Alternative syntheses of methylated sugars. XVI.* Synthesis of methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside

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Benzylation of methyl 2,3-anhydro-β-D-ribopyranoside with benzyl bromide and sodium hydride in 1,2-dimethoxyethane gave methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside in high yield. Alkaline hydrolysis followed by acetylation of the formed methyl 4-*O*-benzyl-β-D-xylopyranoside, and cleavage of the benzyl group by hydrogenolysis gave crystalline methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside. All intermediates of the synthesis were obtained in crystalline state.

В большом выходе был получен метил-2,3-ангидро-4-*O*-бензил-β-D-рибопиранозид бензилированием метил-2,3-ангидро-β-D-рибопиранозида посредством бензилбромида и гидрида натрия в среде 1,2-диметоксиэтана. Гидролизом в щелочной среде и последующим ацетилированием образующегося метил-4-*O*-бензил-β-D-ксилопиранозида и гидрогенолитическим отщеплением бензиловой группы был получен метил-2,3-ди-*O*-ацетил-β-D-ксилопиранозид в кристаллическом состоянии. Все промежуточные продукты были также получены в кристаллическом состоянии.

Opening of the epoxide ring in alkyl 2,3-anhydro-β-D-ribosides (and their L-counterparts) with base occurs predominantly by an attack of the nucleophile at C-3 and the corresponding *xylo* derivative can be isolated in high yield [1]. Since the 2,3-di-*O*-derivatives cannot be obtained in satisfactory yields by partial substitution of the hydroxyl groups in alkyl xylopyranosides, alkyl 2,3-anhydro-β-D-ribosides are important intermediates in the synthesis of 4-*O*-substituted derivatives of D-xylose. However, this type of substances cannot be prepared from

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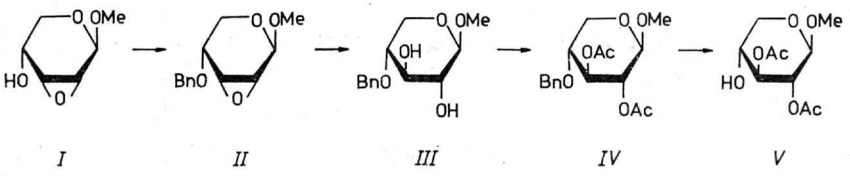
the corresponding alkyl 2,3-anhydro-β-D-ribosides when the 4-*O*-substituent is labile under the conditions of the opening of the anhydro ring or is prone to be modified under these conditions. The present paper describes the synthesis (Scheme 1) of methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside (*V*) having none of the aforementioned drawbacks.



I *II* *III* *IV* *V*

Scheme 1

Benzylation of the L-enantiomorph of *I* by conventional methods has been studied and the maximum yield of the corresponding 4-*O*-benzyl derivative was 60% [2]. *Shmyrina et al.* [3] benzylated methyl 2,3-anhydro-β-L-ribopyranoside with benzyl bromide and silver oxide in *N,N*-dimethylformamide and obtained the 4-*O*-benzyl derivative in 80% yield after a reaction time of 72 h. We have monitored by thin-layer chromatography on Silica gel G the formation of the sodium salt of *I*, affected by treatment of *I* with sodium hydride in 1,2-dimethoxyethane, and found that no unwanted reaction of the starting material occurred during this operation. The sodium salt reacted quickly at room temperature with benzyl bromide, the conversion was complete within 1 h (t.l.c.) and the crystalline product *II* was isolated in high yield.

Opening of the anhydro ring in *II* was accomplished by its treatment with aqueous, 10% potassium hydroxide under mild reflux for 4 h. The D-*xylo* configuration of the crystalline dihydroxy derivative *III* isolated from this conversion, as well as of the products of its further conversion, was proved by p.m.r. spectrometry namely by the values of the coupling constants of the ring protons (see Experimental). Although the yield of compound *III* obtained in this way was good, from the point of view of the preparation of *V* it is more convenient to skip the isolation of *III*, *i.e.* to acetylate the crude reaction product present in the processed reaction mixture of the alkaline hydrolysis of *II*. The conversion *II* → *IV* carried out in this manner gives 79.6% yield of crystalline diacetate *IV*. The title substance *V* was obtained in a virtually theoretical yield by catalytical hydrogenolysis of *IV*.

