Alternative Syntheses of Methylated Sugars. IV.* Methyl Furanosides of 5-*O*-, 2,5-Di-*O*-, 3,5-Di-*O*- and 2,3,5-Tri-*O*-methyl-D-xylose

P. KOVÁČ

Institute of Chemistry, Slovak Academy of Sciences, Bratislava 9

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Methyl furanosides of 5-*O*-, 2,5-di-*O*-, 3,5-di-*O*- and 2,3,5-tri-*O*-methyl-D--xylose have been synthesized starting from 1,2-*O*-isopropylidene-D-xylofuranose. The observed order of elution of the compounds under investigation proves that on silica gel the elution of methyl *O*-methyl-D-xylofuranosides follows the same pattern as known for gas chromatographic elution of methyl-*O*-methyl-glycopyranosides.

This laboratory has recently reported the synthesis of methyl furanosides of 2-*O*-methyl- [1], 3-*O*-methyl- and 2,3-di-*O*-methyl-D-xylose [2] and showed the usefulness of these substances for identification [3] of the products of methylation analysis of polysaccharides containing D-xylopyranose as a structural unit. Gas chromatography of previously synthesized methyl furanosides indicated that for the order of elution of anomeric pairs of methyl *O*-methyl-D-xylofuranosides the same generally accepted rule might be applicable as for methyl *O*-methyl-glycopyranosides [4]. In order to ascertain the validity of the above-mentioned rule in the complete series of methyl *O*-methyl-D-xylofuranosides the remaining theoretically possible members of the series were synthesized. Their gas—liquid chromatography will be published elsewhere [5].

Experimental

Melting points were determined on a Kofler hot stage. Optical rotations were determined on Bendix—Ericsson Authomatic Polarimeter. Thin-layer chromatography (TLC) on Silica gel G coated glass plates (4 × 12 cm) and column chromatography on silica gel (0.05—0.1 mm) was carried out using: A. benzene—ethyl acetate 8 : 1, B. benzene—ethyl acetate 9 : 5, C. chloroform—acetone 9 : 4, D. carbon tetrachloride—acetone 15 : 1, E. carbon tetrachloride—acetone 9 : 2 and F. chloroform—acetone 10 : 1 as irrigants. The solvent ratios are based on volumes. On thin layers the components were located by spraying with 5% sulfuric acid in ethanol and by heating until permanent char spots were visible. The solvents were removed under reduced pressure at temperature below 40°C. Per-*O*-*p*-nitrobenzoyl derivatives of the final products were prepared as described by *Ishikawa* and *Fletcher* [6].

* For part III. see ref. [2].

3-O-Benzyl-1,2-O-isopropylidene-5-O-methyl-D-xylofuranose

1,2-*O*-Isopropylidene-5-*O*-methyl-D-xylofuranose [7] (22 g) was dissolved in benzyl-chloride (35 ml) and powdered potassium hydroxide (25 g) was added. Under vigorous stirring, and with exclusion of moisture, the temperature of the reaction mixture was kept at 100—110°C for one hour after which time TLC in solvent system A showed complete conversion of the starting material (R_F 0.04) into the reaction product (R_F 0.4). Isolation in the usual manner gave after vacuum distillation (b.p. 136—137°C/0.03 Torr) 30.5 g (96%) of a chromatographically pure syrup which could not be induced to crystallize. $[\alpha]_D^{25}$ −36.9° (c = 1.05, ethanol).

For $C_{16}H_{22}O_5$ (294.34) calculated: 65.28% C, 7.53% H, 10.54% CH_3O; found: 65.23% C, 7.49% H, 10.65% CH_3O.

Methyl 3-O-benzyl-5-O-methyl-α- and -β-D-xylofuranoside

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methyl-D-xylofuranose (30 g) was treated with boiling methanol containing 0.8% hydrogen chloride (500 ml) for one hour after which time TLC in solvent system B showed complete disappearance of the starting material (R_F 0.7) from the reaction mixture. Two products were detected (R_F 0.37 and 0.25). The reaction mixture was neutralized with lead carbonate, filtered and concentrated to give 26 g (95%) of an almost colourless syrup which was chromatographed on a column of silica gel (110 × 3 cm) irrigated with solvent B.

