Alternative syntheses of methylated sugars. XXII.* Synthesis of methyl β-xylotrioside

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Condensation of penta-*O*-acetyl-α-xylobiosyl bromide with methyl 2,3-anhydro-β-D-ribopyranoside followed by deacetylation afforded methyl 2,3-anhydro-4-*O*-[4-*O*-(β-D-xylopyranosyl)-β-D-xylopyranosyl]-β-D-ribopyranoside. Subsequent alkaline hydrolysis gave crystalline, hitherto unknown methyl β-xylotrioside which on methylation yielded crystalline heptamethyl ether and on acetylation a crystalline hepta-*O*-acetate. The same acetyl derivative was isolated from the reaction of penta-*O*-acetyl-α-xylobiosyl bromide with methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside.

Деацетилированием продукта конденсации пента-*O*-ацетил-α-ксилобиозилбромида с метил-2,3-ангидро-β-D-рибопиранозидом был получен метил-2,3-ангидро-4-*O*-[4-*O*-(β-D-ксилопиранозил)-β-D-ксилопиранозил]-β-D-рибопиранозид. Щелочным гидролизом последнего был получен до сих пор неописанный кристаллический метил-β-ксилотриозид, из которого метилированием был получен также кристаллический гептаметильный эфир и ацетилированием кристаллический гепта-*O*-ацетат. Одинаковый ацетат был изолирован после реакции пента-*O*-ацетил-α-ксилобиозилбромида с метил-2,3-ди-*O*-ацетил-β-D-ксилопиранозидом.

Xylobiose [4-*O*-(β-D-xylopyranosyl)-D-xylopyranose] and its higher homologues (xylodextrins), the basic structural unit of xylan type polysaccharides, can be obtained from the products of partial hydrolysis of these abundant natural polymers. β-Glycosides of xylodextrins are important model compounds in studies of various properties of xylans because the β-glycosidically linked aglycon imitates the situation in the main polysaccharide backbone composed of β-D-xylopyranoses. Isolation of xylooligosaccharides from products of partial depolymerization of

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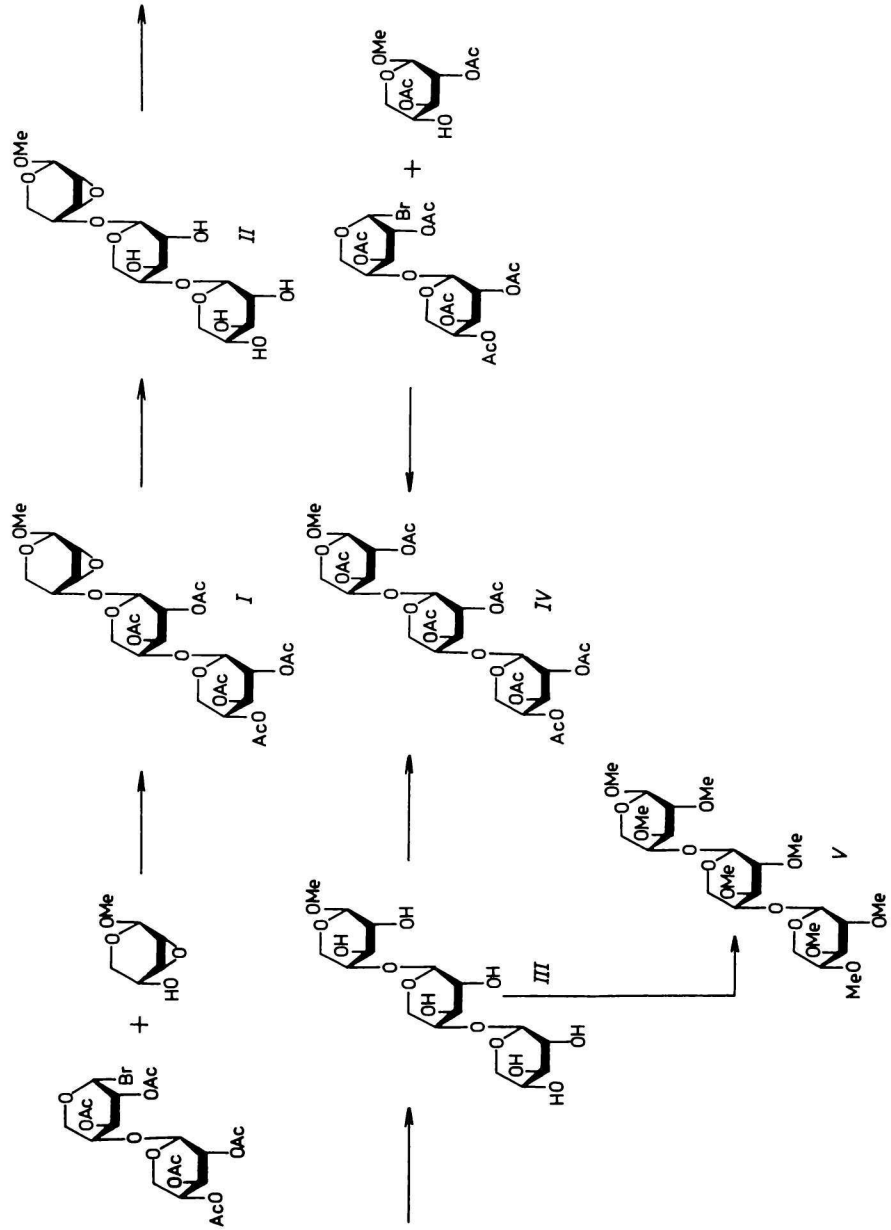
xylans requires separation of complicated mixtures by chromatography making unpractical the preparation of larger amounts of derivatives of xylodextrins from xylooligosaccharides obtained in this way. Nevertheless, the sole methyl β-glycoside in the series of xylodextrins known so far, methyl β-xylobioside, was originally synthesized by *Whistler et al.* [1] starting with xylobiose isolated from a natural source. In this Series we have previously described simple chemical syntheses of xylobiose [2] and its methyl β-glycoside [3] using as nucleophiles in the formation of (1→4)-β-glycosidic linkage benzyl and methyl 2,3-anhydro-β-D-ribopyranosides. This type of compound is very useful for making 4-*O*-substituted D-xylose derivatives since opening of the epoxide ring in alkyl 2,3-anhydro-β-D-ribosides is a highly stereoselective reaction resulting in the formation of D-xylose derivatives in high yield [4]. The present work describes syntheses of methyl β-xylotrioside (*III*) {methyl 4-*O*-[4-*O*-(β-D-xylopyranosyl)-β-D-xylopyranosyl]-β-D-xylopyranoside} based on the condensation of penta-*O*-acetyl-α-xylobiosyl bromide (prepared by treatment of the readily obtainable hexa-*O*-acetyl-β-xylobiose with hydrogen bromide in dichloromethane) with methyl 2,3-anhydro-β-D-ribopyranoside [5] or methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside [6] (Scheme 1).

