DIRECT PREPARATION OF 1,2:3,5-DI-*O*-CYCLOHEXYLIDENE-α-D-XYLOFURANOSE FROM CORNCOBS AND ITS CONVERSION TO 1-*O*-ACETYL-2,3,5-TRI-*O*-BENZOYL-D-RIBOFURANOSE

Mirjana POPSAVIN, Velimir POPSAVIN, Nada VUKOJEVIC and Dusan MILJKOVIC

Institute of Chemistry,
Faculty of Sciences, University of Novi Sad,
Trg Dositeja Obradovica 3, 21000 Novi Sad, Yugoslavia

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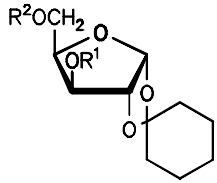
A novel synthesis of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (*I*) has been described starting from 1,2:3,5-di-*O*-cyclohexylidene-α-D-xylofuranose (*II*), obtained directly from the crude xylose syrup originated from corncobs. Partial acid hydrolysis of *II* gave 1,2-*O*-cyclohexylidene-α-D-xylofuranose (*III*). Selective benzoylation of primary C-5 hydroxyl group of *III* followed by tosylation of C-3 hydroxyl group afforded *IV* in an overall yield of 67%. Mild acid methanolysis of *IV* gave the corresponding methyl xylofuranosides *V* which were further benzoylated to afford 2,5-di-*O*-benzoyl derivatives *VI* in 65% yield. Solvolysis of *VI* in 95% DMF gave a mixture of 2,5- and 3,5-di-*O*-benzoylribofuranosides *VII*, which were subsequently converted into the corresponding tribenzoates *VIII*. An acetolysis of *VIII* afforded *I* in an overall yield of 96% related to *VI*.

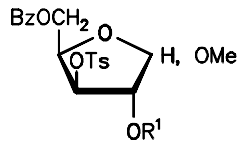
1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (*I*) represents an important starting material for numerous syntheses of ribonucleosides[1] as well as certain *C*-nucleosides[2] with potential antitumor and/or antiviral properties. Although commercially available, compound *I* is usually prepared from D-ribose[3]. In this paper we want to report a new synthesis of *I* starting from crude D-xylose syrup obtained by acid hydrolysis of the xylan fraction from corncobs.

It is well known that D-xylose can be suitably prepared from corncobs or a similar natural waste material containing large amounts of xylan or hemicellulose-B. The method used here is a modification of that described by Whistler and BeMiller[4]. It assumes a previous treatment of corncobs with 1% aqueous sodium hydroxide to remove lignin and acidic impurities. Hydrolysis of such pre-treated corncobs is carried out as described[4], but the yeast fermentation step as well as the crystallization step was omitted since the crude xylose syrup was immediately treated[5] with cyclohexanone in presence of concentrated sulfuric acid. By this modification, highly crystalline 1,2:3,5-di-*O*-cyclohexylidene-α-D-xylofuranose (*II*) was obtained. Partial acid hydrolysis of *II*, under the conditions similar to those already reported[6], gave 1,2-*O*-cyclohexylidene-α-D-xylofuranose (*III*).

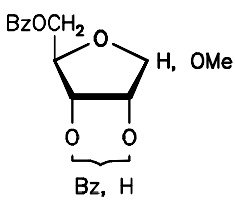
Derivative *IV* was conveniently prepared[7] by "one pot" procedure including selective benzoylation of primary C-5 hydroxyl group in *III*, followed by esterification of the remaining C-3 hydroxyl group with tosyl chloride in pyridine.



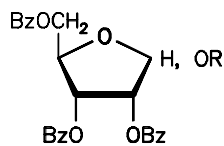
II, $R^1 = R^2$ = cyclohexylidene
III, $R^1 = R^2 = H$
IV, R^1 = Ts; R^2 = Bz



V, $R^1 = H$
VI, R^1 = Bz



VII



VIII, R = Me
I, R = Ac

Compound *IV* upon reflux in dry methanol in presence of trichloroacetic acid gave the corresponding methyl xylofuranoside *V* as an 1 : 1 anomeric mixture. Further treatment of *V* with benzoyl chloride afforded the corresponding 2,5-di-*O*-benzoylxylofuranosides *VI*. Although an analytical sample of *VI*, obtained by recrystallization from EtOH, showed as a single spot in TLC and had a sharp melting point (136 °C), it also represented a mixture of anomers with an α : β anomeric ratio of 3 : 2 (according to NMR). Both α- and β-anomers in the mixture were fully characterized by ^{1}H and ^{13}C NMR data (see Experimental). The ^{1}H assignments were carried out by spin-decoupling experiments, while the ^{13}C assignments were performed by 2D chemical shift correlation method.

