

Alternative syntheses of methylated sugars. XIV.*

Synthesis of methyl 3,4-di-*O*-acetyl- β -D-xylopyranoside

P. KOVÁČ and R. PALOVČÍK

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

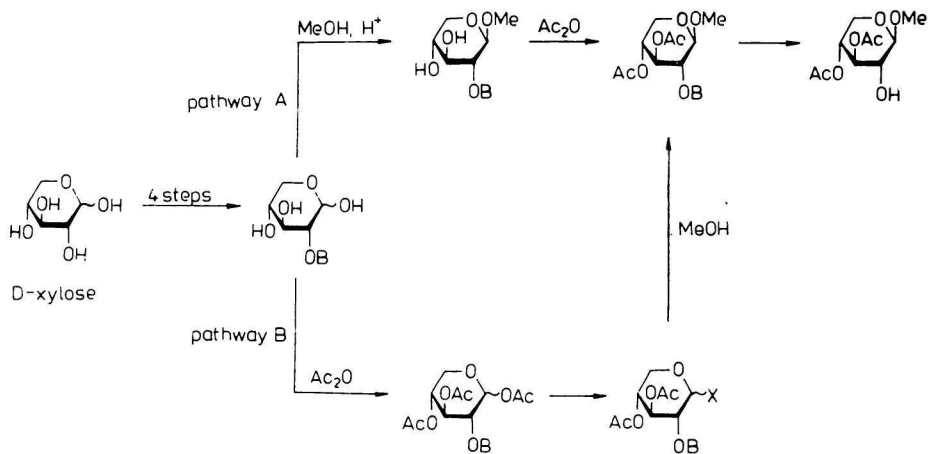
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The amount of per-*O*-acetyl-2-*O*-benzyl-D-xylopyranoses and xylofuranoses in the product of acetylation of 2-*O*-benzyl-D-xylose (*I*) depends greatly on the method of acetylation applied. While standard acetylation with acetic acid anhydride in the presence of sodium acetate at 100°C results in the formation of an appreciable amount of furanoses, the product of acetylation of *I* with acetic acid anhydride in pyridine contains minimum amount of furanoses and crystalline 1,3,4-tri-*O*-acetyl-2-*O*-benzyl- β -D-xylopyranose (*II*) can be isolated from it. When *II* was treated with hydrogen bromide in dichloromethane the β -bromide was formed first; anomerization then produced the thermodynamically more stable α -bromide (*III*). Methanolysis of *III* afforded methyl 3,4-di-*O*-acetyl-2-*O*-benzyl- β -D-xylopyranoside (*IV*) identical with methyl 3,4-di-*O*-acetyl-2-*O*-benzyl- β -D-xylopyranoside obtained by acetylation of the known, independently prepared, methyl 2-*O*-benzyl- β -D-xylopyranoside. The title glycoside *V* was obtained by hydrogenolysis of the benzyl ether *IV*. Synthesis of the hitherto unknown crystalline 1,3,4-tri-*O*-acetyl- β -D-xylopyranose is also described.

Содержание пер-*O*-ацетил-2-*O*-бензил-D-ксилопираноз и ксилофураноз в продукте ацетилирования 2-*O*-бензил-D-ксилозы (*I*) зависит от применяемого метода ацетилирования. Пока что стандартным ацетилированием уксусным ангидридом и ацетатом натрия при 100°C возникает продукт с высоким содержанием фураноз, продукт ацетилирования *I* уксусным ангидридом в пиридине при 20°C содержит минимум фураноз и можно из него получить кристаллическую β -пиранозу *II*. Воздействием HBr в CH₂Cl₂ на *II* образуется вначале соответствующий β -гликозил бромид, который медленно аномеризируется на термодинамически более устойчивый α -бромид *III*. Метанолизом *III* возникает метилгликозид *IV* тождественный с метил-3,4-ди-*O*-ацетил-2-*O*-бензил- β -D-ксилопиранозидом полученным ацетилированием метил-2-*O*-бензил- β -D-ксилопиранозидом, приготовленного независимым способом. В надписи приведенный ацетат *V* получился конвенционным гидронолизом бензил эфира *IV*. Описывается также приготовление до сих пор неизвестной кристаллической 1,3,4-три-*O*-ацетил- β -D-ксилопиранозы.

