Synthesis of methyl 3-deoxy-α/β-D-ribofuranoside by regioselective reductive opening of methyl 2,3-anhydro-α/β-D-ribofuranoside

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Reductive opening of methyl 2,3-anhydro-α/β-D-ribofuranoside derivative 6 with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) is reported to result in the formation of methyl 3-deoxy-β-D-ribofuranoside derivative 8 and methyl 2-deoxy-α-D-ribofuranoside derivative 7. Stereochemistry at the anomeric center is found to control the regioselectivity.

Interest in 3'-deoxyribofuranosyl nucleosides stems from the identification of the metabolite cordycepin from *Cordyceps militaris* (Linn.) Link1-3 and from the fermentation broth of *Aspergillus nidulans* (Eidam) Wint as 9-β-(3'-deoxy-β-ribofuranosyl) adenine 1 (3'-deoxyadenosine). This 3'-deoxyribofuranosyl nucleoside inhibits nucleic acid synthesis in *Ehrlich ascites* cells4,9 and in *Bacillus subtilis*10.

Methyl 3-deoxy-β-D-ribofuranoside required for the synthesis of 1 was earlier prepared by stereospecific reduction of methyl 2,3-anhydro-β-D-ribofuranoside by hydrogenation in ethanol over Raney nickel at high pressure (2.8 kg/cm²) and 80°C temperature11. In another method methyl 2,3-anhydro-β-D-ribofuranoside was reacted with ethyl mercaptan/NaOEt, followed by desulphurisation with Raney nickel to obtain methyl 3-deoxy-β-D-ribofuranoside 312. All these methods involve use of high-pressure reactions and are not environment-friendly.

Accordingly we were encouraged to synthesise 3-deoxy-D-ribofuranosyl nucleosides that could form a substrate for the synthesis of 3-deoxy-D-ribofuranosyl nucleoside 1 and its analogues.

D-xylene was converted to the known 1,2-O-isopropylidene-α-D-xylurfuranoside 2 by reaction with acetone, anhyd. CuSO₄ and conc. H₂SO₄. Compound 2 was reacted with benzyl bromide/NaH in DME at 0°C to obtain 5-O-benzyl-1,2-O-isopropylidene-α-D-xylurfuranoside 3, after separation by column chromatography in 81% yield. Compound 3 was characterized from 1H NMR spectrum by the appearance of H-1 at δ 5.87 as a doublet (J₁,₂=4.0 Hz) and aromatic protons at δ 7.02-7.10 integrating for five protons. 5-O-Benzy1-1,2-O-isopropylidene-α-D-xylurfuranoside 3, was reacted with MeSO₂Cl/NEt₃ in CH₂Cl₂ at RT for 4 hr to obtain the 5-O-benzy1-1,2-O-isopropylidene-3-O-methanesulphonyl-α-D-xylurfuranoside 4 in quantitative yield as syrup. Mesylate derivative 4 was characterized from the 1H NMR spectrum by the appearance of methane sulphonyl group at δ 2.96 as a singlet integrating for three protons, H-1 appeared at δ 5.85 as a doublet (J₁,₂=4.5 Hz). Mesylate derivative 4 was subjected to methanolysis reaction in MeOH/HCl at room temperature for 16 hr to isolate anomeric mixture of methyl 5-O-benzyl-3-O-methanesulphonyl-α-D-ribofuranoside 5 in 98% yield. Diastereomeric mixture of 5 was characterized by the 1H NMR spectrum from appearance of anomeric methoxy protons at δ 3.38 and 3.42 as two singlets together integrating for three protons. 5-O-Benzyl-3-O-methanesulphonyl-α/β-D-ribofuranoside 5 on reaction with a 1N sodium methoxide solution in CHCl₃/MeOH (2:1, 15 mL) at RT for 4 hr gave methyl 2,3-anhydro-5-O-benzyl-α/β-D-ribofuranoside 6 (α/β ratio by 1H NMR 2:3) in 63% yield. Diastereomeric mixture of 6 was characterized from the 1H NMR spectrum from the appearance of anomeric methoxy protons at δ 3.28 and 3.47 as two singlets, anomeric proton at δ 4.88 and 5.16 as two singlets and H-2,3 protons were found merged with H-5,5' and OCH₃ signals. 2,3-Anhydro-5-O-benzyl-α/β-D-ribofuranoside 6 was subjected to reductive ring opening with Red-Al in toluene at reflux temperature for 5 hr to obtain methyl 5-O-benzyl-2-deoxy-α/β-D-ribofuranoside 7 and methyl 5-O-
Scheme I

