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STEREOSELECTIVE SYNTHESIS OF 2,3-*O*-ISOPROPYLIDENE-DL-RIBOFURANOSE AND METHYL β-DL-RIBOPYRANOSIDE FROM FURFURYL ALCOHOL

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ABSTRACT

Methyl 2,3-dideoxy-DL-pent-2-enopyranosid-4-ulose (**2**) and 1-*O*-benzoyl-2,3-dideoxy-DL-pent-2-enopyranos-4-ulose (**3**), obtained from furfuryl alcohol, gave methyl β-DL-*erythro*-pentopyranosid-4-ulose (**6**) and 1-*O*-benzoyl-β-DL-*erythro*-pentopyranos-4-ulose (**7**), respectively, on *cis*-hydroxylation with silver chlorate–osmium tetroxide. Reduction of the isopropylidene derivatives (**8** and **9**) of **6** and **7** with lithium aluminium hydride and sodium borohydride, respectively, afforded DL-ribose derivatives.

INTRODUCTION

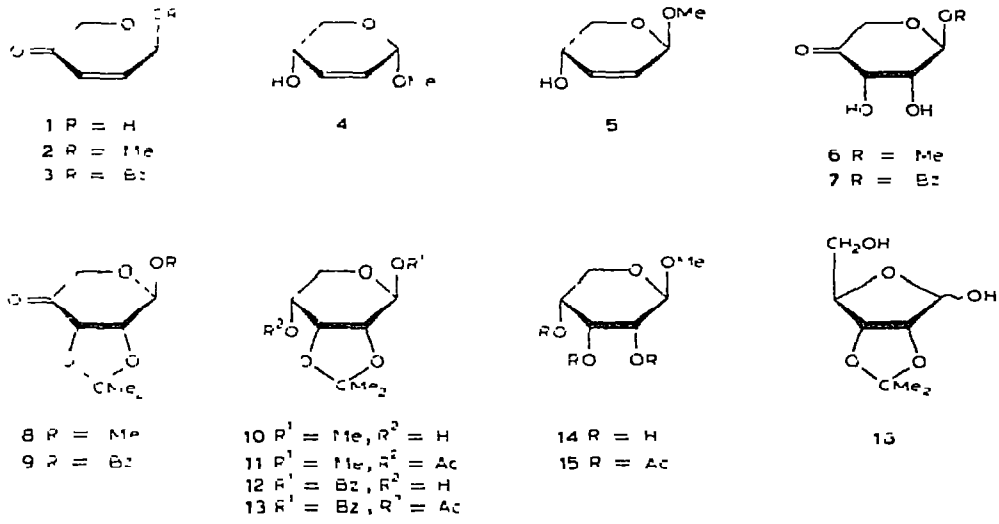
Amongst the sugars occurring in Nature, D-ribose attracts much attention as an invariable component of nucleic acids[1] and as a sugar constituent of numerous antibiotics[2]. The unique function of D-ribose and its low natural abundance promoted the development of efficient methods of synthesis from D-glucose[3]. Several syntheses of DL-ribose have also been reported[4]. We have developed a method[5] of monosaccharide synthesis whereby the methyl glycosides of all the DL-pentoses have been obtained[6] from furfuryl alcohol. However, the yield of methyl β-DL-ribopyranoside was low and we now describe modifications of the general approach which led to an efficient synthesis of DL-ribose derivatives.

RESULTS AND DISCUSSION

2,3-Dideoxy-DL-pent-2-enopyranos-4-ulose (**1**), obtained[5] from furfuryl alcohol, was treated with methyl iodide in the presence of silver oxide[7], or benzoyl chloride in pyridine, to give the glycoside **2** and the benzoate **3**, respectively. Reduction of the C-4 carbonyl group in **2** is highly stereoselective and yields the α-DL-*glycero* isomer **4***, which, on *cis*-hydroxylation, affords methyl α-DL-lyxopyranoside exclusively[6].

*All compounds are racemic mixtures, but for convenience all formulae and configurational prefixes refer to the D series.

Inversion of configuration at C-4 in **4** and subsequent *cis*-hydroxylation of the resulting alcohol **5** leads to a mixture of methyl β-DL-ribo- and β-DL-lyxopyranosides[6].