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Owing to small difference in the reactivity of hydroxyl groups in *D*-xylose dimolar acetylation of alkyl *D*-xylopyranosides gives complex mixtures of isomeric *O*-acetates from which pure, defined substances can be obtained only with difficulties. Two different approaches to the synthesis of partially acetylated alkyl glycopyranosides are shown in Scheme 1 as pathways *A* and *B*. (In principle, the given scheme has general validity, provided methods are available for isolation of pure products. Below the routes leading to the title glycoside are shown.) They comprise: a) treatment of saccharides bearing a temporary blocking group with an alcohol in the presence of an acid catalyst, acetylation of the resulting glycoside(s) and regeneration of the temporarily blocked hydroxyl groups; b) alcoholysis of glycosyl halides derived from temporarily blocked carbohydrate derivatives and removal of the blocking group.



Scheme 1

Ac — acetyl

B — temporary blocking group

Me — methyl

X — halogen

The present work describes synthesis of methyl 3,4-di-*O*-acetyl- β -*D*-xylopyranoside (*V*), a potential intermediate in the synthesis of 1 \rightarrow 2-*D*-xylose-type oligosaccharides, through the two above-mentioned pathways. A comparison of the yields shows that in spite of more steps involved pathway *B* is, in this particular case, more advantageous since it gives a much better overall yield of the final product.

The starting material in the present synthesis of *V* was readily obtainable 2-*O*-benzyl-*D*-xylose (*I*). An earlier report from this laboratory showed [1] that crystalline methyl 2-*O*-benzyl- β -*D*-xylopyranoside can be isolated in \sim 32% yield by chromatographic separation of methyl glycosides formed by treatment of *I* with methanolic hydrogen chloride. Following pathway *A*, methyl 2-*O*-benzyl- β -*D*-xy-

lopyranoside was acetylated and the resulting crystalline diacetate *IV* was hydrogenolyzed to afford the title glycoside *V*. Preparation of *V* through pathway *A* required isolation of the intermediate methyl 2-*O*-benzyl- β -D-xylopyranoside by chromatography and the overall yield ($\sim 25\%$ from *I*) was not quite satisfactory. A different procedure for the conversion of *I* to *V* was therefore devised (pathway *B*).

Standard acetylation of common aldoses of the D-series with acetic acid anhydride in the presence of sodium acetate gives usually [2] good yields of per-*O*-acetyl- β -D-aldopyranoses. When 2-*O*-benzyl-D-xylose was treated in this way a mixture of per-*O*-acetates was formed containing the isomeric pyranoses and furanoses in an approximate ratio $\alpha_p:\beta_p:\alpha_f:\beta_f = 13:35:9:43$. Perchloric acid-catalyzed acetylation of *I* produced the isomeric acetates in the ratio $\alpha_p:\beta_p:\alpha_f:\beta_f = 72:18:\sim 5:5$. The least amount of furanoses was formed when *I* was acetylated with acetic acid anhydride in pyridine ($\alpha_p:\beta_p:\alpha_f:\beta_f = 58:38:\sim 1:3$) and the hitherto unknown 1,3,4-tri-*O*-acetyl-2-*O*-benzyl- β -D-xylopyranose *II* could be crystallized from the crude product in 13.7% yield. The ratio of the per-*O*-acetates in this product depended slightly on the reaction temperature. When acetic acid anhydride was added to a solution of *I* in pyridine and the reaction was allowed to proceed without cooling the product contained (compared to the same reaction conducted first at subambient and then at room temperature) an unaltered amount of β -pyranose and a little more of β -furanose, the latter being formed at the expense of α -acetates. The structure of *II* is confirmed by p.m.r. data (Table 1) and the fact that hydrogenolysis of this substance yielded a 1,3,4-tri-*O*-acetate (*VI*) having physical constants different (m.p. 113.5–114.5°C and $[\alpha]_D - 21.4^\circ$) from those found for the known 1,3,4-tri-*O*-acetyl- α -D-xylopyranose (*VII*) (m.p. 134–137°C, $[\alpha]_D + 123^\circ$) prepared as recommended [3].

The reaction of *II* with hydrogen bromide in dichloromethane was monitored by polarimetry. Calculated specific rotations are plotted against time in Fig. 1, where $[\alpha]_{D,t=0}$ is the optical rotation of *II* in pure dichloromethane. The observed change in the $[\alpha]_D$ values appears to suggest that *II* is initially converted to a β -bromide, or at least to a mixture rich in the β -bromide, and that anomerization then takes place in the presence of hydrogen bromide resulting in the formation of the α -bromide *III*. A similar observation was made [4] in the case of the reaction of per-*O*-*p*-nitrobenzoyl-2-*O*-benzyl derivatives of D-glucose with hydrogen bromide in dichloromethane. The process of anomerization appears to have been speeded-up by working up the reaction mixture, or the anomerization proceeded also in the absence of hydrogen bromide [4]. This was indicated by the fact that when the reaction mixture was concentrated after a reaction time of 20 min (Fig. 1) a product having $[\alpha]_D + 130^\circ$ was obtained and its p.m.r. spectrum was identical with that of *III*.