From the products of condensation of penta-*O*-acetyl-α-xylobiosyl bromide with methyl 2,3-anhydro-β-D-ribopyranoside compound *I* could not be obtained crystalline even after chromatography of the crude product. Some of the material eluted from the silica gel column appeared as one spot on t.l.c. but it was most probably a mixture of *I* with the reaction by-products. This was strongly indicated when the crude product was deacetylated and chromatographed: the amount of *II* which could be crystallized (see Experimental) was substantially smaller than the amount of the fraction having the chromatographic mobility of *II*. Compound *I* could be obtained crystalline only by acetylation of *II*. The mass spectrum of *I* showed, *inter alia*, peaks characteristic of the cleavage of the glycosidic linkage (*m/z* 475, 345, 259, and 129) from which the molecular weight of the substance could be calculated [7] ($M = 475 + 129 + 16 = 620$, or $M = 259 + 345 + 16 = 620$). Thus, from the practical point of view the crystalline intermediate *II* was most conveniently obtained without the isolation of *I*, by deacetylation of the crude condensation product and chromatography. The elemental analysis of *II* (obtained in this way in ~50% yield, based on the amount of methyl 2,3-anhydro-β-D-ribopyranoside) agreed with the compound's being a hemihydrate. Its alkaline hydrolysis with 10% aqueous potassium hydroxide gave, in an excellent yield, crystalline glycoside *III* which, in turn, produced crystalline heptamethyl ether *V*. From the peaks at *m/z* 335 and 175 present in the mass spectrum of *V* the molecular weight of the substance could be calculated [7] ($M = 335 + 175 + 16 = 526$) showing, thus, that it was a fully methylated methylpentotrioside. The (1→3) linkage could be excluded [8], but the two (1→4) interglycosidic linkages could not be confirmed.