benzyl-3-deoxy-α/β-D-ribofuranoside 8 (Scheme I).
2-Deoxy compounds 7 and 8 were separated by column chromatography and compound 7 was characterized from $^1$H NMR from the appearance of 2-deoxy protons at $\delta$ 1.80-2.20 as a multiplet, methoxyl groups at $\delta$ 3.38 integrating for three protons and anomeric proton at $\delta$ 5.14 as a doublet. Compound 8 was characterized from $^1$H NMR spectrum by the appearance of 3-deoxy protons as a multiplet at $\delta$ 1.70-2.00, H-1 appeared as a singlet at $\delta$ 4.75 and H-2 as a multiplet at $\delta$ 4.05-4.20. 2-Deoxy compounds 7 and 8 were acetylated to the corresponding acetates 9 and 10 respectively. The reductive opening of 2,3-anhydro furanoses was found to be dictated by the stereochemistry at the anomeric center. Thus, the β and α-glycosides gave the corresponding 3-deoxy and 2-deoxy furanosides respectively. Exact role played by anomeric substituent and reagent is under study. In conclusion a method has been developed for the preparation of 3-deoxyribofuranoside from D-xylose. Efforts are continuing for finding alternative methods for preparation of 1 in high yield.

Experimental Section

General: All the products were characterized by $^1$H NMR, spectroscopy. $^1$H NMR spectra were recorded on a FT NMR, Varian 200 MHz spectrometer. The solvents and other chemicals used for the reactions were purified and/or dried as per the standard literature methods.
5-O-Benzyl-1,2-O-isopropylidene-α-D-xylofurano­side 3. To a stirred solution of 1,2-O-isopropylidene-α-D-xylofuranose 2 (23.6 g, 124.2 mmole), sodium hydride (60% w/w) (5.96 g, 149 mmole) in 118 mL N,N-dimethylformamide under nitrogen atmosphere at 0°C was added benzyl bromide (14.8 mL, 124 mmole) and stirred at room temperature for 5 hr. The reaction mixture was cooled to 10°C and quenched by adding methanol (5 mL) followed by water (820 mL). The product was isolated by extraction with diethyl ether (2×100 mL). The organic phase was separated, washed with water (2×50 mL), dried over anhyd. Na2SO4 and concentrated to obtain a residue. The residue was purified by column chromatography [ethyl acetate:hexane (1:4)] to isolate the title compound 3 as a syrup (28.2 g, 80.9% yield). 1H NMR (CDCl3): δ 1.23, 1.42 (2s, 6H, Me2CO), 3.45-4.00 (m, 7H, H-2,5, C6H5-CH2), 5.87 (d, 1H, J2,3=4.0 Hz, H-1), 7.20-7.40 (s, 5H, ArH). Anal. Found: C, 65.68; H, 7.61%.

5-O-Benzyl-1,2-O-isopropylidene-3-O-methanesulphonyl-α-D-xylofuranose 4. To a stirred solution of compound 3 (2.0 g, 7.14 mmole) in CH2Cl2 (15 mL) at room temperature was added triethylamine (2mL) at room temperature was added dropwise at 0°C and the reaction mixture was brought to room temperature. After the completion of the reaction the reaction mixture was diluted with CH2Cl2 (50 mL) and water (50 mL). The CH2Cl2 layer was separated, dried over anhyd. Na2SO4 and concentrated under reduced pressure to yield the title compound 4 as a syrup (2.25 g, 98% yield). 1H NMR (CDCl3): δ 1.27, 1.49 (2s, 6H, Me2CO2), 2.96 (s, 3H, MeSO3), 3.50-4.10 (m, 2H, H-3,5), 4.20-4.80 (m, 5H, H-2,4 and C6H5-CH2), 5.85 (d, 1H, J1,2=4.5 Hz, H-1), 7.20-7.40 (m, 5H, ArH). Anal. Found: C, 65.97; H, 6.67. Calcd for C29H32O8: C, 58.88; H, 6.79%.

