An easy route to 2-*O*-substituted D-xylose derivatives

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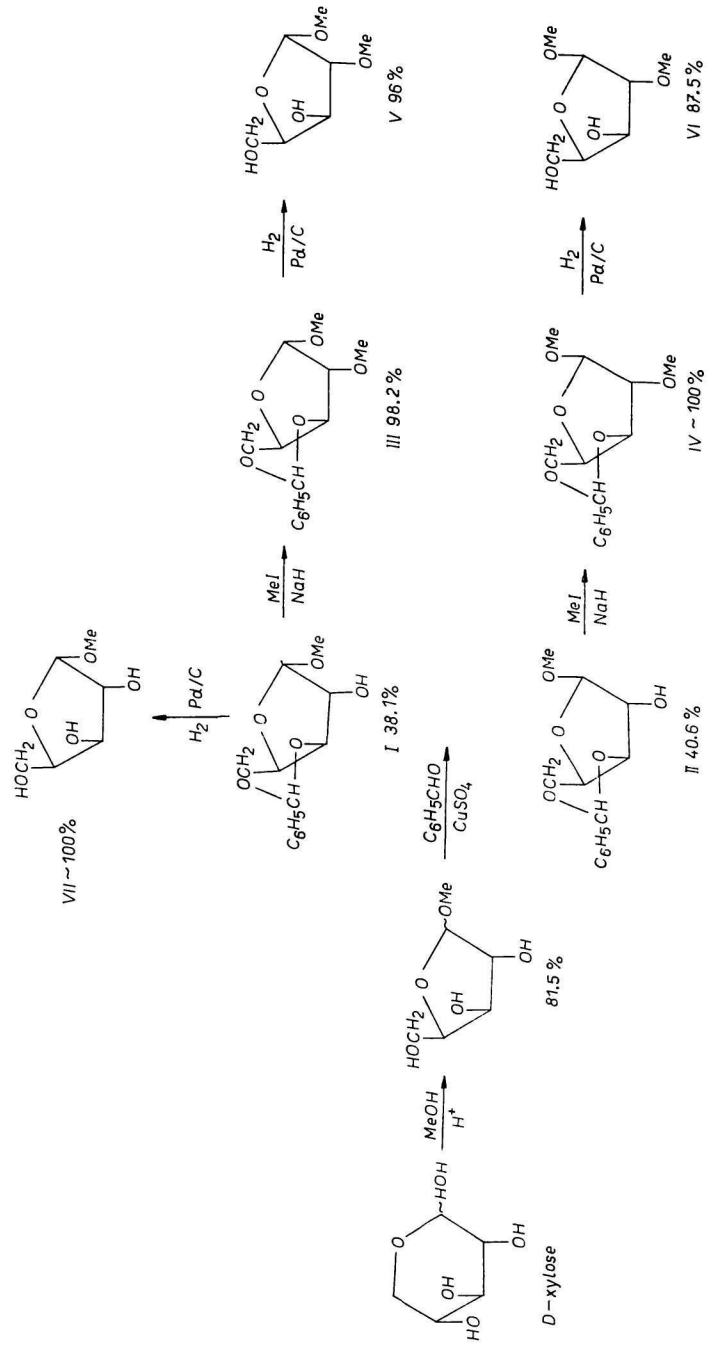
The synthesis of crystalline, hitherto unknown, methyl 3,5-*O*-benzylidene-α- and -β-D-xylofuranosides *I* and *II* is described. By methylation of the foregoing furanosides and splitting of the blocking benzylidene groups by hydrogenolysis methyl furanosides of 2-*O*-methyl-D-xylose were obtained through a sequence by two steps shorter than is known in the literature. Catalytic hydrogenolysis of *I* and *II* afforded methyl α- and β-D-xylofuranosides in high yields.

