Note

Synthesis of 3-amino-3-deoxy-D-ribose and D-ribose derivatives by means of methyl sulfoxide–phosphorus pentaoxide and periodate oxidation*

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A convenient route for the synthesis of 3-amino-3-deoxyaldoses, component sugars of some antibiotics[1], involves aldofuranos-3-ulose derivatives, which are converted into oximes or *endo*-sulfonates for subsequent metal hydride reduction or bimolecular, nucleophilic replacement-reactions[2,3]. For the procedure to be more effective than other preparative methods[4], the proper combination and selection of protective groups, starting and intermediate sugar derivatives, and the oxidant for preparing the aldosulose, all need to be considered.

The present work describes the synthesis of 3-amino-3-deoxy-D-ribose derivatives and D-ribose derivatives from 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**1**) via aldofuranos-3-ulose and pentodialdo-1,4-furanose derivatives obtained by means of methyl sulfoxide–phosphorus pentaoxide and periodate oxidation. A similar route via an *O*-isopropylidene-D-xylose derivative was studied by Sowa[5]. Phosphorus pentaoxide was recently used in preference to acetic anhydride in some oxidations with methyl sulfoxide, where increased yield of aldosuloses[6,7], successful oxidation of a primary hydroxyl group to an aldehyde[7], and no formation of acetates or (methylthio)methyl ethers[8], was observed.

1,2:5,6-Di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose (**2**) (see scheme I) was obtained in 85–95% yield from one mole of compound **1** by oxidation with 4 moles of methyl sulfoxide and 1 mole of phosphorus pentaoxide in *N*,*N*-dimethylformamide[9], and no 3-(methylthio)methyl ether could be detected. A procedure reported that used acetic anhydride recorded a 28% yield of the thio derivative and only 50% of the aldosulose[10]. Compound **2** was converted into the oxime **3**, which was reduced with lithium aluminum hydride to give 3-amino-1,2:5,6-di-*O*-cyclohexylidene-3-deoxy-α-D-allofuranose (**4**). Compound **6**, derived from compound **4** by acetylation and partial hydrolysis to remove the 5,6-*O*-cyclohexylidene group, was subjected to periodate oxidation to afford compound **7**. Reduction of compound **7** with sodium borohydride, followed by acetylation gave 3-acetamido-5-*O*-acetyl-3-