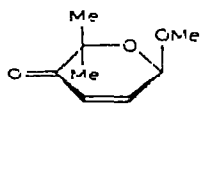
In seeking a stereoselective route to the ribose derivatives, *cis*-hydroxylation of **2** and **3** was attempted before reduction of the C-4 carbonyl group. Due to the relatively limited stability[9] of **2** and **3**, most of the *cis*-hydroxylating reagents[10] (*e.g.*, Milas or Woodward reagents) were unsatisfactory. With the *cis*-hydroxylating reagent (silver chlorate with a catalytic amount of osmium tetroxide) introduced by Braun[11] for water-soluble olefins, **2** and **3** reacted under homogeneous conditions (tetrahydrofuran–water) at room temperature to give, after 1–2 days, methyl β-DL-*erythro*-pentopyranosid-4-ulose (**6**) and 1-*O*-benzoyl-β-DL-*erythro*-pentopyranos-4-ulose (**7**), respectively, as single products (t.l.c.). The unstable ketodiols **6** and **7** were converted without purification into the corresponding isopropylidene acetals **8** and **9** which exhibited expected analytical and spectral data. Both **8** and **9** had i.r. absorbtion for carbonyl group (1740 cm^{-1}), and **9** had additional bands (1725, 1240 cm^{-1}) for the benzoyl residue. The ^{1}H-n.m.r. spectra contained signals for the isopropylidene methyl groups, five ring-protons, a methoxyl group (for **8**), and five aromatic protons (for **9**). Because of steric hindrance, *cis*-hydroxylation of **2** and **3** occurs *trans* to the C-1 substituents: consequently, the β-*erythro* configuration can be assigned to **6** and **7**.

The desired, high stereoselectivity of reduction of the C-4 carbonyl group was assured by carrying out the reaction on the isopropylidene derivatives **8** and **9**. For the analogous compound methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*ribo*-hexopyranosid-4-ulose, the pyranoid ring exists[12] in the $^0S_4$ conformation, so that the *trans* approach of the reducing agent to the isopropylidene group is favoured

Reduction of **8** with lithium aluminium hydride and **9** with sodium borohydride afforded a single product, **10** and **12**, respectively, in each reaction, as shown by t.l.c

Compounds **10** and **12** and the respective acetates, **11** and **13**, exhibited correct analytical and spectral data. The couplings $J_{1,2}$ 2.8, $J_{2,3}$ 6.7, $J_{4,5}$ 6.5, and $J_{4,5'}$ 7.7 Hz in the ^{1}H-n.m.r. spectrum of **11**, and $J_{1,2}$ 3.3, $J_{2,3}$ 6.1, $J_{3,4}$ 3.5, and $J_{4,5}+J_{4,5'}$ 15.0 Hz for **13**, were compatible with the β-ribopyranoid structure. The similar values of $J_{4,5}$ and $J_{4,5'}$ found for **11** indicate that both $^4C_1$ and $^1C_4$ conformations are significantly populated. The *β-ribo* configuration of the reduction products was proved by comparison with derivatives of D-ribose. Acidic hydrolysis of the isopropylidene residue in **10** or **11** followed by acetylation gave the triacetate **15**, which was identical (t.l.c., i.r. and ^{1}H-n.m.r. spectra) with methyl 2,3,4-tri-*O*-acetyl-β-D-ribopyranoside. Saponification of the benzoate **12** with sodium methoxide in methanol yielded the isopropylidene derivative **16** which was identical (t.l.c., i.r. and ^{1}H-n.m.r. spectra) with 2,3-*O*-isopropylidene-D-ribofuranose.

Using the foregoing, general route, methyl 2,3-*O*-isopropylidene-5,5-di-*C*-methyl-β-DL-ribopyranoside (**20**) was obtained. The ketone **17** prepared from 2-(2-furyl)-propan-2-ol[13] was treated with silver chlorate–osmium tetroxide to give the stable, crystalline diol **18** as the sole product (t.l.c.) Reduction of the isopropylidene derivative (**19**) of **18** with lithium aluminium hydride was stereoselective, yielding the β-ribopyranoside derivative **20**.



