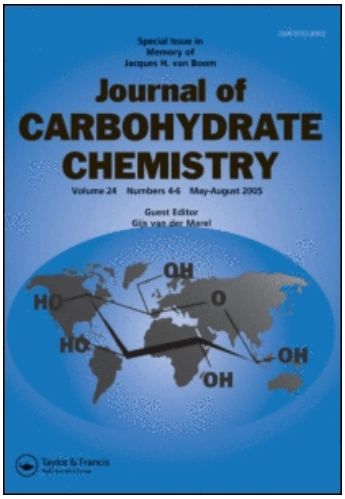

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A NEW SYNTHESIS OF 3-DEOXY-D-ARABINO-HEXOSE AND ITS TAUTOMERIC EQUILIBRIUM

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ABSTRACT

The title compound was synthesized in four steps from D-glucono-1,5-lactone. Reduction of 2,4,6-tri-O-benzoyl-3-deoxy-D-arabino-hexono-1,5-lactone (1) with disiamylborane afforded 2,4,6-tri-O-benzoyl-3-deoxy-D-arabino-hexopyranose (2) which, on debenzoylation, gave 3-deoxy-D-arabino-hexose (3). Tautomeric equilibrium of 3 was studied by ^{1}H and ^{13}C NMR spectroscopy.

INTRODUCTION

Aldonolactones have been used in our laboratory as starting materials for the synthesis of deoxy,[1,2] dideoxy[3,4] and trideoxy sugars[5,6] via β-elimination reactions. Thus, 2,4,6-tri-O-benzoyl-3-deoxy-D-arabino-hexono-1,5-lactone (1) was obtained[7] in two steps from D-glucono-1,5-lactone. The high yield and simplicity of the reactions suggested the use of 1 for the synthesis of 3-deoxy-D-arabino-hexose by reduction with a dialkylborane.[8]

On the other hand, it was interesting to study the tautomeric equilibrium of this sugar to substantiate

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the previous observation that removal of the hydroxyl group from C-3 causes an increase in the furanose forms. Apparently, this equilibrium was not reported for 3-deoxy-D-arabino-hexose, although quantitative data obtained from analysis of the ^{1}H NMR spectrum[9] and ^{13}C NMR studies were published for the epimeric 3-deoxy-D-ribo-hexose (4).[10]

RESULTS AND DISCUSSION

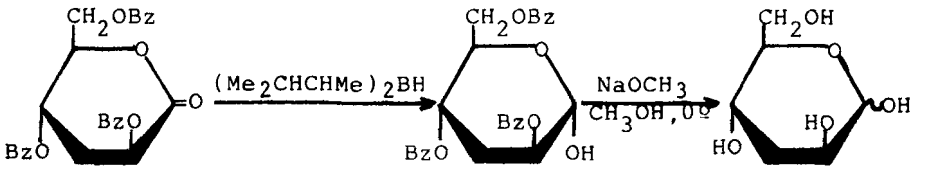
2,4,6-Tri-O-benzoyl-3-deoxy-D-arabino-hexono-1,5-lactone (1) obtained as previously reported[7] was reduced with disiamylborane in tetrahydrofuran to afford 2,4,6-tri-O-benzoyl-3-deoxy-D-arabino-hexopyranose (2) as a syrup. The yield (81%) was determined by the anthrone reaction[11] after debenzoylation with methanolic sodium methoxide in chloroform solution and extraction of the sugar into water. The ^{1}H NMR spectrum showed only the more stable α-anomer with H-1 at δ 5.3 and $J_{1,2}$ = 1 Hz. Also, only signals for one anomer appeared in the ^{13}C NMR spectrum (Table 1). Assignments for lactone 1 were made by comparison with the ^{13}C NMR data of 2,4-di-O-benzoyl-3,6-dideoxy-L-arabino-hexono-1,5-lactone[12] (5) previously assigned by single frequency decoupling. As expected the chemical shifts of C-1, C-2 and C-3 are very similar for these deoxy lactones. The C-4 resonance in 1 is shifted upfield (-3.49 p.p.m.) in comparison with C-4 in 5 due to steric crowding produced by the benzoyloxy group on C-6 of 1, which adopts a distorted chair conformation.[7] Debenzoylation of 2 with sodium methoxide in chloroform was very fast, and after 0.5 h at 0 °C, the free sugar was obtained crystalline from isopropanol. This is a convenient procedure to synthesize 3-deoxy-D-arabino-hexose (3) in four steps from inexpensive D-glucono-1,5-lactone.

