Preparation of intermediates for the sequential synthesis of xylodextrins

P. KOVÁČ, A. ČULÁKOVÁ, E. PETRÁKOVÁ, and J. HIRSCH

Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava

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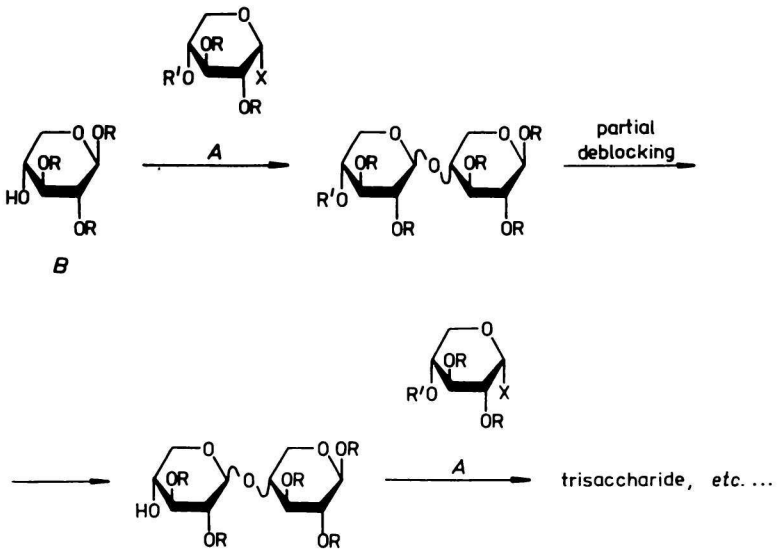
Hydrolysis of methyl 4-*O*-benzyl-β-D-xylopyranoside followed by acetylation of the formed 4-*O*-benzyl-D-xylose gave 1,2,3-tri-*O*-acetyl-4-*O*-benzyl-β-D-xylopyranose in good yield. The foregoing compound, bearing at C-4 a selectively removable blocking group, is a precursor of a glycosyl halide which can be used for sequential construction of β-(1→4)-D-xylooligosaccharides (xylodextrins). 1,2,3-Tri-*O*-acetyl-β-D-xylopyranose, the key nucleophile in the sequential synthesis of xylodextrins, was conveniently obtained from 1,2,3-tri-*O*-acetyl-4-*O*-benzyl-β-D-xylopyranose by hydrogenolysis.

Гидролизом метил 4-*O*-бензил-β-D-ксилопиранозида и последующим ацетилированием возникшей 4-*O*-бензил-D-ксилозы ацетангидридом в присутствии безводного ацетата натрия была получена 1,2,3-три-*O*-ацетил-4-*O*-бензил-β-D-ксилопираноза. Последнее вещество, содержащее избирательно удалительную, блокирующую группу на С-4, является прекурсором гликозилгалида подходящего для постепенного синтеза β-(1→4)-D-ксилоолигосахаридов (ксилодекстринов). Тоже описан более простой синтез 1,2,3-три-*O*-ацетил-β-D-ксилопиранозы, являющейся фундаментальным нуклеофилем постепенного синтеза ксилодекстринов, осуществлен отщеплением бензильной группы из 1,2,3-три-*O*-ацетил-4-*O*-бензил-β-D-ксилопиранозы гидрогенолизом.

β-(1→4)-D-Xylooligosaccharides (xylodextrins) are found in partial hydrolyzates of xylans from plants and they can be isolated, albeit laboriously and only in low yields, by chromatography [1—3]. Of the xylodextrin series only xylobiose has been chemically synthesized [4—6]. Chemical synthesis of higher oligosaccharides with defined site and stereochemistry of the inter sugar linkages requires methods of stepwise construction of the desired molecule (sequential synthesis). An important factor here is the selection of blocking groups in the reacting molecules, namely, a glycosyl halide and a nucleophile, which should assure the formation of the glycosidic linkage at the desired position. Further, certain of the blocking groups should be selectively removable to yield, thus, the nucleophile suitable for the next condensation step. Also, in the last step of the synthesis it should be

possible to remove the blocking groups completely without affecting the desired structure. The sequential synthesis of β-(1→4)-D-xylooligosaccharides requires a glycosyl halide of the *A* type (Scheme 1) containing permanent blocking groups