The faster moving component was methyl 3-*O*-benzyl-5-*O*-methyl-α-D-xylofuranoside. Vacuum distillation (b.p. 122—123°C/0.02 Torr) gave 12 g (42.9%) of a colourless oil which could not be induced to crystallize. $[\alpha]_D^{24}$ +106.7° (c = 1.06, ethanol).

For $C_{14}H_{20}O_5$ (268.30) calculated: 62.67% C, 7.51% H, 23.13% CH_3O; found: 63.02% C, 7.42% H, 23.01% CH_3O.

The slower moving component (b.p. 156—157°C/0.06 Torr), $[\alpha]_D^{24}$ −85.1° (c = 1.05, ethanol) was methyl 3-*O*-benzyl-5-*O*-methyl-β-D-xylofuranoside. Yield 10.7 g (39.2%).

Found: 62.49% C, 7.55% H, 22.78% CH_3O.

An intermediate, mixed fraction was also obtained.

Methyl 5-O-methyl-α-D-xylofuranoside

Methyl 3-*O*-benzyl-5-*O*-methyl-α-D-xylofuranoside (5 g) was dissolved in 1,2-dimethoxy-ethane (10 ml) and added to liquid ammonia (100 ml). Sodium (0.9 g) cut into small pieces was added with stirring and exclusion of moisture. The last portion of sodium caused an intense blue colour to develop, which indicated that the reaction was complete. The reaction mixture was worked up as described previously [1]. TLC in solvent C revealed no starting material (R_F 0.95). The product (R_F 0.42) was vacuum distilled (b.p. 92 to 93°C/0.03 Torr) and collected as a colourless oil which could not be induced to crystallize. Yield 3.1 g (90%), $[\alpha]_D^{24}$ +157.9° (c = 1.14, ethanol).

For $C_7H_{14}O_5$ (178.18) calculated: 47.18% C, 7.92% H, 34.83% CH_3O; found: 46.83% C, 7.94% H, 35.09% CH_3O.

Methyl 5-*O*-methyl-α-D-xylofuranoside gave crystalline methyl 5-*O*-methyl-2,3-bis-*O*-*p*-nitrobenzoyl-α-D-xylofuranoside (fibrous needles) having m.p. 128—129°C and $[\alpha]_D^{25}$ +229.3° (c = 1.03, chloroform).

For $C_{21}H_{20}O_{11}N_2$ (476.39) calculated: 52.94% C, 4.23% H, 5.88% N, 13.02% CH_3O; found: 52.96% C, 4.21% H, 5.81% N, 13.14% CH_3O.

Methyl 5-O-methyl-β-D-xylofuranoside

Debenzylation of methyl 3-*O*-benzyl-5-*O*-methyl-β-D-xylofuranoside (5 g, R_F 0.9, system C) carried out as described above gave 2.7 g (78.2%) of a chromatographically pure (R_F 0.42) oil which could not be induced to crystallize. B.p. 108—109°C/0.04 Torr, $[\alpha]_D^{24}$ −85.8° (c = 1.13, ethanol).

Found: 46.70% C, 7.91% H, 34.43% CH_3O.

Methyl 5-*O*-methyl-β-D-xylofuranoside gave crystalline (prisms) methyl 5-*O*-methyl-2,3-bis-*O*-*p*-nitrobenzoyl-β-D-xylofuranoside having m.p. 126—127°C and $[\alpha]_D^{24}$ +75.2° (c = 1.11, chloroform).

For $C_{21}H_{20}O_{11}N_2$ (476.39) calculated: 52.94% C, 4.23% H, 5.88% N, 13.02% CH_3O; found: 52.86% C, 4.29% H, 5.78% N, 13.07% CH_3O.