Table 1

Chemical shifts and coupling constants for II—VII (CDCl₃)^a

Compound	Chemical shifts ^b (δ)										Coupling constants (Hz)							
	H-1	H-2	H-3	H-4	H-5'	H-5''	OMe	OH	OAc	Arom	H _A ^d	H _B ^d	J _{1,2}	J _{2,3}	J _{3,4}	J _{4,5}	J _{4,5'}	J _{5,5'}
II	5.66 d	3.54 q	5.21 t	4.89 sx	4.04 q	3.46 q	—	—	2.06, 2.01, 1.96	7.30	4.68 d	4.61 d	7.0	8.6	8.6	4.9	9.0	-11.9
III	6.37 d	3.48 q	5.48 t	4.93 sx	3.92 ^c	3.82 ^c	—	—	2.07, 2.07	7.28	4.68 d	4.41 d	3.7	9.7	9.7	5.7 ^c	10.0 ^c	-11.0 ^c
IV	4.34 d	3.34 q	5.14 t	4.85 sx	4.03 q	3.29 q	3.50	—	2.04, 2.10	7.25	4.79 d	4.57 d	7.0	8.9	8.7	4.6	8.8	-11.6
V	4.28 d	3.53 q	5.13 t	4.91 sx	4.08 q	3.35 q	3.54	~3.54	2.09, 2.04, 2.11	—	—	—	6.7	8.2	8.2	4.8	9.0	-11.0
VI	5.62 d	3.65 t	5.14 t	4.93 sx	4.10 q	3.50 q	—	3.29	2.15, 2.06	—	—	—	6.5	8.5	8.3	4.6	8.5	-11.5
VII	6.14 d	3.89 q	5.28 t	4.95 sx	3.88 ^c q	3.65 ^c q	—	3.39	2.18, 2.10, 2.04	—	—	—	3.8	9.4	9.4	5.2 ^c	9.8 ^c	-11.0 ^c

a) Data obtained from spectra recorded at a sweep width 100 Hz.

b) Observed multiplicities: d — doublet, t — triplet, q — quartet, sx — sextet, o — octet.

c) The C-5 proton resonating at lower field is denoted H-5.

d) Benzylic protons.

e) Chemical shifts and coupling constants calculated by ABX analysis of the spectrum.

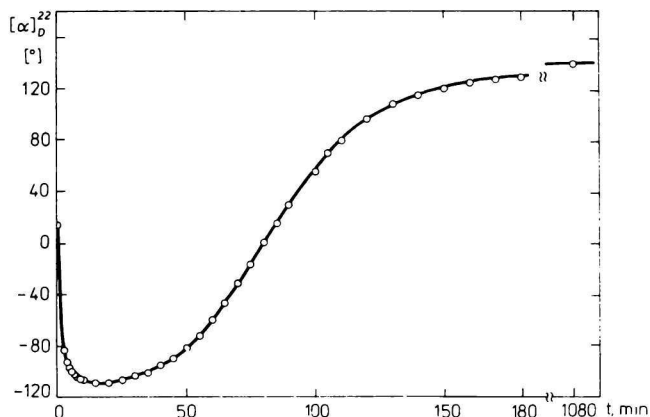
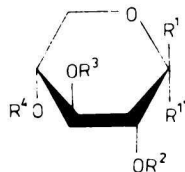


Fig. 1. Plot of specific rotation against time in reaction of 1,3,4-tri-*O*-acetyl-2-*O*-benzyl- β -*D*-xylopyranose with hydrogen bromide in dichloromethane.

The synthesis of the title glycoside does not require the isolation of pure *II*. The reaction of hydrogen bromide in dichloromethane with the mixture of 2-*O*-benzyl-per-*O*-acetates containing almost exclusively pyranoses gave a product rich in *III* and when this was allowed to react with methanol under the conditions of modified Koenigs—Knorr synthesis of β -glycosides [5, 6] the acetate *IV* was formed in high yield. In addition to *IV* the thus obtained reaction mixture contained four minor products which were not further examined but, according to their chromatographic mobility, could be: methyl 3,4-di-*O*-acetyl-2-*O*-benzyl- α -*D*-xylopyranoside, the product of hydrolysis of the bromide *III* and the two acetylated methyl furanosides of 2-*O*-benzyl-*D*-xylose (formed from the corresponding glycofuranosyl bromides present in crude *III* as a result of the per-*O*-acetyl-2-*O*-benzyl-*D*-xylofuranoses contained in the starting acetate). A portion of *IV*, identical with the substance obtained through pathway *A*, was isolated from the reaction mixture by crystallization and further amount was obtained by chromatography of the mother liquor (total yield of *IV* \sim 60% based on *I*). Debenzylation of *IV* by catalytic hydrogenolysis then readily gave the wanted title glycoside *V*.

