **5** (160 mg) was debenzoylated by treatment with 0.1M sodium methoxide in methanol (10 mL).

After 2 h at room temperature, the solution was made neutral with Amberlite IR-120 (H^+) resin and evaporated to a syrup that crystallized from 1:1 acetone–ethyl ether. Recrystallization from the same solvent gave pure **6** (42 mg, 74%); m.p. 81–83°, $[\alpha]_D^{20}$ +47.62 (*c* 0.3, water); ^{1}H-n.m.r. see Table I and ^{13}C-n.m.r. see Table II.

Anal. Calc. for $C_7H_{14}O_5$: C, 47.19; H, 7.87. Found: C, 47.38; H, 7.96.

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