The subsequent important step leading towards the target ribofuranosyl acetates *I* included the C-3 epimerization of xylofuranosides *VI*. This was achieved by a solvolysis of *VI* in wet *N*,*N*-dimethylformamide at 150 °C, in presence of $CaCO_3$ as a proton acceptor. The resulting mixture of 2,5- and 3,5-di-*O*-benzoylribofuranosides *VII* (most likely formed via cyclic benzoxonium ion[8]) was subsequently treated with benzoyl

chloride in pyridine to give known[9] methyl 2,3,5-tri-*O*-benzoylribofuranosides *VIII*. A treatment of crude *VIII* with a mixture of acetic acid–acetic anhydride–concentrated sulfuric acid afforded the desired ribofuranosyl acetates *I* as a mixture of anomers. By crystallization of the mixture from EtOH, the pure β-anomer of *I* was obtained in an overall yield of 45% (from *VI*). After evaporation of mother liquor an oily mixture remained containing the α-anomer of *I* as the predominant component. By integration of the signals at δ 6.73 d (H-1α) and δ 6.44 s (H-1β), the α : β anomeric ratio in the mother liquor was determined as 20 : 3. All three steps concerning the conversion of *VI* to *I* were carried out successively, whereupon the intermediates *VII* and *VIII* were used in the subsequent steps without any purifications. The final product *I* (α + β) was obtained in an overall yield of 96% related to the intermediate *VI*.

Both α- and β-anomers *I* represent suitable intermediates for preparation of various *N*- and *C*-nucleosides[1,2].

EXPERIMENTAL

Melting points were determined on Büchi SMP 20 apparatus and were not corrected. Optical rotations were measured on automatic polarimeter Polamat A (Zeiss, Jena) at 23 °C in chloroform solutions if not stated otherwise. ^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on Bruker AC 250 E instrument in deuteriochloroform with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale) and coupling constants (*J*) in Hz. Thin-layer chromatography (TLC) was performed on DC Alufolien Kieselgel 60 F_{254} (Merck). Column chromatography was carried out on Kieselgel 60. The extracts were dried with Na_2SO_4 if not stated otherwise.

1,2:3,5-Di-*O*-cyclohexylidene-α-D-xylofuranose (*II*)

A suspension of grounded corncobs (85 g) in 1% aqueous NaOH (500 ml) was refluxed for 2.5 h. The precipitate was collected, washed with hot water and hydrolyzed with boiling 7% aqueous H_2SO_4 (500 ml) for 2.5 h. The reaction mixture was filtered and solution neutralized with $CaCO_3$. The precipitate was filtered off and aqueous solution concentrated under reduced pressure to a pale yellow syrup (23.7 g). So obtained crude D-xylose was treated with cyclohexanone (40 ml) and concentrated H_2SO_4 (3 ml) in ether (100 ml). The reaction mixture was stirred at room temperature for 24 h and then transferred into a separatory funnel to remove the aqueous phase. The etheral solution was washed with saturated $NaHCO_3$, dried (Na_2CO_3) and evaporated to a yellow syrup. Crystallization from hexane followed by recrystallization from aqueous ethanol (20% of water) afforded pure *II* (18 g, 21%) as colourless needles, m.p. 104 – 105 °C (ref.[5] m.p. 102.5 – 103 °C, ref.[10] m.p. 105 °C).

1,2-*O*-Cyclohexylidene-α-D-xylofuranose (*III*)

A suspension containing finely powdered compound *II* (34.14 g, 184.43 mmol) in 50% aqueous acetic acid (500 ml) was stirred at 100 °C until the solution became clear (20 – 30 min). After cooling to 30 °C, the solution was neutralized with solid $NaHCO_3$ and extracted with chloroform. The extract was dried and evaporated to a yellow syrup (23.36 g). After crystallization from benzene–hexane, the pure product *III* (19.1 g, 75%) was obtained as colourless needles, m.p. 89 – 89.5 °C (ref.[10] m.p. 91 – 92 °C), and $[\alpha]_D$ –11.6° (*c* 0.9, water); ref.[10] $[\alpha]_D$ –12.4° (*c* 0.89).