Methyl 3-O-benzyl-2,5-di-O-methyl-α-D-xylofuranoside

Methyl 3-*O*-benzyl-5-*O*-methyl-α-D-xylofuranoside (5.5 g) was dissolved in tetrahydrofuran (20 ml) and powdered sodium hydroxide (5 g) was added. With stirring, methyl sulfate (5 ml) was added dropwise, and the temperature was kept at 50°C for 30 minutes after which time TLC in solvent D showed complete conversion of the starting material (R_F 0.25) into the reaction product (R_F 0.33). Isolation in the usual manner was followed by vacuum distillation of the product (b.p. 126—127°C/0.02 Torr) which gave 5.5 g (95%) of a chromatographically pure syrup. $[\alpha]_D^{24}$ +128.9° (c = 1.1, ethanol).

For $C_{15}H_{22}O_5$ (282.33) calculated: 63.80% C, 7.85% H, 32.9% CH_3O; found: 63.52% C, 7.75% H, 32.25% CH_3O.

Methyl 3-O-benzyl-2,5-di-O-methyl-β-D-xylofuranoside

Methylation of methyl 3-*O*-benzyl-5-*O*-methyl-β-D-xylofuranoside (6 g) under the same conditions as described above gave after vacuum distillation (b.p. 118—119°C/0.02 Torr) 5.9 g (93.3%) of a chromatographically pure (R_F 0.48, system D, *cf.* R_F 0.15 for the starting material) syrup which could not be induced to crystallize. $[\alpha]_D^{24}$ −64.9 (c = 1.06, ethanol).

Found: 63.66% C, 7.68% H, 32.21% CH_3O.

Methyl 2,5-di-O-methyl-α-D-xylofuranoside

Methyl 3-*O*-benzyl-2,5-di-*O*-methyl-α-D-xylofuranoside (5 g) was debenzylated with sodium (0.9 g) in liquid ammonia (100 ml) and the debenzylation product (R_F 0.12, solvent E, *cf.* R_F 0.8 for the starting material) was vacuum distilled (b.p. 81—82°C/0.1 Torr). A chromatographically pure syrup was obtained which crystallized upon cooling in large prisms (3 g, 88%). The compound was recrystallized from ether at −10°C. M.p. 24—28°C. Yield of the recrystallized product 1 g (29.5%). $[\alpha]_D^{25}$ +169.9° (c = 1.13, ethanol).

For $C_8H_{16}O_5$ (192.21) calculated: 49.98% C, 8.39% H, 48.43% CH_3O; found: 49.95% C, 8.37% H, 48.03% CH_3O.

Methyl 2,5-di-*O*-methyl-α-D-xylofuranoside gave crystalline methyl 2,5-di-*O*-methyl-3-*O*-*p*-nitrobenzoyl-α-D-xylofuranoside. M.p. 120—121°C, $[\alpha]_D^{24}$ +136.6° (c = 0,96, chloroform).

For $C_{15}H_{10}O_8N$ (332.24) calculated: 4.21% N, 28.02% CH_3O; found: 4.22% N, 27.95% CH_3O.

Methyl 2,5-di-O-methyl-β-D-xylofuranoside

Under the above described conditions methyl 3-*O*-benzyl-2,5-di-*O*-methyl-β-D-xylofuranoside (5 g) gave upon debenzylation 2.9 g (85%) of material which was vacuum distilled (b.p. 74—75°C/0.1 Torr) and collected as a chromatographically pure syrup (R_F 0.38, system E, *cf.* R_F 0.9 for the starting material). $[\alpha]_D^{24}$ −72.9° (*c* = 1, ethanol).

Found: 49.61% C, 8.40% H, 48.16% CH_3O.

Methyl 3,5-di-O-methyl-α- and -β-D-xylofuranoside

1,2-*O*-Isopropylidene-3,5-di-*O*-methyl-D-xylofuranose (31 g), obtained in a chromatographically pure state (R_F 0.72, system F) by vacuum distillation (b.p. 71—72°C/0.05 Torr) of a crude product [8], was refluxed in methanol containing 0.8% hydrogen chloride (500 ml) until conversion of the starting material was complete (about one and a half hour). The product (R_F 0.45 and 0.25) was isolated in the usual manner which gave 26.4 g (95.5%) of the title anomers. Chromatography on a silica gel column (100 × 4 cm) in the solvent system F was followed by vacuum distillation of the isolated furanosides.