TABLE 1

^{13}C NMR Chemical Shifts of Compounds 1-5 (δ p.p.m.)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C=O (benzoates)
1	167.20	64.73	30.95	66.78	77.70	63.46	165.72 165.09
5[a]	167.58	64.79	30.09	70.27	76.62	19.14	165.12
2	90.93	68.75	28.72	65.39	70.44	63.57	166.32 165.53 165.27
3 α-p	93.54	68.82	33.95	62.55	74.36	62.02	
3 β-p	95.50	68.62	37.76	62.44	80.73	62.26	
3 α-f	102.89	76.14	33.12	79.00	73.70	63.70	
4[b] α-p	91.79	67.44	34.69	65.18	73.05	61.63	
4 β-p	98.78	69.68	39.27	65.32	82.83	61.87	
4 α-f	97.35	73.85	31.92	77.57	71.59	63.45	
4 β-f	102.61	76.53	33.65	79.96	73.94	63.81	

[a] The data for compound 5 are taken from Ref. 12, [b] Ref. 10.



1 2 3

The overall yield (70%) compares favorably with previously reported methods. The epimeric mixture of 3-deoxy-D-ribo-hexose and 3-deoxy-D-arabino-hexose was prepared from 2-deoxy-D-erythro-pentose[13] by the nitromethane chain-lengthening method in combined yield of 65%. Another route involved reductive opening of methyl-2,3-anhydro-4,6-O-benzylidene- α -D-manno-pyranoside. Subsequent acid hydrolysis gave 3-deoxy-D-arabino-hexose with an overall yield of 3% from D-glucose.[14]

Tautomeric equilibrium of compound 3 in aqueous solution was studied by ^{1}H NMR and ^{13}C pulsed Fourier-transform NMR spectroscopy. Three anomeric signals could be assigned in the ^{1}H NMR spectrum, at δ 5.27 (α -furanose, $J_{1,2} < 1$); 5.00 (α -pyranose, $J_{1,2} < 1$) and 4.88 (β -pyranose, $J_{1,2} = 1.2$). Also, only three signals were evident for C-1 and all the other carbons in the ^{13}C NMR spectrum (Fig. 1). A small signal at δ_C 32.1 could be attributed to C-3 of the β-furanose form. Taking into account that the spectrum was recorded after 50,495 scans, only traces of this form would be present. Assignments were made by comparison of the chemical shifts of the corresponding carbons for 3 and those for the pyranose and furanose forms of 3-deoxy-D-ribo-hexose[10] (4), respectively (Table 1). Also, the relative intensities of the peaks were taken into account. The most significative differences for the pyranose