5-*O*-Benzoyl-1,2-*O*-cyclohexylidene-3-*O*-*p*-toluenesulfonyl-α-D-xylofuranose[7] (*IV*)

To a solution of compound *III* (1.039 g, 4.52 mmol) in dry pyridine (10 ml), benzoyl chloride (0.58 ml, 5 mmol) was added during 0.5 h at –20 °C. The reaction mixture was left at this temperature for 48 h and then at room temperature for 24 h. Finally, tosyl chloride (2.58 g, 13.55 mmol) was added and the resulting mixture kept at room temperature for additional 72 h. The reaction mixture was poured into ice and diluted HCl (1 : 1) and extracted with chloroform. The combined extracts were washed with water, saturated $NaHCO_3$, dried and evaporated. Upon crystallization from ethanol the pure compound *IV* was obtained (1.46 g, 67%) in a form of colourless crystals, m.p. 104 – 106 °C, $[\alpha]_D$ –65.22° (*c* 1.2). ^{1}H NMR spectrum: 1.28 – 1.84 m, 10 H (cyclohexylidene ring); 2.26 s, 3 H (CH_3, Ts); 4.27 dd, 1 H, *J*(5a,5b) = 12.3, *J*(4,5a) = 6.7 (H-5a); 4.41 dd, 1 H, *J*(4,5b) = 6 (H-5b); 4.55 ddd, 1 H, *J*(3,4) = 2.9 (H-4); 4.82 d, 1 H, *J*(1,2) = 3.7 (H-2); 4.96 d, 1 H (H-3); 6.0 d, 1 H (H-1); 7.12 – 8.16 m, 9 H (Bz and Ts). ^{13}C NMR spectrum: 21.53 (CH_3, Ts), 23.44, 23.78, 24.75, 35.63 and 36.22 (5 × CH_2, cyclohexylidene), 60.95 (C-5), 76.44, 81.59 and 82.83 (C-2, C-3 and C-4), 104.42 (C-1), 113.38 (qC from cyclohexylidene), 127.78, 128.3, 129.39, 129.71, 130.02, 132.58, 133.17 and 145.52 (C-atoms from aromatic rings), 163.9 (C=O, Bz). For $C_{25}H_{28}O_8S$ (488.3) calculated: 61.44% C, 5.78% H, 6.57% S; found: 61.69% C, 6.08% H, 6.79% S.

Methyl 5-*O*-Benzoyl-3-*O*-*p*-toluenesulfonyl-D-xylofuranosides (*V*)

A solution of compound *IV* (0.15 g, 0.31 mmol) and trichloroacetic acid (0.64 g, 3.91 mmol) in dry methanol (2 ml) was refluxed for 32 h. The reaction mixture was poured into cold water, neutralized ($NaHCO_3$) and extracted with chloroform. The extract was dried and evaporated to give a crude mixture as a yellow oil. After chromatographic purification on a column of silica gel (toluene–ethyl acetate 4 : 1), the pure *V* was obtained (0.082 g, 63%) as an anomeric mixture (α : β = 1 : 1; according to NMR) that moved as a single spot in TLC with different solvents. ^{1}H NMR spectrum: 2.21 and 2.4 2 s (2 × CH_3, Ts); 2.41 and 2.6 2 d (2 × OH); 3.35 and 3.5 2 s (2 × CH_3O); 4.36 – 5.01 m (H-2, H-3, H-4, H-5a, H-5b and H-1β); 5.04 d, *J*(1,2) = 4.8 (H-1α); 7.2 – 8.09 m (Bz and Ts). ^{13}C NMR spectrum: 22.5 (2 overlapping CH_3 from 2 × Ts), 56.1 and 56.8 (2 × CH_3O), 62.5 (C-5α), 63.6 (C-5β), 75.0, 76.9, 78.3, 80.0, 83.6 and 84.3 (C-2, C-3 and C-4), 101.8 (C-1α), 109.4 (C-1β), 128.7 – 145.8 (partially overlapping C-atoms from Bz and Ts), 166.1 (2 overlapping C=O).

Methyl 2,5-Di-*O*-benzoyl-3-*O*-*p*-toluenesulfonyl-D-xylofuranosides (*VI*)