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 for solutions in chloroform-*d* were obtained with a Tesla BS-487B spectrometer at 80 MHz. Proton-signal assignments were made by INDOR technique. The ratio of isomeric per-*O*-acetates in the products of acetylation of 2-*O*-benzyl-*D*-xylose was based on the integrated areas for H-1 in the p.m.r. spectra resonating at δ 6.14, $J_{1,2}$ 3.8 Hz (H-1, α_p); δ 5.66, $J_{1,2}$ 7 Hz (H-1, β_p); δ 6.18, $J_{1,2} \sim$ 4.5 Hz (H-1, α_t); δ 6.03, $J_{1,2} < 1$ Hz (H-1, β_t). The H-1-signal assignments for



	R ¹	R ^{1'}	R ²	R ³	R ⁴
<i>I</i>		HOH	CH ₂ Ph	OH	OH
<i>II</i>	OAc	H	CH ₂ Ph	Ac	Ac
<i>III</i>	H	Br	CH ₂ Ph	Ac	Ac
<i>IV</i>	OMe	H	CH ₂ Ph	Ac	Ac
<i>V</i>	OMe	H	H	Ac	Ac
<i>VI</i>	OAc	H	H	Ac	Ac
<i>VII</i>	H	OAc	H	Ac	Ac

the 2-*O*-benzyl-D-xylofuranose per-*O*-acetates were made in analogy with the series of methyl *O*-methyl- α - and β -D-xylofuranosides [7].

Thin-layer chromatography on Silica gel G and preparative chromatography on dry-packed silica gel columns (Merck, A.G., Darmstadt, Product No. 9385) were performed with benzene—acetone mixtures: A. 15: 1, B. 25: 1, and C. 10: 1. Before packing the silica gel was equilibrated with 40% (v/w) of the mobile phase, instead of the recommended [8] 10%. Detection was effected by charring with 5% (v/v) sulfuric acid in ethanol. The reagent for the conversion of per-*O*-acetyl-2-*O*-benzyl-D-xylose to the corresponding glycosyl bromide was prepared by passing bromine-free hydrogen bromide [9] into dichloromethane at -10°C . The resulting solution containing ~ 0.06 g HBr/ml (determined by weighing), when stored in a refrigerator at $+5^{\circ}\text{C}$ in a tightly closed bottle, remained colourless during a period of several months. Solutions were concentrated at 2 kPa and 40°C .

Acetylation of 2-*O*-benzyl-D-xylose

a) Compound *I* (1 g) was added at 100°C to a mixture of acetic acid anhydride (3 ml) and fused sodium acetate (0.5 g) and the mixture was stirred with the exclusion of moisture at 100 — 110°C for 2 h. T.l.c. in solvent A then showed only a spot at $R_F \sim 0.6$ and the product was isolated in the usual manner. After drying at $40^{\circ}\text{C}/2$ kPa the obtained syrup (1.4 g; 92%) had $[\alpha]_D^{22} + 8^{\circ}$ (c 1.02, chloroform) and its p.m.r. spectrum showed that the isomeric per-*O*-acetates were present in a ratio of $\alpha_p : \beta_p : \alpha_t : \beta_t = 13 : 35 : 9 : 43$.

For $\text{C}_{18}\text{H}_{22}\text{O}_8$ (366.36) calculated: 59.00% C, 6.05% H; found: 59.15% C, 5.84% H.

b) Compound *I* (1 g) was added portionwise at 0°C to a mixture of acetic acid anhydride (3 ml) and perchloric acid (70%; 0.05 ml) and the mixture was left at room temperature with the exclusion of moisture for 2 h. Work-up in the usual manner gave a syrup a solution of which in benzene was decolorized with a little silica gel. Concentration of the filtrate gave 1.2 g (79%) of a mixture of isomeric per-*O*-acetates of *I* having $[\alpha]_D^{24} + 66^{\circ}$ (c 1, chloroform) and the amount of the individual acetates, found by p.m.r. spectrometry, was $\alpha_p : \beta_p : \alpha_t : \beta_t = 72 : 18 : \sim 5 : 5$.