The coupling constants $J_{1,2}$ and $J_{2,3}$ (~5.5 and 7 Hz, respectively) found for *III* in its p.m.r. spectrum are smaller than would be expected for a diaxial arrangement of H-1, H-2, and H-3. This suggests that compound *III* exists under the conditions of the measurement as a mixture of $^4C_1$ and $^1C_4$ conformers. The location of the

acetoxy groups at C-2 and C-3 in *IV* and *V* follows from the observed downfield shift of the H-2 and H-3 signals, compared to the chemical shift of the signals of the same protons in the spectrum of *III*. The signal of H-3 in the spectrum of the 4-hydroxy derivative *V* is shifted upfield, compared to the signal of the same proton in *IV*. The signal corresponding to H-3 appears in the spectrum of *IV* at a lower field as a result of the paramagnetic deshielding effect of the aromatic ring of the benzyl group at C-4.

Experimental

Melting points were determined on a Kofler hot-stage. Optical rotations were measured with a Perkin—Elmer automatic polarimeter, Model 141. P.m.r. spectra (80 MHz) for solutions in chloroform-d were obtained with a Tesla BS 487 B spectrometer using tetramethylsilane as internal standard. The proton-signal assignments were made by the Indor technique. Below, only the data extracted from definite signals are presented. Thin-layer chromatography on Silica gel G (Merck, A. G., Darmstadt) and preparative chromatography on columns of dry-packed silica gel (Merck, A.G., Darmstadt, prod. No. 9385) which, prior to packing was equilibrated with 40% of the mobile phase, instead of the recommended 10% [4], was performed with: *A*. benzene—acetone 10:1, *B*. chloroform—acetone 6:1, *C*. benzene—ethyl acetate 10:1, and *D*. benzene—ethyl acetate 6:1. Detection was carried out by spraying with 5% (v/v) sulfuric acid in ethanol and heating until permanent char spots were visible. Unless otherwise stated the solutions were dried with anhydrous sodium sulfate and concentrated at 40°C/2 kPa. 1,2-Dimethoxyethane was dried [5] and stored over sodium hydride.

Methyl 2,3-anhydro-4-O-benzyl-β-D-ribopyranoside (II)

Powdered sodium hydride (1.7 g) was added at 0°C to the solution of *I* [6] (5 g) in 1,2-dimethoxyethane (50 ml) and the solution was stirred with the exclusion of atmospheric moisture and carbon dioxide for 10 min at room temperature. Only the starting material (R_f 0.2) could be then detected by t.l.c. (solvent *A*). After addition of benzyl bromide (4.9 ml) the mixture was stirred for 1 h at room temperature and t.l.c. then showed that the conversion of the starting material to the product *II* (R_f 0.4) was complete. The excess of the benzylating reagent was destroyed by an addition (0°C) of methanol (~20 ml), water (100 ml) was added, and the organic solvents were removed. The aqueous phase was extracted with chloroform and the extracts were backwashed with water, dried and concentrated to give the crude product containing, as shown by t.l.c., a single sugar component. Crystallization from isopropanol—hexane gave *II* (4.5 g). Further crops of the same material (2.5 g, total yield 86.6%) were obtained from the mother liquor by crystallization and chromatography. A portion was recrystallized from the same solvent to give the analytical sample of *II* melting at 44—44.5°C and having $[\alpha]_D^{22}$ +16° (*c* 0.8, chloroform). For the L-enantiomorph Ref. [2] gives m.p. 44—45°C and $[\alpha]_D$ −12° (*c* 1, chloroform), Ref. [3] gives m.p. 42—43°C and $[\alpha]_D$ −6.8°.

P.m.r. data (δ): 4.80 (1-proton singlet, H-1), 3.15 (1-proton doublet, H-2, $J_{2,3}$ 4 Hz), ~3.43 (quartet of H-3 overlapped with the signal of the methyl protons, $J_{3,4}$ ~3.5 Hz), 3.48 (singlet, OCH_3) 4.60, 4.78 (two doublets, CH_2, J_{gem} 12 Hz), 7.29 (sharp 5-proton singlet, aromatic protons).

For $C_{13}H_{16}O_4$ (236.26) calculated: 66.08% C, 6.82% H; found: 65.96% C, 7.00% H.

Methyl 4-O-benzyl-β-D-xylopyranoside (III)

A suspension of *II* (5.5 g) in 10% aqueous potassium hydroxide (275 ml) was stirred at 105—110°C with the exclusion of atmospheric carbon dioxide. After 4 h, at which time a clear, colourless solution was formed, t.l.c. (solvent *A*) showed that no starting material was present. The solution was cooled to room temperature, neutralized with dilute sulfuric acid, thoroughly extracted with chloroform, the extracts were dried and processed in the usual manner. Crystallization from isopropanol—hexane gave the product *III* (R_f 0.4, solvent *B*, 4.9 g, 83%). A portion, when recrystallized from the same solvent melted at 99—100°C and had $[\alpha]_D^{20}$ −76° (*c* 1.1, chloroform).