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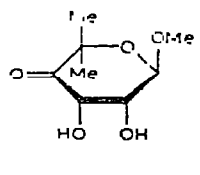

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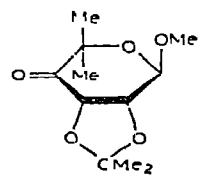

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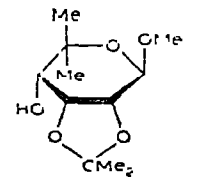

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EXPERIMENTAL

General. — Melting points were determined on a Kofler apparatus. Boiling points refer to air-bath temperature during semimicro-scale distillations and are not corrected. I.r. spectra were measured on KBr discs for solids and on thin films for oils with a Unicam SP-200 spectrophotometer. ^{1}H-N.m.r. spectra were recorded on Jeol JMN-4H-100 (100 MHz) and Varian EM-360 (60 MHz) spectrometers for solutions in $CDCl_3$ (internal Me_4Si). Silica gel G (Merck) was used for t.l.c., and MN-Kieselgel (100–200 mesh) (Machery Nagel & Co.) for column chromatography.

2,3-Dideoxy-DL-pent-2-enopyranos-4-ulose[5] (**1**), glycosides **2**[7] and **17**[7], methyl 2,3,4-tri-*O*-acetyl-β-D-ribopyranoside[14], and 2,3-di-*O*-isopropylidene-D-ribofuranose[15] were obtained by literature procedures. Acetylation was carried out conventionally with pyridine–acetic anhydride (1:1) overnight at room temperature. Anhydrous magnesium sulphate was used for drying of solutions in organic solvents.

1-O-Benzoyl-2,3-dideoxy-DL-pent-2-enopyranos-4-ulose (**3**). — To a solution of **1** (1.14 g, 10 mmol) in dichloromethane (10 ml), dry pyridine (5 ml) was added,

followed dropwise, with stirring, by a solution of benzoyl chloride (1.62 g, 11.5 mmol) in dichloromethane (5 ml), the temperature being kept below 5°. On completion of the reaction (t.l.c.; light petroleum–ethyl acetate, 4:1), dichloromethane (20 ml) was added, the reaction mixture was washed several times with cold water, and the organic layer was dried, and concentrated under diminished pressure with toluene (3 × 10 ml). The solid residue was crystallised from hexane–ether to give **3** (1.72 g, 79%), m.p. 82–83°; ν_{max}^{KBr} 1710, 1250 (ester), and 1695 cm^{-1} (α,β-unsaturated ketone). ^{1}H-N.m.r. data: δ 8.15 and 7.60 (m, 5 H, aromatic), 7.15 (dd, 1 H, $J_{1,2}$ 3, $J_{2,3}$ 10 Hz, H-2), 6.80 (d, 1 H, H-1), 6.40 (d, 1 H, H-3), 4.50 (dd, 2 H, $J_{5,5'}$ 17.0 Hz, H-5,5').

Anal. Calc. for $C_{12}H_{10}O_4$: C, 61.1; H, 4.6. Found: C, 61.1; H, 4.8.

cis-Hydroxylation reactions. — A mixture of the 2,3-unsaturated-4-ulose (5 mmol), silver chlorate (1.5 g), osmium tetroxide (10 mg), tetrahydrofuran (10 ml), and water (5 ml) was stirred at room temperature. After t.l.c. (ethyl acetate ethanol, 95:5) had revealed that all of the starting material had reacted, the solvents were removed under reduced pressure and the residual syrup was extracted with hot ethyl acetate (5 × 15 ml). The combined extracts were dried, filtered, and concentrated to dryness. In this way, the following compounds were obtained. Methyl *β*-DL-*erythro*-pentopyranosid-4-ulose (**6** from **2**), colourless syrup, ν_{max}^{liquid} 3500 (OH) and 1715 cm^{-1} (C=O). 1-*O*-Benzoyl-*β*-DL-*erythro*-pentopyranos-4-ulose (**7** from **3**), colourless syrup, ν_{max}^{liquid} 3500 (OH), 1730, and 1710 cm^{-1} (C=O). Methyl 5,5-di-*C*-methyl-*β*-DL-*erythro*-pentopyranosid-4-ulose (**18** from **17**), m.p. 96° (from ethyl acetate), ν_{max}^{KBr} 3400 (OH) and 1720 cm^{-1} (C=O). ^{1}H-N.m.r. data: δ 4.90 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 4.45 (m, 1 H, H-3), 3.60 (m, 1 H, H-2), 3.58 (s, 3 H, OMe), 1.52 and 1.45 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_8H_{14}O_5$: C, 50.5; H, 7.4. Found: C, 50.8; H, 7.5.