Scheme 1

Since the intermediate *II* could not be obtained without recourse to chromatography an attempt was made to synthesize *III via* condensation of penta-*O*-acetyl-α-xylobiosyl bromide with methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside. The latter compound can be easily obtained [6] in 60—70% yield from methyl 2,3-anhydro-β-D-ribopyranoside and if its reaction with the xylobiosyl bromide gave a good yield of *IV*, isolable without chromatography by crystallization, this route to *III* would be more advantageous. The successful condensation of acetobromoxylobiose with methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside was confirmed by the mass spectrum of *IV* containing peaks at *m/z* 475, 447, 259, and 231 from which the molecular weight ($M = 475 + 231 + 16 = 722$, or $M = 447 + 259 + 16 = 722$) could be calculated [7]. Unfortunately, the per-*O*-acetate *IV*, although crystalline and identical with the substance obtained from *III* by acetylation, could be obtained pure again only with the aid of chromatography. Moreover, the yield of pure *IV* obtained in this way was somewhat lower than the yield of *II* obtained over the two steps. Thus, of the two procedures leading to *III* the one using methyl 2,3-anhydro-β-D-ribopyranoside as the starting mateial is preparatively more feasible.

Experimental

Melting points were determined on a Kofler hot-stage. Optical rotations were measured using a Perkin—Elmer Model 141 automatic polarimeter. Mass spectra (74 eV) were obtained with a JMS 100 D instrument. Thin-layer chromatography (t.l.c.) on Silica gel G and preparative chromatography on columns of dry-packed silica gel which, prior to packing, was equilibrated with 40% (v/w) of the mobile phase, was performed with: *A*. benzene—acetone 8:1, *B*. carbon tetrachloride—acetone 3.5:1, *C*. chloroform—methanol 3.5:1, and *D*. benzene—acetone 4:1. Detection was effected by spraying with 5% (v/v) sulfuric acid in ethanol and heating until permanent char spots were visible. The solution of hydrogen bromide in dichloromethane [9] used in the preparation of penta-*O*-acetyl-α-xylobiosyl bromide contained 0.1 g HBr/ml (determined by weighing). The solutions in organic solvents were dried with anhydrous sodium sulfate and concentrated at 40°C/2 kPa.

Methyl 2,3-anhydro-4-O-[4-O-(β-D-xylopyranosyl)-β-D-xylopyranosyl]-β-D-ribopyranoside (II) and its penta-O-acetate (I)

A solution of hydrogen bromide in dichloromethane (41 ml; 50.66 mmol) was added to a solution of hexa-*O*-acetyl-β-xylobiose [2] (11 g; 20.58 mmol) in dichloromethane (40 ml). After 1/2 h at room temperature, at which time t.l.c. (solvent *A*) showed complete

conversion of the starting material (R_f 0.5) to the product (R_f 0.6)*, the solution was concentrated with addition of toluene. A solution of the thus prepared glycosyl halide in a minimum amount of acetonitrile was added with stirring to a mixture of methyl 2,3-anhydro-β-D-ribopyranoside (2 g; 13.7 mmol), drierite (6 g), and mercuric cyanide (2.6 g; 10.3 mmol) in acetonitrile (40 ml), which had been stirred for 1/2 h. The mixture was stirred with the exclusion of moisture for 1 h and t.l.c. (solvent *B*) then showed the absence of the bromide (R_f 0.6) and that only traces of the nucleophile (R_f 0.45) were present. The main component of the reaction mixture was material having R_f 0.35 and a small amount of penta-*O*-acetyl-α,β-xylobiose (R_f 0.25) was also present. The mixture was concentrated and the residue was partitioned between chloroform and 1 M aqueous potassium bromide. The chloroform solution was washed with water, dried, concentrated and methanolic 1 M sodium methoxide (2 ml) was added to the solution of the residue in methanol. After 2 h at room temperature t.l.c. (solvent *B* and *C*) showed that the reaction was complete and the crude product was eluted from a column of silica gel. The main product (R_f 0.6, solvent *C*) was collected and *II* crystallized readily from water—acetone (1:3) in a chromatographically pure state (2.4 g), m.p. 111—114°C, $[\alpha]_D^{22} = -59.9°$ (*c* 1, water). Further amount of the same material (0.45 g, total yield 50.9%), sufficiently pure for the next step, was obtained from the concentrated mother liquor. The material that now remained in the mother liquor (~2 g) had the same chromatographic mobility as *II* and could not be induced to crystallize. It was discarded and in the work described below only crystalline material was used. After recrystallization the above given physical constants of *II* did not change significantly.

For $C_{16}H_{26}O_{12} \cdot 0.5H_2O$ (419.38) calculated: 45.82% C, 6.49% H; found: 45.83% C, 6.62% H.

To a solution of compound *II* (50 mg) in pyridine (0.5 ml) was added acetic anhydride (0.5 ml) and the mixture was left at room temperature for 16 h. Isolation in the usual manner gave *I* (66 mg; 89%), m.p. 129—131°C (from ethanol, twice), $[\alpha]_D^{22} = -78.8°$ (*c* 0.83, chloroform).