Three practical routes leading to 2-*O*-substituted D-xylose derivatives are reported in the literature. The first [1] is based on methanolysis of 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-D-xylofuranose to give a mixture of methyl furanosides of 3,5-di-*O*-benzyl-D--xylose having C_2—OH free to further substitution. The sequence [1] was successfully applied in the synthesis of methyl furanosides of 2-*O*-methyl-D-xylose [2] which were thus made in six steps (starting from D-xylose). A newer procedure [3] takes advantage of the conversion of a syrupy mixture of methyl furanosides of D-xylose to 3,5-*O*-phenylboronates separable by fractional crystallization. The third method, utilizing easily obtainable methyl 3,5-*O*-isopropylidene-α,β-D-xylofuranoside permitted the synthesis [4] and isolation of a small amount of one of the first synthetic aldobiouronic acids namely 2-*O*-(β-D-glucuronopyranosyl)-D-xylopyranose. With the aim to prepare a C_2—OH-free D-xylose derivative bearing easy-to-remove blocking groups we have synthesized crystalline, hitherto unknown, methyl 3,5-*O*-benzylidene-α-D-xylofuranoside *I* and methyl 3,5-*O*-benzylidene-β-D-xylofuranoside *II*. Using compounds *I* and *II* as intermediates the known route for the synthesis of methyl furanosides of 2-*O*-methyl-D-xylose [2] was cut by two steps (Scheme 1). A practical procedure for the preparation of larger amounts of methyl furanosides of D-xylose *VII* and *VIII* by catalytic hydrogenolysis of *I* and *II* is also described. The use of *I* and *II* in the synthesis of oligosaccharides will be the subject of a subsequent publication.

Experimental

Melting points were determined on a Kofler hot stage. Optical rotations were measured using a Bendix—Ericsson automatic polarimeter Model 143 A. Thin-layer chromatography (TLC) on Silica gel G and preparative chromatography on silica gel (0.05—0.1 mm) was carried out with: *A*. chloroform—methanol 6 1, *B*. benzene—acetone 8 1, *C*. benzene—acetone 10 : 1, and *D*. benzene—acetone 15 1 (v/v). Detection was by charring with 5% sulfuric acid in ethanol. Solutions were concentrated under reduced pressure at < 40°C. 1,2-Dimethoxyethane was dried as described in [5] and stored over sodium hydride.


D-xylose
MeOH
H+
81.5 %
C6H5CHO
CuSO4
I 38.1%
II 40.6 %
MeI
NaH
III 98.2 %
IV ~ 100 %
H2
Pd/C
V 96 %
VI 87.5 %
VII ~ 100 %
VIII ~ 100 %

Scheme 1

Methyl 3,5-O-benzylidene-α- (I) and -β-D-xylofuranoside (II)

D-Xylose (30 g) in dry methanol (600 ml) was treated at 0°C with 15.9% methanolic hydrogen chloride (62.5 ml) for 65 hours. The solution was neutralized with lead carbonate, filtered, and concentrated to dryness. The resulting syrup was extracted with ethyl acetate (6 × 100 ml) in which, as recommended by the previous authors [6], unchanged D-xylose and its methyl pyranosides remained undissolved. The combined extracts were concentrated to give 26.7 g (81.5%) of methyl α,β-D-xylofuranosides.

To the foregoing furanosides (21 g) in benzaldehyde (105 ml) anhydrous copper sulfate was added (84 g) and the mixture was vigorously stirred at room temperature for 20 hours at which time TLC showed that the reaction was complete. Two products were detected (R_F 0.6 and 0.75, *cf.* 0.4 for the starting material) in the solvent system *A*. The reaction mixture was filtered and evaporated with several additions of water to remove the excess of benzaldehyde. The obtained syrup (32 g) was chromatographed on a column of silica gel (110 × 4.5 cm) using system *C*.

The faster moving component was methyl 3,5-*O*-benzylidene-α-D-xylofuranoside (*I*) (12.2 g, 38.1%); m.p. 94°C (from benzene—heptane, twice), $[\alpha]_D^{25}$ +54.3° (*c* 0.95, chloroform).

For $C_{13}H_{16}O_5$ (252.26) calculated: 61.89% C, 6.39% H, 12.30% CH_3O; found: 62.01% C, 6.37% H, 12.45% CH_3O.

The slower moving component was methyl 3,5-*O*-benzylidene-β-D-xylofuranoside (*II*) (13 g, 40.6%); m.p. 98—99°C (from benzene—heptane, twice), $[\alpha]_D^{25}$ −92.2° (*c* 0.97, chloroform).