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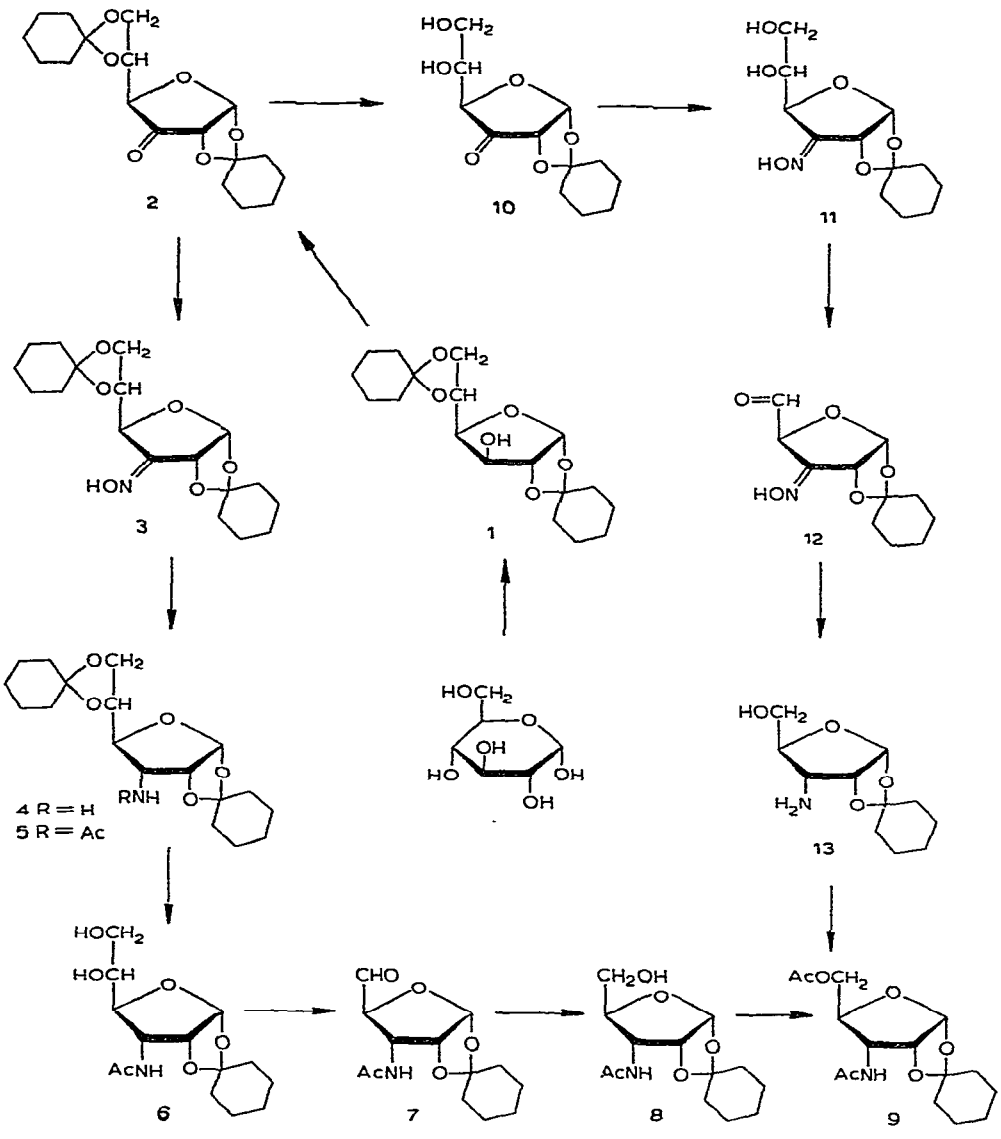
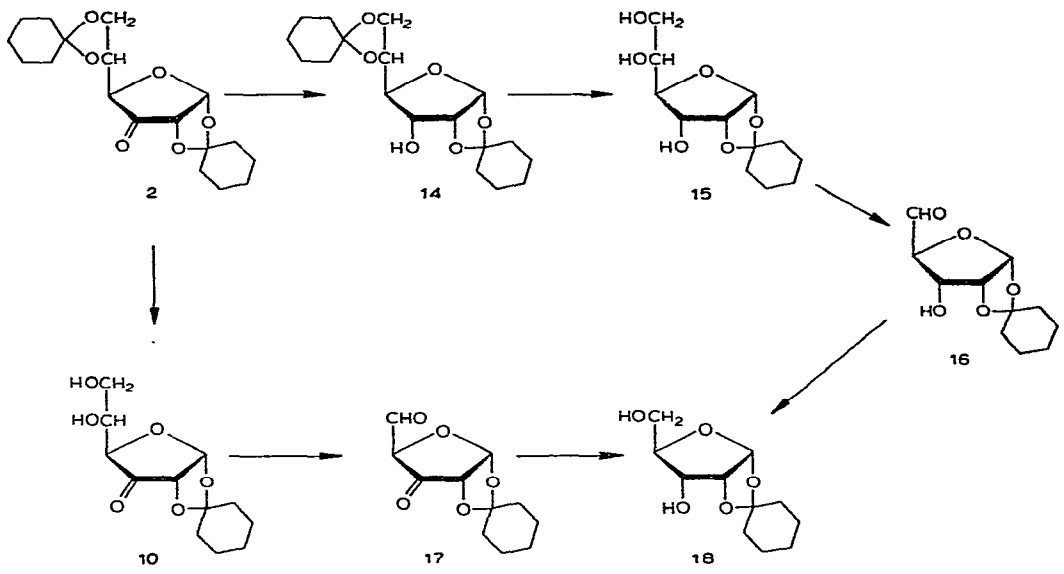


deoxy-α-D-ribofuranose (**9**). Compound **9** was also synthesized by lithium aluminum hydride reduction of 1,2-*O*-cyclohexylidene-3-oximino-α-D-*erythro*-pentodialdo-1,4-furanose (**12**), which was obtained in three steps from compound **2**. The overall yield of compound **9**, starting from D-glucose, was 5% by the route via compound **11**, whereas the route via compound **3** gave a 3% yield.

1,2-*O*-Cyclohexylidene-α-D-ribofuranose (**18**) (see scheme II) was also obtained by two routes. Periodate oxidation of 1,2-*O*-cyclohexylidene-α-D-allofuranose (**15**), followed by borohydride reduction gave compound **18** in 3% overall yield (based on



D-glucose). On the other hand, periodate oxidation of 1,2-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose (**10**) followed by reduction afforded compound **18** in 10% overall yield.