Scheme 1

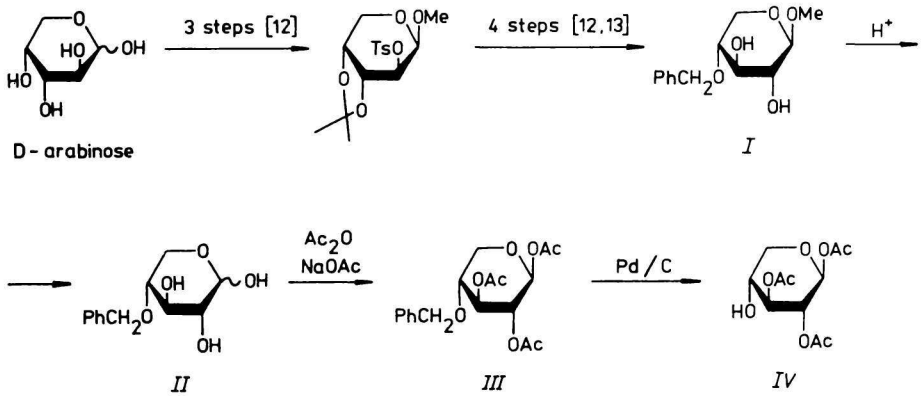
(R) at C-2 and C-3, and a temporary blocking group at C-4 (R′) that can be selectively removed. Condensation of the halide *A* with a suitable nucleophile, for example *B*, would yield a disaccharide derivative having at C-4 of its nonreducing end-group a selectively removable substituent R′. Removal of this group would produce a suitable nucleophile for another condensation with *A*. Theoretically, repeating the outlined scheme several times would then afford higher (1→4)-D-xylooligosaccharides. Practical limitation of this approach lies in yields of the desired products and the availability of methods of their isolation from reaction mixtures. Owing to difficulties involved in the preparation of intermediates of the *A* and *B* types a systematic sequential synthesis of β-(1→4)-D--xylooligosaccharides has not been carried out as yet.

Recently *Utille et al.* described a synthesis of 2,3-di-*O*-acetyl-4-*O*-chloroacetyl-α-D-xylopyranosyl bromide [7] (a glycosyl halide of *A* type) and also of 1,2,3-tri-*O*-acetyl-β-D-xylopyranose [8] (a nucleophile of *B* type). However, preparation of these substances requires isolation of several of precursors by chromatography and, therefore, the procedures [7, 8] are not suitable for large-scale work. Only xylobiose per-*O*-acetate has been synthesized by the cited

authors [9] (by condensation of 1,2,3-tri-*O*-acetyl-β-D-xylopyranose with the readily obtainable [10] 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide).

In the present work we describe preparation of 1,2,3-tri-*O*-acetyl-β-D-xylopyranose (*IV*) by an alternative, shorter pathway which does not require isolation of any of the intermediates by chromatography and the desired compound is obtained in a very good overall yield. The precursor of *IV*, namely, 1,2,3-tri-*O*-acetyl-4-*O*-benzyl-β-D-xylopyranose (*III*) can be converted by treatment with hydrogen bromide into the corresponding glycosyl bromide, another glycosyl halide of the *A* type, which, according to Scheme 1, was proved suitable for sequential synthesis of (1→4)-D-xylooligosaccharides [11].