Found: 61.90% C, 6.39% H, 12.21% CH_3O.

Methyl 3,5-O-benzylidene-2-O-methyl-α- and -β-D-xylofuranoside (III and IV)

To a solution of *I* (3 g) in 1,2-dimethoxyethane (30 ml) sodium hydride (0.85 g) was added at 0°C with stirring. After fifteen minutes methyl iodide (1.5 ml) was added and the mixture was stirred with the exclusion of atmospheric moisture and carbon dioxide for additional 2 hours at which time TLC in system *D* showed complete disappearance of the starting material (R_F 0.3) and formation of one product (R_F 0.4). Water (20 ml) was added slowly and the organic solvent was removed. The separated solid product was filtered and combined with the chloroform extract of the filtrate. The resulting chloroform solution was washed with water until neutral, dried with anhydrous sodium sulfate and concentrated to give 3.1 g (98.2%) of *III*; m.p. 118.5°C (from ethanol, twice), $[\alpha]_D^{22}$ +66.1° (*c* 1.065, chloroform).

For $C_{14}H_{18}O_5$ (266.286) calculated: 63.14% C, 6.81% H, 23.31% CH_3O; found: 62.86% C, 6.65% H, 23.41% CH_3O.

Compound *II* (2 g) was methylated as described above. The reaction was complete after 45 minutes and *IV* (2.1 g, ~100%) was obtained as a syrup which crystallized after vacuum distillation. Recrystallization from ether—heptane (1 : 2) gave pure *IV* melting at 41.5—42°C, $[\alpha]_D^{25}$ −80° (*c* 1.12, chloroform).

Found: 63.01% C, 6.77% H, 23.19% CH_3O.

Methyl 2-O-methyl-α- and -β-D-xylofuranoside (V and VI)

Compound *III* (1.9 g) in dry methanol (80 ml) was hydrogenated at room temperature over palladium-on-charcoal catalyst until TLC in system *D* showed complete disappearance of the starting material (R_F 0.4). The reaction mixture was worked up in the

usual manner and *V* (1.2 g, 96%), which was chromatographically homogeneous (R_F 0.45, system *A*), was crystallized from ether. M.p. 71—73°C. Ref. [2] gives m.p. 72—73°C.

Catalytic hydrogenolysis of *IV* (1.2 g) under the above-described conditions gave *VI* (R_F 0.45, system *A*) which was vacuum distilled (b.p. 56°C/0.05 torr) and collected as a colourless syrup (0.7 g, 87.5%), $[\alpha]_D^{24}$ −80° (*c* 1.35, ethanol). Ref. [2] gives $[\alpha]_D^{24}$ −83.5° (*c* 1.3, ethanol).

Methyl α- and -β-D-xylofuranoside (VII and VIII)

Compound *I* (5 g) in dry methanol (150 ml) was hydrogenated over palladium-on-charcoal catalyst until TLC showed complete disappearance of the starting material in the system *A*. The reaction mixture was filtered and concentrated to give 3.25 g (~100%) of crystalline, chromatographically pure *VII*. After crystallization from ethyl acetate the compound melted at 80—81°C. Ref. [7] gives m.p. 83—84°C.

Similar hydrogenolysis of *II* gave chromatographically pure syrupy *VIII* in theoretical yield; $[\alpha]_D^{25}$ −79° (*c* 4.5, water). Ref. [7] $[\alpha]_D$ −80°.

Results and discussion

Each of the previously described 3,5-*O*-substituted methyl D-xylofuranosides, as a possible intermediate in the synthesis of oligosaccharides containing 2-*O*-substituted D-xylose unit, has its advantages as well as drawbacks.

The advantage of 3,5-di-*O*-benzyl ethers lies in the fact that the hydroxyl groups can be easily regenerated by hydrogenolysis. On the other hand these compounds are prepared in four steps [1, 2] (starting from D-xylose) and, so far, have been obtained only as syrups. A shorter way leads to crystalline 3,5-*O*-phenylboronates [3, 8] which, however, are obtained in lower yield; the fact that triphenylboroxol, the key reagent for their preparation, is not a cheap commodity, is itself a disadvantage of this class of compounds.