For $C_{26}H_{36}O_{17}$ (620.55) calculated: 50.32% C, 5.84% H; found: 50.18% C, 6.01% H.

Methyl 4-O-[4-O-(β-D-xylopyranosyl)-β-D-xylopyranosyl]-β-D-xylopyranoside (methyl β-xylotrioside) (III)

A solution of *II* (2 g) in 10% aqueous potassium hydroxide (100 ml) was heated at 100°C with the exclusion of atmospheric carbon dioxide for 4 h after which time t.l.c. (solvent *C*) showed that the reaction was complete. The solution was cooled to room temperature, diluted with ethanol (100 ml), deionized with Dowex 50 W (H^+ form) resin, filtered, the

* Penta-*O*-acetyl-α-xylobiosyl bromide is very reactive and partially decomposes during t.l.c. to give penta-*O*-acetyl-α,β-xylobiose (R_f 0.1), which can be seen by comparison with the authentic sample [2]. Chromatograms with samples of the bromide left on silica gel for longer periods reveal on the base-line a product of its further decomposition.

resin was washed with water and the combined filtrates were concentrated. The product, obtained first as a solid foam, slowly crystallized from methanol (0.8 g) and melted unsharply at ~183—186°C $[\alpha]_D^{22} = -80.5°$ (*c* 1.05, water). The second crop (0.9 g, total yield 83.3%), obtained from the concentrated mother liquor showed m.p. 184—188°C (sint. at 182°C) and $[\alpha]_D^{22} = -81.5°$ (*c* 1, water). Several recrystallizations from methanol raised the melting point to 190—191°C (sint. at 183°C) while the specific optical rotation remained practically unchanged ($[\alpha]_D^{22} = -82°$).

For $C_{16}H_{28}O_{13}$ (428.38) calculated: 44.86% C, 6.59% H; found: 44.65% C, 6.78% H.

Methyl hepta-O-acetyl-β-xylotrioside (IV)

a) Compound *III* (0.2 g) in pyridine (1 ml) was treated with acetic anhydride (1 ml) and left at room temperature for 16 h. The mixture was worked up in the usual manner to give 0.34 g (~100%) of a sirup which was chromatographically homogeneous. Crystallization from methanol gave *IV*, m.p. 108—113°C, $[\alpha]_D^{22} = -105°$ (*c* 0.98, chloroform). These values remained practically unchanged on recrystallization.

For $C_{30}H_{42}O_{20}$ (722.64) calculated: 49.86% C, 5.86% H; found: 49.68% C, 5.96% H.

b) A solution of penta-*O*-acetyl-α-xylobiosyl bromide (prepared as described above from hexa-*O*-acetyl-β-xylobiose (1.6 g; 3 mmol)) in a minimum amount of acetonitrile was added to a mixture of methyl 2,3-di-*O*-acetyl-β-D-xylopyranoside (0.5 g; 2 mmol), drierite (2 g), and mercuric cyanide (0.76 g; 3 mmol) in acetonitrile (10 ml). After a reaction period of 1 h the mixture was worked up as described above and the main product, isolated by chromatography, was crystallized from methanol (0.6 g; 41%), m.p. 109—114°C.

Methyl hepta-O-methyl-β-xylotrioside (V)

Sodium hydride (0.5 g) was added to a solution of *III* (0.4 g) in *N*,*N*-dimethylformamide (10 ml) and the mixture was stirred for 15 min with the exclusion of atmospheric moisture and carbon dioxide. After addition of methyl iodide (1.5 ml) the mixture was stirred for 2 h. Water (10 ml) was added cautiously followed by a few drops of dilute acetic acid (pH 7.5) and the mixture was partitioned between chloroform and water. The chloroform solution was concentrated with several additions of xylene to remove *N*,*N*-dimethylformamide and t.l.c. (solvent *D*) then showed that *V* (R_f 0.4) was the main reaction component. Small amount of material resulting from undermethylation was removed by elution of the crude product from a column of silica gel and the chromatographically homogeneous, colourless sirup (0.45 g; 91.5%) solidified after trituration with cyclohexane. Crystallization from isopropyl ether (twice) gave *V*, m.p. 102.5—103.5°C, $[\alpha]_D^{22} = -83°$ (*c* 1, chloroform).

For $C_{23}H_{42}O_{13}$ (526.56) calculated: 52.46% C, 8.04% H; found: 52.51% C, 8.12% H.

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