*Methyl 2,3-O-isopropylidene-β-*DL*-erythro-pentopyranosid-4-ulose* (**8**). — To a solution of **6** (1.45 g, 9 mmol) in acetone (20 ml), 2,2-dimethoxypropane (2 ml) was added followed by toluene-*p*-sulphonic acid (20 mg) and anhydrous cupric sulphate (2 g). The mixture was stirred at room temperature for 2 days, then neutralized with one drop of triethylamine, filtered, and concentrated under reduced pressure. The syrupy residue was eluted from silica gel with light petroleum–ethyl acetate (9:1), to give **8** (0.99 g, 49% from **2**), m.p. 64–65° (from hexane–ether), ν_{max}^{KBr} 1740 (C=O) and 1100 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 4.85 (s, 1 H, H-1), 4.45 and 4.20 (2 s, 2 H, H-5,5'), 4.55–3.65 (m, 2 H, H-2,3), 3.50 (s, 3 H, OMe), 1.50 and 1.35 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_9H_{14}O_5$: C, 53.5; H, 7.0. Found: C, 53.7; H, 7.3.

*1-O-Benzoyl-2,3-O-isopropylidene-β-*DL*-erythro-pentopyranos-4-ulose* (**9**). — Using the procedure described above for **6**, **7** was converted into **9** (43% from **3**), m.p. 94–95° (from hexane–ethyl acetate); ν_{max}^{KBr} 1750, 1240 (ester), 1720 (C=O), and 1090 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 8.15 and 7.65 (2 m, 5 H, aromatic), 6.40 (s, 1 H, H-1), 4.70–4.30 (m, 4 H, H-2,3,5,5'), 1.55 and 1.40 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{15}H_{16}O_6$: C, 61.6; H, 5.5. Found: C, 61.6; H, 5.6.

*Methyl 2,3-O-isopropylidene-5,5-di-C-methyl-β-*DL*-erythro-pentopyranosid-4-ulose* (**19**). — Using the procedure for **6**, **18** was converted into **19** (58%), b.p.

120°/0.4 torr; ν_{max}^{liquid} 1730 (C=O), 1090, and 1030 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 4.75–4.40 (m, 3 H, H-1,2,3), 3.50 (s, 3 H, OMe), 1.43, 1.36, 1.31, and 1.27 (4 s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.4; H, 7.9.

*Methyl 2,3-O-isopropylidene-β-*DL*-ribopyranoside* (**10**). — To a stirred solution of **8** (0.505 g, 2.5 mmol) in ether (25 ml), lithium aluminium hydride (40 mg) was added. After 30 min, 2 drops of water were added, followed by 2 drops of 15% aqueous sodium hydroxide and 0.1 ml of water. The precipitate was removed and the filtrate was dried and concentrated to afford **10** (0.5 g, 98%) as a colourless oil, b.p. 90°/0.01 torr; ν_{max}^{liquid} 3500 (OH) and 1090–1040 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 4.55 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 4.50–3.50 (m, 5 H, H-2,3,4,5,5'), 3.45 (s, 3 H, OMe), 1.55 and 1.40 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_9H_{16}O_5$: C, 52.9; H, 7.9. Found: C, 52.7; H, 8.0.

*Methyl 4-O-acetyl-2,3-O-isopropylidene-β-*DL*-ribopyranoside* (**11**). — Acetylation of **10** gave **11**, m.p. 94° (from hexane–ether); ν_{max}^{KBr} 1740, 1240 (ester), and 1090–1040 cm^{-1} (C–O). ^{1}H-N m.r. data: δ 5.23 (dt, 1 H, $J_{3,4}$ 3.7, $J_{4,5}$ 6.5, $J_{4,5'}$ 7.7 Hz, H-4), 4.45 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 4.25 (dd, 1 H, H-3), 3.93 (dd, 1 H, $J_{2,3}$ 6.7 Hz, H-2), 3.72 (dd, 1 H, $J_{5,5'}$ 10.0 Hz, H-5), 3.65 (dd, 1 H, H-5'), 3.13 (s, 3 H, OMe), 1.65 (s, 3 H, AcO), 1.45 and 1.15 (2 s, 6 H, CMe_2).

Anal. Calc for $C_{11}H_{18}O_6$: C, 53.7; H, 7.4. Found: C, 53.8; H, 7.4.