The above results provide a facile preparative route for both 3-amino-3-deoxy-D-ribose and D-ribose, starting from a readily available derivative of D-glucose. The intermediate 3-ulose derivatives (**3**, **10**, and **11**) and pentodialdo-1,4-furanose derivatives (**7**, **12**, **16**, and **17**) may have other synthetic utility.

EXPERIMENTAL

Methods. — T.l.c. was effected on 0.25-mm layers of Silica Gel G (Merck), and the products were made visible by spraying with 50% aqueous sulfuric acid followed by heating. N.m.r. spectra were obtained with a Varian A-60 spectrometer. Optical rotations were measured with a Yanagimoto Model OR-20 direct-reading polarimeter. I.r. spectra were measured with a Shimadzu Model AR-7 spectrometer.

*Synthesis of 3-amino-3-deoxy-*D*-ribose derivatives*

*1,2:5,6-Di-*O*-cyclohexylidene-α-*D*-*ribo*-hexofuranos-3-ulose* (**2**). — In 60 ml of *N,N*-dimethylformamide was dissolved 20.0 g of 1,2:5,6-di-*O*-cyclohexylidene-α-D-glucofuranose (**1**), and 19.8 g of anhydrous methyl sulfoxide was added to the solution. Phosphorus pentaoxide (16.6 g) was then added, and the mixture was stirred for 1 h at 60°. A chloroform extract of the mixture was washed with saturated, aqueous sodium hydrogen carbonate, and water, and after concentration the syrup was crystallized from methanol; yield 18.8 g (94%), m.p. 65–70°. Recrystallization from ligroin gave 17.0 g, m.p. 122–124°, $[\alpha]_D^{20}$ +96.7° (*c* 0.3, chloroform); ν_{max}^{nujol} 1770 cm^{-1}

(C=O); n.m.r. ($CDCl_3$): τ 3.85 (H-1, doublet, $J_{1,2}$ 4.3 Hz); t.l.c. (benzene–ethyl acetate, 17:3, *v/v*): **2**, R_F 0.54; **1**, R_F 0.43.

Anal. Calc. for $C_{18}H_{26}O_6$; C, 63.88; H, 7.74. Found: C, 63.89; H, 8.03.

1,2:5,6-Di-O-cyclohexylidene-3-oximino-α-D-ribo-hexofuranose (**3**). — To a mixture of **2** (17.8 g), ethanol (50 ml), and anhydrous pyridine (50 ml) was added hydroxylamine hydrochloride (11.0 g). The solution was refluxed for 2 h, and then extracted with chloroform. The extract washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Concentration gave a syrup that crystallized from ethanol; yield 12.8 g (69%), m.p. 143–147°, $[\alpha]_D^{16}$ +133° (*c* 1.0, methanol); n.m.r. ($CDCl_3$): τ 3.97 (H-1, doublet, $J_{1,2}$ 4.5 Hz).

Anal. Calc. for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 60.90; H, 7.75; N, 4.01.

3-Amino-1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-allofuranose (**4**). — To a solution of **3** (3.0 g) in anhydrous tetrahydrofuran (50 ml) was added 1 g of powdered lithium aluminum hydride with cooling, and the reaction mixture was refluxed for 4 h. The solution was poured onto ice–water, the mixture was extracted with chloroform, and the extract was washed with water and concentrated to a syrup. Crystallization from ether gave **4** in 63% yield; m.p. 140–144°, $[\alpha]_D^{14}$ +118.0° (*c* 0.5, chloroform); n.m.r. (CD_3OD): τ 4.24 (H-1, doublet, $J_{1,2}$ 3.5 Hz); t.l.c. (benzene–ethyl acetate, 3:2, v/v): **3**, R_F 0.83; **4**, R_F 0.25.

Anal. Calc. for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.60; H, 8.71; N, 4.02.

3-Acetamido-1,2:5,6-di-O-cyclohexylidene-3-deoxy-α-D-allofuranose (**5**). — *3*-Amino-1,2:5,6-di-*O*-cyclohexylidene-3-deoxy-α-D-allofuranose (**4**) was acetylated with acetic anhydride–pyridine for 3 days at room temperature to give compound **5**, m.p. 61–63°, $[\alpha]_D^{12}$ +78° (*c* 1.0, methanol); n.m.r. ($CDCl_3$): τ 7.98 (CH_3CON, 3 H), 4.19 (H-1, doublet, $J_{1,2}$ 3.4 Hz); t.l.c. (benzene–ethyl acetate, 7:3 *v/v*), R_F 0.22.