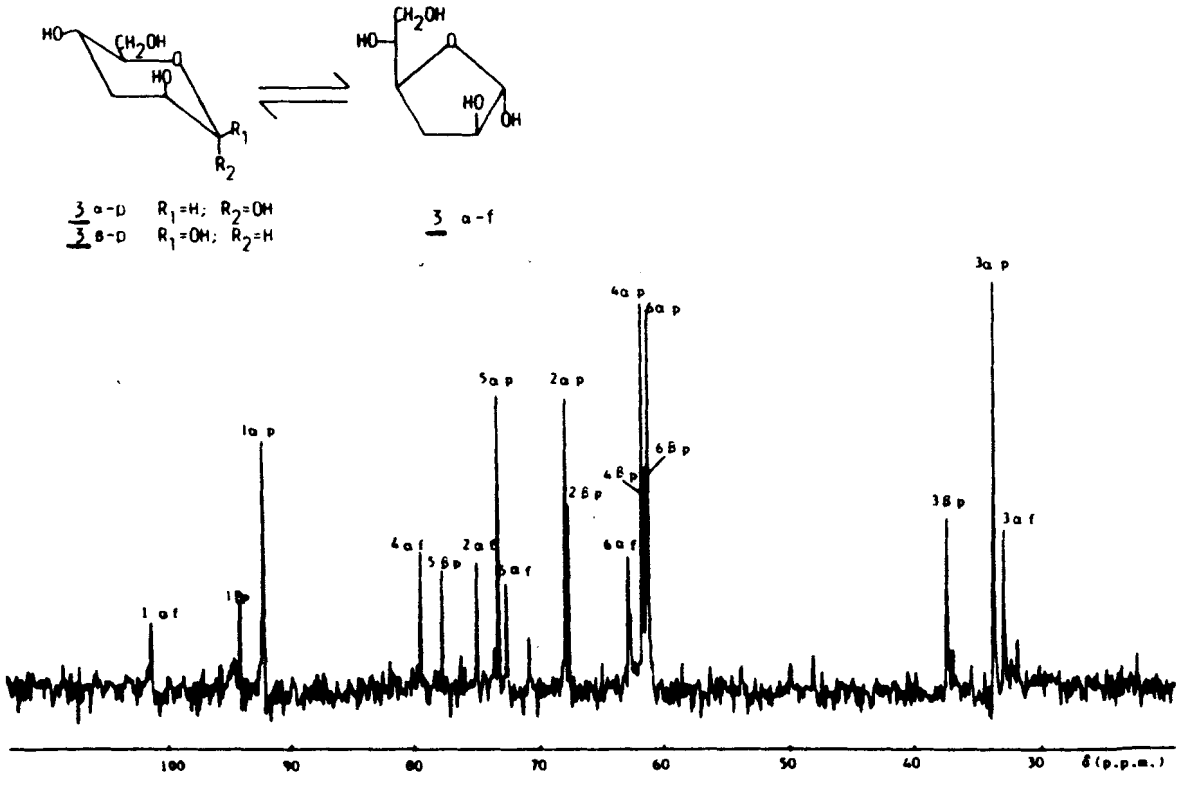


Fig. 1. ^{13}C NMR spectrum (25.2 MHz) of 3-deoxy-D-arabino-hexopyranose (80 mg in 4 mL H_2O-D_2O); 50,495 pulses; spectral width 3000 Hz; pulse delay 0.5 s; pulse width 40 μs.

forms of the epimeric 3-deoxy sugars (3 and 4) are observed between the C-4 resonances. The signals appear at about 3 p.p.m. higher field in compound 3 due to the axial interaction between H-4 and the 2-OH. A similar difference was shown by the anomeric carbons of the β-pyranose forms. Agreement was found between the values for the α-furanose form of 3 and those for the β-furanose of 4 with the same relationship between C-1 and C-2.

Horton and Walaszek[15] have demonstrated that partially relaxed ^{13}C NMR spectra can be used to determine the equilibrium composition. The proportions of tautomeric forms of compound 3 were estimated by averaging the integrated intensities of the resonances of C-1 and C-3, which were well separated from others, in the respective anomers (Table 2). A good correlation

TABLE 2

Equilibrium Composition of 3-Deoxy-D-arabino-hexose.

Tautomeric form	Composition of mixture[a]	
	^{1}H NMR	^{13}C NMR
3-deoxy-D-arabino-hexose		
α-pyranose	53.4	56.6
β-pyranose	30.0	25.7
α-furanose	16.6	17.6
3-deoxy-D-ribo-hexose		
α-pyranose	24.5[b]	26[c]
β-pyranose	55[b]	51[c]
α-furanose	5[b]	6[c]
β-furanose	15.5[b]	17[c]

[a] Percentages (± 2%); [b] Ref.9; [c] Ref.10

with the data from ^{1}H NMR spectroscopy was obtained. The furanose form is present in a substantial amount, while only 0.6% of the α-furanose and 0.3% of the β-furanose tautomer were detected in the configurationally related D-mannose.[16] This is because replacement of the 3-OH by H removes the cis interaction with the bulky side chain in the furanose configuration. It is interesting to compare the data with those reported for compound 4. As expected the α-anomers are the more stable forms of compound 3 at equilibrium.