The starting point in the present synthesis of *IV* (for overall reaction pathway, see Scheme 2) was methyl 4-*O*-benzyl-β-D-xylopyranoside (*I*), a substance readily



Scheme 2

obtainable from D-arabinose [12, 13]. Acid hydrolysis of *I* afforded hitherto unknown, crystalline 4-*O*-benzyl-D-xylopyranose (*II*) which was acetylated with acetic anhydride in the presence of sodium acetate to give a good yield of the crystalline β-acetate *III*. That the low yield observed in the conversion *I*→*II* (see Experimental) was caused by irreversible adsorption of *II* on the ion-exchange resin used to neutralize the reaction mixture was confirmed when high yield of *III* was obtained in the conversion *I*→*III* without isolation of *II*. Cleavage of the benzyl group from *III* by hydrogenolysis afforded an excellent yield of the 4-hydroxy derivative *IV*, the physical constants of which agreed with the data in the literature [8]. Good crystallizing properties of the acetate *III* make it possible to prepare this substance conveniently from crystalline methyl 3,4-*O*-isopropylidene-2-*O*-tosyl-β-D-arabinopyranoside without isolation of intermediates (see Experimental, preparation of *III*, procedure *c*). In this way compound *III* can be obtained in an overall yield of ~45%.

Experimental

Melting points were detected on a Kofler hot-stage. Optical rotations were measured at 22°C with a Perkin—Elmer Model 141 automatic polarimeter. Thin-layer chromatography on Silica Gel G and preparative chromatography on dry-packed columns of Silica Gel 60 was carried out with *A*. chloroform—acetone 2 : 1, *B*. benzene—acetone 5 : 1, and *C*. benzene—acetone 10 : 1. Detection was effected by spraying with 5% (v/v) sulfuric acid in ethanol and heating until permanent char spots were visible. Solutions were dried with anhydrous sodium sulfate and concentrated at 40°C/2 kPa.

The ^{13}C-n.m.r. spectra (for solvents and standards see Table 1) were measured in a deuterium-lock mode and at room temperature using Jeol JNM FX-60 spectrometer. Proton decoupled FT spectra were taken at a pulse width of 4 μs (45° flip angle), a repetition time of 2 s, sweep width 4000 Hz, and 8 K real data points.

4-O-Benzyl-D-xylopyranose (II)

A mixture of *I* (2 g) and 1 mol dm^{-3} HCl (40 ml) was heated at 90°C for 21/2 h at which time t.l.c. (solvent *A*) showed complete conversion of the starting material (R_f 0.6) into a product (R_f 0.2). The mixture was neutralized with Amberlite IRA 45 (CO_3^{2-}) resin, filtered, the resin was washed several times with hot water and methanol and the combined filtrates were concentrated. The solid residue was crystallized from ethanol to give *II* (0.8 g, 42%) which was chromatographically pure. Recrystallization from the same solvent yielded an anomeric mixture of the title compound melting unsharply at 167—169°C (with sintering at 159°C), $[\alpha]_D = +39°$ (extrapolation) → $+32.5°$ (6 min) → $+9.9°$ (const., 21/2 h, *c* 0.6, water).

For $C_{12}H_{16}O_5$ (240.25) calculated: 59.99% C, 6.71% H; found: 60.03% C, 6.74% H.

1,2,3-Tri-O-acetyl-4-O-benzyl-β-D-xylopyranose (III)

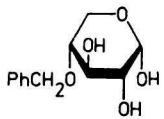
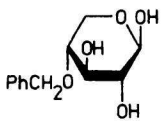
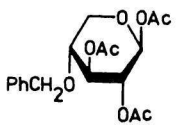
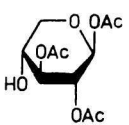
a) Compound *II* (1 g) was added at 100°C to a stirred mixture of acetic anhydride (2 ml) and anhydrous sodium acetate (0.5 g). The mixture was stirred at 100°C for 2 h and processed conventionally to give *III* (1.2 g, 79%), m.p. 102—104°C. The ^{13}C-n.m.r. spectrum showed a sole signal in the region of anomeric resonances (Table 1), confirming that pure β-anomer was obtained. Recrystallization of a portion from the same solvent gave the analytical sample melting at 103—104°C and having $[\alpha]_D = -27.8°$ (*c* 1, chloroform).