Found: 59.17% C, 5.99% H.

c) Acetic acid anhydride (15 ml) was added to a cold (0°C) solution of *I* (5 g) in dry pyridine (15 ml), the cooling was removed after 15 min, and the reaction mixture was worked-up in the usual manner after additional 2 h. The colourless product (7.6 g; $\sim 100\%$)

had $[\alpha]_D^{24} + 61^\circ$ (*c* 1.04, chloroform) and its p.m.r. spectrum showed that the isomeric per-*O*-acetates were present in a ratio of $\alpha_p : \beta_p : \alpha_t : \beta_t = 58 : 38 : \sim 1 : 3$. When the same reaction was carried out without cooling at the initial reaction stage the obtained product contained trace amount of α -furanose, had $[\alpha]_D^{24} + 52^\circ$ and the ratio between the isomeric *O*-acetates, found by p.m.r. spectrometry, was $\alpha_p : \beta_p : \beta_t = 56 : 38 : 6$.

Found: 58.91% C, 6.00% H.

The β -acetate *II* slowly crystallized from isopropyl ether—heptane. The obtained crystalline material (1.2 g) was recrystallized from isopropyl ether to give 1.05 g (13.7%) of pure 1,3,4-tri-*O*-acetyl- β -D-xylopyranose (*II*), m.p. 88.5—89.5°C, $[\alpha]_D^{22} + 21^\circ$ (*c* 1, chloroform).

Found: 59.15% C, 6.18% H.

Catalytic hydrogenolysis of *II*, in the manner described for the preparation of *V*, gave 1,3,4-tri-*O*-acetyl- β -D-xylopyranose (*VI*), m.p. 113.5—114.5°C (from ether at 0°C), $[\alpha]_D^{20} - 21.4^\circ$ (*c* 1, chloroform).

For $C_{11}H_{16}O_8$ (276.24) calculated: 47.82% C, 5.83% H; found: 49.01% C, 5.97% H.

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

a) Methyl 2-*O*-benzyl- β -D-xylopyranoside [1] (0.85 g) in dry pyridine (2 ml) was treated with acetic acid anhydride (2 ml) for 2 h and after usual work-up *IV* was crystallized from isopropyl ether. The obtained crystalline material (970 mg; 85.8%) was recrystallized from the same solvent to give pure *IV* having m.p. 82.5—83.5°C and $[\alpha]_D + 17.4^\circ$ (*c* 1.03, chloroform).

For $C_{17}H_{22}O_7$ (338.35) calculated: 60.34% C, 6.56% H; found: 60.31% C, 6.57% H.

b) 2-*O*-Benzyl-D-xylose (5 g) was acetylated as described above (c) and the crude product was treated with a solution of hydrogen bromide in dichloromethane (100 ml) for 1 1/2 h at room temperature. The solution was concentrated with co-distillation with toluene to give crude bromide *III*, $[\alpha]_D^{22} + 130^\circ$ (*c* 1, chloroform) as a syrup. A solution of this product in a small amount of toluene was added to a mixture of dry methanol (65 ml), yellow mercuric oxide (4.5 g), mercuric bromide (0.1 g), and Drierite (10 g) which had been stirred for 2 h. After stirring for 1 h the mixture was filtered, the solids washed with chloroform, and the filtrate combined with the washings was concentrated. A solution of the residue in chloroform was washed with 1 M aqueous potassium bromide solution to remove mercuric salts, with water, dried and concentrated. Crystallization from isopropyl ether, after seeding with the above-described material, gave 3.6 g (51.5%) of *IV*, m.p. 81—83°C. T.l.c. of the mother liquor in solvent *A* showed the presence of *IV* [R_F 0.5] and small amount of components having R_F 0.2, 0.35, 0.4, and 0.6 (not further examined). Chromatography with solvent *B* gave a further amount of *IV* (0.6 g; total yield 59.6% based on *I*).

Methyl 3,4-di-O-acetyl-β-D-xylopyranoside (V)

Compound *IV* (1 g) in methanol (20 ml) was stirred in a hydrogen atmosphere in the presence of 5% palladium-on-charcoal catalyst (0.1 g) until t.l.c. (solvent *A*) showed that the reaction was complete (~2 h). The product, isolated by filtration and concentration of the filtrate, spontaneously crystallized. Recrystallization from isopropyl ether gave 0.67 g (91%) of *V* which, when crystallized again from the same solvent, had m.p. 113.5–114.5°C and $[\alpha]_D^{25} - 29^\circ$ (*c* 1, chloroform).

For C₁₀H₁₆O₇ (248.23) calculated: 48.38% C, 6.50% H; found: 48.05% C, 6.40% H.

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