EXPERIMENTAL

General Procedures. Melting points were determined with a Kofler hot plate apparatus and are uncorrected. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter and IR spectra with a Perkin-Elmer Model 421 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian XL-100-15 spectrometer for solutions in chloroform-d with tetramethylsilane as internal standard for the benzoylated sugar, and in D_2O with sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) as internal reference for the free sugar. To reduce the H_2O signal, the solution of the sugar in D_2O was repeatedly lyophilized. Proton decoupled, natural abundance ^{13}C Fourier-transform NMR spectra were obtained at 25.2 MHz using a 620 L-100 computer interfaced to a Sykes 7000 dual disk drive. Samples were spun in 12 mm tubes at ∿30 °C. Substituted sugars were dissolved in chloroform-d with tetramethylsilane as internal standard. The free sugar was dissolved in H_2O-D_2O (1:1), and dioxane was used as external standard (δ_c 67.4 ppm downfield from Me_4Si). Spectra were recorded at ∿30 °C after complete mutarotation. TLC was performed on silica gel G (Merck) with benzene-ethyl acetate (9:1). Detection was effected with iodine vapor.

2,4,6-Tri-O-benzoyl-3-deoxy-D-arabino-hexopyranose (2)

2,4,6-Tri-O-benzoyl-3-deoxy-D-arabino-hexono-1,5-lactone (1) was prepared as previously reported[7] in 90% yield from D-glucono-1,5-lactone and was reduced with disiamylborane according to the procedure described by Kohn et al.[8] To a solution containing 5.2 mmol of freshly prepared bis-(3-methyl-2-butyl)borane in terahydrofuran under nitrogen, 0.500 g (1.05 mmol) of 1 in 3 mL of tetrahydrofuran was added. After stirring for 20 h at room temperature, the reaction was interrupted by the slow addition of 5 mL of water and further stirred for 0.5 h. After cooling to 0 °C, 3 mL of 30% hydrogen peroxide was slowly added while keeping the pH of the solution between 7 and 8 with 3M sodium hydroxide. After 1 h the solution was extracted with dichloromethane, the organic layer was washed with water, dried (magnesium sulfate) and concentrated to a syrup. An aliquot was debenzoylated[8] and reducing sugar was determined by the anthrone method (81% yield).[11] The crude product was purified by dry column chromatography on silica gel (Davison) using benzene with increasing concentrations of ethyl acetate as eluent. 2,4,6-Tri-O-benzoyl-3-deoxy-D-arabino-hexopyranose (2) having R_F 0.38 was obtained as a chromatographically homogeneous syrup: $[\alpha]_D^{23}$ +4.7° (c 4.5, chloroform); ν_{max}^{Nujol} 3300 (OH) and 1700 cm^{-1} (benzoyl C=O); ^1H NMR: δ 8-7.2 (m, 15 H, 3 BzO), 5.6 (m, H-4), 5.3 (d, $J_{1,2}$ 1Hz, H-1), 5.25 (m, H-2), 4.60-4.44 (m, H-5,6,6'), 3.84 (broad, disappeared on deuteration, OH), 2.5-2.25 (m, H-3a, H-3e). ^{13}C NMR data are shown in Table 1.

Anal. Calcd for $C_{27}H_{24}O_8$: C, 68.06; H, 5.04. Found: C, 68.08; H, 5.32.

3-Deoxy-D-arabino-hexose. Compound 2 (187 mg, 0.39 mmol) was dissolved in chloroform(5 mL) and sodium

methoxide in methanol (5 mL, 0.5 M) was added. After 0.5 h at 0 °C, the solution was extracted with water, decationized with Amberlite IR 120 (H^+) and evaporated to a syrup that crystallized from isopropanol (yield 76.5%): mp and mmp 140-142 °C; $[\alpha]_D^{20}$ +51.8° (c 0.5, water); lit[13] mp 143-144 °C, $[\alpha]_D^{20}$ +52° (water); lit[14] mp 141-142 °C, $[\alpha]_D^{20}$ +53.1° (water); ^{1}H NMR (after mutarotation): δ 5.27 (H-1 α-f), 5.00 (H-1 α-p), 4.88 (d, $J_{1,2}$=1.2 Hz, H-1 β-p).

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