Methyl 5-O-benzyl-3-O-methanesulphonyl-α/β-D-ribofuranoside 5. To a solution of compound 4 (2.7 g, w/w 7.5 mmole) in methanol (3 mL) was added methanolic hydrochloric acid (3%, 15 mL) at room temperature and stirred at RT for 16 hr. The reaction mixture was neutralized by adding lead carbonate (8.0 g), the heterogeneous mixture was filtered, the residue washed with MeOH (2×25 mL) and the combined filtrate was concentrated to obtain the title compound 5 as a syrup (2.28 g, 98% yield). 1H NMR (CDCl3): δ 2.94 (s, 3H, CH3SO2), 3.20-5.00 (m, 8H, H-1-5, C6H5CH2), 3.38, 3.44 (2s, 3H, OCH3), 7.15-7.40 (m, 5H, Ar-H). Anal. Found: C, 58.12; H, 6.61. Calcd for C13H15O5: C, 55.99; H, 6.71%.

Methyl 2,3-anhydro-5-O-benzyl-α/β-D-ribofuranoside 6. To a stirred solution of compound 5 (2.7 g, 8.108 mmole) in CH2Cl2 (10 mL) at room temperature was added sodium methoxide (1N, 5 mL). At the end of the reaction the reaction mixture was neutralized with acetic acid (1 mL) and concentrated under reduced pressure to obtain a residue. The residue was extracted into CH2Cl2 (2×50 mL), dried over anhyd. Na2SO4 and solvent was removed to obtain a residue. The residue was purified by column chromatography [EtOAc-hexane (1:4)] to obtain the title compound 6 as syrup (1.2 g, 63% yield). 1H NMR (CDCl3): δ 3.27, 3.48 (2s, 3H, OCH3), 3.30-3.80 (m, 4H, H-2,3,5,5'), 4.18-4.35 (m, 1H, H-4), 4.48, 5.16 (2s, 1H, H-1), 7.15-7.40 (m, 5H, ArH). Anal. Found: C, 66.38; H, 6.74. Calcd for C13H15O5: C, 66.08; H, 6.82%.

Methyl 5-O-benzyl-2-deoxy-α/β-D-ribofuranoside 7 and methyl 5-O-benzyl-3-deoxy-α/β-D-ribofuranoside 8. To a stirred solution of compound 6 (0.21 g, 0.9 mmole) in dry toluene (5 mL) at room temperature was added Red-Al in toluene (0.17 g, 8.9 mmole) and refluxed for 5 hr. At the end of the reaction the reaction mixture was quenched by addition of ethyl acetate (0.5 mL), MeOH (0.5 mL) and concentrated under reduced pressure to a residue. The residue was separated by column chromatography [SiO2, 60-120 mesh, EtOAc-hexane (1:4)] to isolate compound 7 (0.1 g, 46%) followed by compound 8 (0.095 g, 45%). 1H NMR (CDCl3) of 7: δ 1.80-2.20 (m, 2H, H-2,2'), 3.38 (1s, 3H, OCH3), 3.25-3.60 (m, 2H, H-5,5'), 4.00-4.40 (m, 2H, H-4), 4.50 (s, 2H, Ph-CH2), 5.14 (2d, 1H, H-1), 7.20-7.40 (m, 5H, ArH). Anal. Found: C, 65.68; H, 7.53. Calcd for C13H15O5: C, 65.52; H, 7.61%.

1H NMR (CDCl3) of 8: δ 1.70-2.00 (m, 2H, H-3,3'), 3.21 (s, 3H, OCH3), 3.31-3.50 (m, 2H, H-5,5'), 4.05-4.20 (m, 1H, H-2), 4.40-4.60 (m, 3H, H-4, PhCH2), 4.75 (s, 1H, H-1), 7.20-7.40 (m, 5H, ArH). Anal. Found: C, 65.79; H, 7.51. Calcd for C13H15O5: C, 65.52; H, 7.61%.

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References
10 Rottman F & Guarino A T, Biochim Biophys Acta, 80, 1964, 632.
12 Prepared from xylene in 7 steps according to the method described by Anderson C D, Goodman L & Baker B R, J Am Chem Soc, 80, 1958, 5247.