For $C_{18}H_{22}O_8$ (366.36) calculated: 59.01% C, 6.05% H; found: 59.23% C, 6.27% H.

b) Compound *I* (2 g) was hydrolyzed as described for the preparation of *II*, the hydrolyzate was neutralized with solid sodium hydrogen carbonate and concentrated, finally with coevaporation with toluene to assure dehydration. Anhydrous sodium acetate (1.5 g) was added, followed by acetic anhydride (6 ml), the mixture was stirred at 100°C for 2 h and processes conventionally. Crystallization from ethanol gave 2.2 g (72%) of material melting at 102—104°C.

Table 1

^{13}C-NMR spectral data for the prepared substances

Compound	Solvent	Chemical shift (p.p.m.)					
		C-1	C-2	C-3	C-4	C-5	CH_2 (benzylic)
	D_2O[a]	93.4	72.8	73.3	78.4	60.4	74.3
	D_2O[b]	97.9	75.4	76.3	78.4	64.6	74.3
	$CDCl_3$[c]	92.3	70.4	73.2	74.5	64.1	72.7
	$CHCl_3$[c]	92.3	69.9	74.7	67.8	65.8	

a) Internal standard methanol (chemical shift *vs.* tetramethylsilane 50.15 p.p.m.).
b) Preponderating form at the equilibrium.
c) Internal standard tetramethylsilane.

c) Methyl 3,4-*O*-isopropylidene-2-*O*-*p*-toluenesulfonyl-β-D-arabinopyranoside (214 g) was deisopropylidenated by heating in 50% acetic acid and then processed conventionally. The solution of the crude product (190 g) in methanol (190 ml) was treated with a solution of sodium (43 g) in methanol (1075 ml). After 1/2 h at room temperature t.l.c. (solvent *B*) showed complete conversion of the starting material (R_f 0.3) into a product (R_f 0.5). The separated sodium *p*-toluenesulfonate was filtered off, the filtrate was neutralized (pH 7.5) with dilute sulfuric acid and concentrated (~300 ml). The aqueous solution was thoroughly extracted with chloroform and the crude product, obtained on concentration of the chloroform extracts and containing chromatographically almost pure methyl 2,3-anhydro-β-D-ribopyranoside, was benzylated [13]. A mixture of the crude benzylation product was heated (100—105°C) with stirring and exclusion of atmospheric carbon dioxide in 10% aqueous potassium hydroxide (3500 ml) and when t.l.c. [13] showed that the reaction was complete (~10 h) the mixture was neutralized with solid carbon dioxide. The mixture was extracted with chloroform and the crude product was hydrolyzed with 1 mol dm^{-3} HCl as described above. The hydrolyzate was neutralized (pH 5) with solid sodium carbonate and then with sodium hydrogen carbonate (pH 7), and concentrated to dryness. The solid residue was pulverized and added to a stirred mixture of acetic anhydride (250 ml) and anhydrous sodium acetate (70 g). When the acetylation was complete (1 h, 100°C, t.l.c.) the mixture was processed conventionally and the brown solution of the crude product in benzene was decolorized by filtration through a layer of silica gel (~100 g). The filtrate was concentrated and crystallization from ethanol (twice) gave chromatographically pure (R_f 0.6, solvent *C*), colourless product (81 g) melting at 103—104°C. The combined mother liquors were deacetylated (Zemplén) and crystallization from methanol gave 4-*O*-benzyl-D-xylose (16 g) which, when acetylated as described in *a* afforded a further crop of *III* (19 g, total yield 45.8%), m.p. 102—104°C.

1,2,3-Tri-O-acetyl-β-D-xylopyranose (IV)

A mixture of *III* (4.6 g) and 5% palladium-on-charcoal (0.5 g) in methanol (250 ml) was stirred at room temperature under hydrogen, and when t.l.c. showed that the reaction was complete the mixture was processed conventionally. Crystallization from ethanol gave *IV* (3.1 g, 89%), m.p. 112—113°C, Ref. [8] gives m.p. 112°C.

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