3-Acetamido-1,2-O-cyclohexylidene-3-deoxy-α-D-allofuranose (**6**). — A mixture of **5** (1.3 g), acetic acid (82 ml), and water (8 ml) was kept for 30 min at 75°, and concentrated to a syrup that was dissolved in benzene. The solution was evaporated under diminished pressure, and the sequence of dissolution and evaporation was repeated three times to afford syrupy **6**, yield 0.85 g (83%); t.l.c. (benzene–ethyl acetate, 3:7, *v/v*): **5**, R_F 0.95; **6**, R_F 0.09; n.m.r. ($CDCl_3$): τ 7.93 (CH_3CON, 3 H), 4.15 (H-1, doublet, $J_{1,2}$ 3.6 Hz).

3-Acetamido-5-O-acetyl-1,2-O-cyclohexylidene-3-deoxy-α-D-ribofuranose (**9**). — To a solution of **6** (0.85 g) in ethanol (20 ml) was added 80 ml of water and 0.1 g of periodic acid ($HIO_4 \cdot 2H_2O$). The mixture was kept for 2 days at 0–5° in the dark. T.l.c. (benzene–ethyl acetate, 3:7, *v/v*) showed that the reaction product (**7**, R_F 0.23) was not contaminated with starting material (**6**, R_F 0.07). The mixture was neutralized with sodium carbonate, filtered, and the filtrate concentrated to dryness. The residue was extracted with ethanol and to the extract was added 0.2 g of sodium borohydride. The mixture was stirred for 3 h at room temperature and extracted with chloroform. The extract was washed with water, and concentrated to a syrup. The dried syrup was

acetylated with acetic anhydride–pyridine to afford syrupy **9**; yield 0.4 g (45%), $[\alpha]_D^{12}$ +22° (*c* 1.0, methanol); n.m.r. ($CDCl_3$): τ 7.91, 7.97 (CH_3CON and CH_3CO_2, 6 H), 4.14 (H-1, doublet, $J_{1,2}$ 3.6 Hz), ν_{max} 1650 (amide) cm^{-1}.

Anal. Calc. for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.37; H, 7.54; N, 4.72.

*1,2-O-Cyclohexylidene-α-*D*-ribo-hexofuranose-3-ulose* (**10**). — A solution of **2** (20.0 g) in 100 ml of acetic acid and 10 ml of water was stirred for 30 min at 75°. The mixture was concentrated with the addition of benzene. This treatment was repeated three times, and the syrup thus obtained was crystallized from ligroin; yield 12.9 g (85%), m.p. 108–110°, $[\alpha]_D^{16}$ +41.2° (*c* 1.0, methanol); ν_{max}^{KBr} 1758 (C=O) cm^{-1}.

Anal. Calc. for $C_{12}H_{18}O_6$; C, 55.80; H, 7.03. Found: C, 55.84; H, 7.15.

*1,2-O-Cyclohexylidene-3-oximino-α-*D*-ribo-hexofuranose* (**11**). — A mixture of **10** (20.0 g), ethanol (100 ml), pyridine (100 ml), and hydroxylamine hydrochloride (10.8 g) was refluxed for 2 h, and concentrated to a syrup that was crystallized from ethyl acetate; yield 16.0 g (76%), m.p. 184.5–185.5°, $[\alpha]_D^{16}$ +133.0° (*c* 1.0, methanol); t.l.c. (ethyl acetate–benzene–methanol, 6:4:0.5, *v/v/v*): **11**, R_F 0.41; **10**, R_F 0.70; n.m.r. (CD_3OD): τ 4.30 (H-1, doublet, $J_{1,2}$ 4.2 Hz).

Anal. Calc. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.04; N, 5.13. Found: C, 52.46; H, 7.17; N, 5.09.