P.m.r. data (δ): 4.24 (1-proton doublet, H-1, $J_{1,2}$ ~5.5 Hz), ~3.40 (quartet, H-2, $J_{2,3}$ 7 Hz), ~3.61 (broadened triplet, H-3) 3.48 (singlet, OCH_3), 3.75 (broadened 2-proton singlet which disappeared on deuteration, 2 × OH), 4.58, 4.72 (two doublets, CH_2, J_{gem} 12 Hz), 7.33 (sharp 5-proton singlet, aromatic protons).

For $C_{13}H_{18}O_5$ (254.27) calculated: 61.40% C, 7.13% H; found: 61.28% C, 7.04% H.

Methyl 2,3-di-O-acetyl-4-O-benzyl-β-D-xylopyranoside (IV)

a) Acetic anhydride (10 ml) was added to a solution of *III* (5.2 g) in dry pyridine (20 ml) and the reaction mixture was left at room temperature for 3 h. After addition of methanol, to destroy the excess of the acetylating agent, the solution was concentrated, finally with toluene (60°C) to remove all pyridine. Crystallization from ethanol (0°C) gave *IV* (5 g, R_f 0.4, solvent *C*), and a further crop of the same material (0.8 g, total yield 84%) was obtained from the concentrated mother liquors by crystallization from isopropyl ether. The analytical sample was obtained by recrystallization of a portion from ethanol, m.p. 73—74°C, $[\alpha]_D^{20}$ −60° (*c* 1, chloroform).

P.m.r. data (δ): 4.31 (1-proton doublet, H-1, $J_{1,2}$ 7.1 Hz), 4.81 (1-proton quartet, H-2, $J_{2,3}$ 9 Hz), 5.14 (1-proton triplet, H-3, $J_{3,4}$ 8.5 Hz), 3.63 (1-proton octet, H-4), 3.42 (3-proton singlet, OCH_3), 1.88 (6-proton singlet, 2 × $COCH_3$), 4.57 (2-proton singlet, CH_2), 7.13 (5-proton singlet, aromatic protons).

For $C_{17}H_{22}O_7$ (338.35) calculated: 60.34% C, 6.55% H; found: 60.30% C, 6.52% H.

b) A suspension of *II* (11.7 g) in aqueous 10% potassium hydroxide solution (600 ml) was heated in a 2 l round-bottom flask for 4 h under gentle reflux and with the exclusion of atmospheric carbon dioxide. The solution was cooled (0°C) and neutralized (pH 7.5) at the same temperature with carbon dioxide. After concentration, finally with co-distillation with toluene at 60°C, pyridine (50 ml) and acetic anhydride (50 ml) were added, and the mixture

was left at room temperature for 18 h. The excess of the acetylating reagent was destroyed by an addition of methanol and the mixture was concentrated. Water (0°C) was added to the solid residue, the insoluble material was collected by filtration, washed with ice-water and partitioned between chloroform and water. The chloroform solution was dried, concentrated and the product was crystallized from ethanol to give *IV* (13.3 g, total yield of the conversion *II*→*IV* 79.6%).

Methyl 2,3-di-O-acetyl-β-D-xylopyranoside (V)

A mixture of *IV* (5.5 g) and 5% palladium-on-charcoal catalyst (0.5 g) in methanol (100 ml) was stirred in the atmosphere of hydrogen until t.l.c. (solvent *D*) showed complete conversion of the starting material (R_f 0.6) to one product (R_f 0.1). The reaction mixture was processed in the usual manner and crystallization from ether—isopropyl ether gave *V* (3.6 g, 89%). A portion, when recrystallized from the same solvent mixture melted at 82—83°C and had $[\alpha]_D^{20}$ −77.4° (*c* 1.2, chloroform).

P.m.r. data (δ): 4.36 (1-proton doublet, H-1, $J_{1,2}$ 7.2 Hz), 4.75 (triplet, H-2, $J_{2,3}$ 9 Hz), 4.81 (quartet, H-3), 3.44 (3-proton singlet, OCH_3), 2.06 (6-proton singlet, $2 \times COCH_3$), ~3.59 (broadened singlet which disappeared on deuteration, OH).

For $C_{10}H_{16}O_7$ (248. 23) calculated: 48.38% C, 6.50% H; found: 48.21% C, 6.57% H.

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