*Methyl 2,3-O-isopropylidene-5,5-di-C-methyl-β-*DL*-ribopyranoside* (**20**). — Reduction of **19** with lithium aluminium hydride, as described for **10**, gave **20** (96%) as a syrup, b.p 130°/0.4 torr, which crystallized after distillation; m.p. 108–110°; ν_{max}^{KBr} 3500 (OH), 1080, and 1040 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 4.78 (d, 1 H, $J_{1,2}$ 5.8 Hz, H-1), 4.46 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 4.0 Hz, H-3), 4.08 (dd, 1 H, H-2), 3.76 (t, 1 H, H-4), 3.48 (s, 3 H, OMe), 2.64 (d, 1 H, J 4.5 Hz, OH), 1.54, 1.40, 1.37, and 1.27 (4 s, 12 H, 2 CMe_2).

Anal. Calc. for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7. Found: C, 57.0; H, 8.6.

*1-O-Benzoyl-2,3-O-isopropylidene-β-*DL*-ribopyranose* (**12**). — A solution of **9** (0.584 g, 2 mmol) in tetrahydrofuran–water (4:1, 10 ml) was stirred with sodium borohydride (40 mg) for 15 min at room temperature. The mixture was extracted with chloroform, and the extract was dried, filtered, and concentrated *in vacuo* to give **12** (0.580 g, 98.5%), m.p. 119° (from ether); ν_{max}^{KBr} 3500 (OH), 1730, 1250 (ester), and 1090–1070 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 8.20 and 7.65 (2 m, 5 H, aromatic), 6.20 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.57 (dd, 1 H, $J_{2,3}$ 6.6, $J_{3,4}$ 3.8 Hz, H-3), 4.33 (dd, 1 H, H-2), 4.18 (m, 1 H, H-4), 3.92 (dd, 1 H, $J_{4,5}$ 5.0, $J_{5,5'}$ 10.0 Hz, H-5), 3.78 (dd, 1 H, $J_{4,5'}$ 10.0 Hz, H-5'), 2.55 (broad s, 1 H, OH), 1.61 and 1.45 (2 s, 6 H, CMe_2).

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.2. Found: C, 61.2; H, 6.2.

*4-O-Acetyl-1-O-benzoyl-2,3-O-isopropylidene-β-*DL*-ribopyranose* (**13**). — Acetylation of **12** gave **13**, m.p. 126° (from hexane–ethyl acetate); ν_{max}^{KBr} 1730, 1240 (ester), 1090, and 1050 cm^{-1} (C–O). ^{1}H-N.m.r. data: δ 7.90 and 7.30 (2 m, 5 H, aromatic), 6.02 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 5.25 (m, 1 H, H-4), 4.57 (dd, 1 H, $J_{2,3}$ 6.0,

$J_{3,4}$ 3.5 Hz, H-3), 4.24 (dd, 1 H, H-2), 3.88 and 3.80 (2 s, 2 H, $J_{4,5(5')}$ 7.5 Hz, H-5,5'), 2.10 (s, 3 H, AcO), 1.58 and 1.40 (2 s, 6 H, CMe_2)

Anal. Calc. for $C_{17}H_{20}O_7$ C, 60.7; H, 6.0. Found C, 61.0; H, 6.0.

Methyl 2,3,4-tri-O-acetyl-β-DL-ribopyranoside (**15**). — To a solution of **10** (0.204 g, 1 mmol) in methanol (5 ml), toluene-*p*-sulphonic acid (10 mg) was added. When all the substrate had reacted (t.l.c.), the methanol was evaporated, and the residue was treated conventionally with acetic anhydride–pyridine to give syrupy **15** (0.258 g, 89%) identical (t.l.c., i.r. and ^{1}H-n.m.r. spectra) with methyl 2,3,4-tri-*O*-acetyl-β-D-ribopyranoside.

2,3-O-Isopropylidene-DL-ribofuranose (**16**). — To a solution of **12** (0.292 g, 1 mmol) in methanol (10 ml), sodium (10 mg) was added. The solution was boiled under reflux until all of the starting material had been consumed (~2 h, t.l.c., benzene–ether, 1:1), and was then cooled, neutralized with acetic acid, and concentrated to dryness. The oily residue was dissolved in ethyl acetate, and the solution was filtered through a short column of silica gel and concentrated to give **16** (0.177 g, 93%) which was identical (t.l.c., i.r. and ^{1}H-n.m.r. spectra) with 2,3-*O*-isopropylidene-D-ribofuranose.

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