To a solution of compound *V* (1.0 g, 2.36 mmol) in dry dichloromethane (10 ml) and dry pyridine (2 ml) was added benzoyl chloride (1.1 ml, 9.46 mmol) at 0 °C. The mixture was stored at room temperature for 48 h, then acidified with aqueous HCl (1 : 1) to pH 2 and extracted with dichloromethane. The combined extracts were washed with water and saturated aqueous $NaHCO_3$ dried (Na_2CO_3) and evaporated. The syrupy residue was crystallized from ethanol to give *VI* (0.81 g, 65%) as an anomeric mixture (α : β = 3 : 2), m.p. 132 – 133 °C. An analytical sample of *VI* obtained by recrystallization from ethanol showed m.p. 136 °C. ^{1}H NMR spectrum: 2.03 s (CH_3, Ts; α-anomer), 2.12 s (CH_3, Ts; β-anomer); 3.14 s (α-CH_3O), 3.2 s (β-CH_3O); 4.52 – 4.7 m (H-4α, H-5aα, H-5aβ, H-5bα and H-5bβ); 4.86 broad dd (H-4β); 4.99 broad s (H-1β); 5.21 – 5.28 m (H-1α, H-2α and H-3β); 5.37 d, *J*(2,3) = 2.1 (H-2β); 5.43 – 5.5 m (H-3α); 7.12 – 8.11 m (Bz and Ts). ^{13}C NMR spectrum: 21.8 (2 overlapping CH_3, Ts), 55.5 and 55.6 (CH_3, Ts), 62.2 (C-5α), 63.1 (C-5β), 73.4 (C-4α), 77.3 (C-2α), 78.2 (C-4β), 80.2 (C-2β), 80.4 (C-3β), 80.7 (C-3α), 99.9 (C-1α), 106.9 (C-1β), 128.6 – 145.7 (partially overlapping C-atoms from Bz and Ts), 165.0, 165.4 and 166.1 (4 partially overlapping C=O). For $C_{27}H_{26}O_9S$ (526.3) calculated: 61.56% C, 4.98% H, 6.10% S; found: 61.54% C, 4.93% H, 5.75% S.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (*I*)

To a solution of compound *VI* (0.704 g, 1.34 mmol) in 95% aqueous *N*,*N*-dimethylformamide (12 ml) was added calcium carbonate (0.2 g, 2 mmol). The reaction mixture was stirred at 150 °C for 16 h, then concentrated under reduced pressure. The remaining mixture was treated with chloroform, filtered and the solvent was evaporated. Resulting crude mixture of 2,5- and 3,5-di-*O*-benzoyl derivatives *VII* was dissolved in dry pyridine (9 ml) and allowed to react with benzoyl chloride (0.59 ml, 5.07 mmol) for 48 h at room temperature. The mixture was poured onto ice, acidified with aqueous HCl (1 : 1) to pH 2 and extracted with dichloromethane. The extract was washed with water and saturated $NaHCO_3$, dried and evaporated to afford crude *VIII* (0.81 g) as an anomeric mixture moving as a single spot in TLC with different solvents. To stirred and cooled (0 °C) solution of crude *VIII* in a mixture of glacial acetic acid (15 ml) and acetic anhydride (3.5 ml) was added concentrated H_2SO_4 (0.7 ml). The mixture was stirred at room temperature for 4 h, then poured onto ice (30 g) and extracted with dichloromethane. The extract was washed with water and saturated $NaHCO_3$, dried and evaporated. Crystallization of the residue from ethanol gave β-anomer of *I* (0.301 g, 45%), m.p. 130 °C and $[\alpha]_D$ + 38.0° (*c* 1.38); ref.[3] m.p. 130 – 131 °C; $[\alpha]_D$ + 44.2° (*c* 1.32). ^{1}H NMR spectrum: 2.0 s, 3 H (CH_3, Ac); 4.53 dd, 1 H, *J*(5a,5b) = 12.8, *J*(4,5a) = 5.4 (H-5a); 4.8 m, 2 H, *J*(4,5b) = 3.7 (H-4 and H-5b); 4.81 dd, 1 H, *J*(1,2) = 0.9, *J*(2,3) = 4.7 (H-2); 5.93 dd, 1 H, *J*(3,4) = 6.7 (H-3); 6.44 broad s, 1 H (H-1); 7.25 – 8.16 m, 15 H (arom. from 3 Bz). The mother liquor was evaporated to give an oil (0.343 g, 51%) containing α-anomer of *I* as the major component (α : β = 20 : 3, according to NMR). ^{1}H NMR spectrum: 2.16 s, 3 H (CH_3 from Ac); 4.63 dd, 1 H, *J*(5a,5b) = 12.2, *J*(4,5a) = 3.6 (H-5a); 4.73 dd, 1 H, *J*(4,5b) = 3.2 (H-5b); 4.83 m, 1 H, *J*(3,4) = 2.6 (H-4); 5.65 dd, 1 H, *J*(1,2) = 4.5; *J*(2,3) = 6.5 (H-2); 5.85 dd, 1 H (H-3); 6.73 d, 1 H (H-1); 7.4 – 8.07 m, 15 H (arom. 3 × Bz).

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