Preparation of **9** *via 1,2-O-cyclohexylidene-3-oximino-α-*D*-erythro-pentodialdo-1,4-furanose* (**12**). — A mixture of **11** (1.5 g), methanol (100 ml), and periodic acid (1.9 g) was kept for 3 days at 0–5° in the dark. After neutralization with saturated, aqueous sodium carbonate, the mixture was filtered, and the filtrate evaporated. T.l.c. (benzene–ethyl acetate, 5:5, *v/v*) showed that the product **12** (R_F 0.41) was the only sugar derivative present. The syrup was dissolved in tetrahydrofuran (100 ml) and refluxed for 3 h with lithium aluminum hydride (0.5 g). The reaction was terminated by addition of ethyl acetate, and the mixture was filtered. The filtrate was evaporated and the dried syrup was acetylated with acetic anhydride–pyridine. The chloroform extract was treated by the usual procedure. The syrup obtained was dissolved in the minimum amount of benzene, and subjected to column chromatography on Silica Gel G (Merck). The eluant was ethyl acetate–benzene (2:98, *v/v*), and the fractions having R_F 0.31 by t.l.c. (ethyl acetate–benzene, 2:98, *v/v*) were collected and concentrated. The syrup obtained (0.33 g, 19%) was identical with **9** by t.l.c. and n.m.r. spectroscopy.

Anal. Calc. for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.61; H, 7.23; N, 4.31.

Synthesis of D*-ribose derivatives*

*1,2:5,6-Di-O-cyclohexylidene-α-*D*-allofuranose* (**14**). — To a solution of **2** (29.8 g) in ethanol (200 ml) was added sodium borohydride (3.0 g) with cooling. The mixture was stirred for 30 min at room temperature, and then extracted with chloroform. The syrup obtained on concentration of the extract was crystallized from ethanol; yield 12.6 g (42%), m.p. 123–125.5°, $[\alpha]_D^{14}$ +12.4° (*c* 0.93, chloroform) [lit.[10], m.p. 121.5–

122.5°, lit.[11], m.p. 125–126°; $[\alpha]_D^{20}$ +47.4° (*c* 1.0, chloroform), $[\alpha]_D^{25}$ +41.4° (*c* 0.65, ethanol][11]; n.m.r. ($CDCl_3$): τ 4.18 (H-1, doublet, $J_{1,2}$ 3.7 Hz).

Anal. Calc. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.68; H, 8.32.

1,2-O-Cyclohexylidene-α-D-allofuranose (**15**). — A solution of **14** (20.0 g) in 10mM methanolic hydrochloric acid (135 ml) was stirred for 5 h at 30°. The mixture was made slightly alkaline, filtered, and concentrated to a syrup that was triturated with heptane and extracted with water. The water layer was evaporated to a syrup that crystallized from ethyl acetate–ligroin; yield 9.1 g (59%), m.p. 107–108°, $[\alpha]_D^{24}$ +23° (*c* 1.0, methanol) [lit.[11], m.p. 111–112°, $[\alpha]_D^{25}$ +46.1° (*c* 0.56, ethanol)]; n.m.r. (CD_3OD): τ 4.26 (H-1, doublet, $J_{1,2}$ 3.7 Hz).

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.60; H, 7.68.

1,2-O-Cyclohexylidene-α-D-ribofuranose (**18**). — *A.* A mixture of **15** (7.7 g), water (350 ml), and periodic acid (6.8 g) was kept for 42 h at 0–5° in the dark, neutralized with sodium carbonate, and filtered. The filtrate was evaporated to a syrup (**16**), which was extracted with ethanol, and to this was added sodium borohydride (1.0 g) in small portions with cooling. After stirring for 30 min, acetic acid was added to the mixture, which was then filtered. The filtrate was evaporated and the resultant syrup was taken up with a minimum amount of methanol, and adsorbed on a column of Silica Gel G, which was then eluted with benzene–ethyl acetate (1:9, *v/v*). The fractions having R_F 0.29 (t.l.c. with the same solvent system) were collected and concentrated to a syrup that was crystallized from ethyl acetate–ligroin; yield 0.79 g (17%), m.p. 172–174°, $[\alpha]_D^{24}$ +40° (*c* 0.5, methanol); n.m.r. (CD_3OD): τ 4.26 (H-1, doublet, $J_{1,2}$ 3.6 Hz).

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.30; H, 7.74.

B. To a solution of **10** (5.2 g) in methanol (40 ml) was added a mixture of periodic acid (12.2 g) and methanol (200 ml). The mixture was kept for 2 days at 0–5° in the dark, neutralized with sodium carbonate, and filtered. The filtrate was concentrated to a syrup (**17**) that was extracted with ethanol. Sodium borohydride (0.70 g) was added in small portions with cooling to the extract, and the mixture was stirred for 2 h at room temperature. The subsequent procedures were the same as those described in *A*; yield 1.4 g (31%); mixed m.p. with **18** undepressed.

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