3,5-*O*-Isopropylidene derivatives of methyl α- and β-D-xylofuranoside are readily obtainable [4] from inexpensive chemicals. Apart from being syrups, the main drawback of these compounds in oligosaccharide synthesis lies in the fact that the removal of the *O*-isopropylidene group has to be carried out under acidic conditions which may, at the same time, cleave the glycosidic bonds and thus decrease the yield of the synthesized oligosaccharide.

In view of the ease of their preparation, inexpensive reagents involved as well as the possibility of the removal of the blocking groups under mild conditions (hydrogenolysis of the benzylidene residues and hydrolysis of the methyl glycofuranoid structure under milder conditions [9] than those used for the removal of the *O*-isopropylidene group [4]), benzylidene derivatives *I* and *II* possess all desirable features required of an intermediate in oligosaccharide synthesis.

Treatment of D-xylose with dilute methanolic hydrogen chloride at 0°C gave rise to a mixture of methyl glycosides from which by extraction with ethyl acetate, as recommended previously [6], methyl furanosides were obtained. Subsequent treatment of these with benzaldehyde in the presence of anhydrous copper sulfate as dessicant produced a mixture of methyl 3,5-*O*-benzylidene-α-D-xylofuranoside and methyl 3,5-*O*-benzylidene-β-D-xylofuranoside. These were separated by column silica gel chromatography and both anomers obtained crystalline. It is worth mentioning that the preparative chromatography of *I* and *II* in the given system is very effective. Pure compounds, with practically no intermediate fraction containing a mixture of anomers, as usual when

anomeric mixtures are preparatively chromatographed [2, 9—11], can be obtained even when working with heavily loaded columns.

Methylation of *I* and *II* gave the corresponding crystalline, hitherto unknown, 2-*O*-methyl ethers *III* and *IV*. Following hydrogenolysis produced the known methyl furanosides of 2-*O*-methyl-D-xylose, the physical constants of which agreed well with the reported values [2]. The advantage of the procedure for obtaining *V* and *VI* described here lies in the fact that compounds *II* and *IV*, the precursors of the syrupy methyl 2-*O*-methyl-β-D-xylofuranoside, are readily crystallizable substances which is thus a good assumption of the anomeric purity of *VI*, obtained by catalytic hydrogenolysis of *IV*.

Hydrogenolysis of *I* and *II* gave methyl furanosides of D-xylose *VII* and *VIII* in theoretical yields. Comparing the known procedures [3, 11] with the present one using *I* and *II* as intermediates, the latter is, due to its simplicity, inexpensive reagents involved and good yields of the pure anomers, most suitable for making larger quantities of methyl α- and β-D-xylofuranosides.

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References

1. Bowering, W. D. S. and Timell, T. E., *Can. J. Chem.* ***36***, 283 (1958).
2. Kováč, P. and Petríková, M., *Carbohyd. Res.* ***16***, 492 (1971).
3. Ferrier, R. J., Prasad, D., and Rudowski, A., *J. Chem. Soc.* ***1965***, 858.
4. Bowering, W. D. S. and Timell, T. E., *J. Amer. Chem. Soc.* ***82***, 2827 (1960).
5. Perrin, D. D., Armarego, W. L. F., and Perrin, D. R., *Purification of Laboratory Chemicals*. Pergamon Press, Oxford, 1966.
6. Percival, E. E. and Zobrist, R., *J. Chem. Soc.* ***1952***, 4306.
7. Bishop, C. T. and Cooper, F. P., *Can. J. Chem.* ***41***, 2743 (1963).
8. Ferrier, R. J. and Prasad, D., *J. Chem. Soc.* ***1965***, 7429.
9. Kováč, P. and Hirsch, J., *Chem. Zvesti* ***27***, 668 (1973).
10. Kováč, P., *Chem. Zvesti* ***25***, 460 (1971).
11. Augestad, I. and Berner, E., *Acta Chem. Scand.* ***8***, 251 (1954).

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