The faster moving component (b.p. 62—63°C/0.02 Torr) was methyl 3,5-di-*O*-methyl--α-D-xylofuranoside. $[\alpha]_D^{24}$ +134.5° (*c* = 1.08, ethanol), yield 10.5 g (38.6%).

For $C_8H_{16}O_5$ (192.21) calculated: 49.98% C, 8.39% H, 48.43% CH_3O; found: 49.97% C, 8.27% H, 48.29% CH_3O.

The slower moving component was methyl 3,5-di-*O*-methyl-β-D-xylofuranoside. $[\alpha]_D^{24}$ −115° (*c* = 1, ethanol), b.p. 96—97°C/0.02 Torr, yield 10.8 g (39.7%).

Found: 49.81% C, 8.40% H, 48.20% CH_3O.

An intermediate, mixed fraction was also obtained.

Methyl 3,5-di-*O*-methyl-β-D-xylofuranoside gave crystalline methyl 3,5-di-*O*-methyl--2-*O*-*p*-nitrobenzoyl-β-D-xylofuranoside having m.p. 106—107°C and $[\alpha]_D^{24}$ −39° (*c* = 1, chloroform).

For $C_{15}H_{10}O_8N$ (332.24) calculated: 4.21% N, 28.02% CH_3O; found: 4.23% N, 27.58% CH_3O.

Methyl 2,3,5-tri-O-methyl-α-D-xylofuranoside

Methyl 3,5-di-*O*-methyl-α-D-xylofuranoside (6 g) was methylated in tetrahydrofuran (25 ml) with methyl sulfate (7 ml) and powdered sodium hydroxide (7 g). After 30 minutes of vigorous stirring at 50°C no starting material (R_F 0.45) was present in the reaction mixture, as showed by TLC in solvent system F. The product (R_F 0.64) was isolated as usual and vacuum distilled (b.p. 57—58°C/0.03 Torr) to give 5.9 g (91%) of a syrup which crystallized on cooling. Recrystallization from *n*-hexane afforded material melting at 29—31.5°C and having $[\alpha]_D^{24}$ +162° (*c* = 1.04, ethanol). Yield of the recrystallized material 4.2 g (65%).

For $C_{10}H_{18}O_5$ (206.23) calculated: 52.41% C, 8.79% H, 60.19% CH_3O; found: 52.47% C, 8.73% H, 60.15% CH_3O.

Methyl 2,3,5-tri-O-methyl-β-D-xylofuranoside

Under the conditions described above methylation of methyl 3,5-di-*O*-methyl-β-D-xylofuranoside (5 g) gave 5 g (93%) of the title compound (R_F 0.80, system F, *cf.* R_F 0.25 for the starting material) which was after vacuum distillation (b.p. 52—53°C/0.03 Torr) collected as a colourless mobile syrup. $[\alpha]_D^{24}$ −88.3° (*c* = 1.03, ethanol).

Found: 52.10% C, 8.67% H, 60.25% CH_3O.

Discussion

The synthesis of the title methyl *O*-methyl-D-xylofuranosides was accomplished by applying the procedures which had originally led to equally substituted free sugar methyl ethers [9].

Methyl furanosides of 5-*O*- and 2,5-di-*O*-methyl-D-xylose were synthesized *via* a synthetic route of *Levene* and *Raymond* [7] who obtained 5-*O*-methyl-D-xylose from 1,2-*O*-isopropylidene-5-*O*-methyl-D-xylofuranose by acid hydrolysis. As preliminary experiments showed that methyl furanosides of 5-*O*-methyl-D-xylose, given rise to by methanolysis of 1,2-*O*-isopropylidene-5-*O*-methyl-D-xylofuranose, do not separate on silica gel, methanolysis was applied after the hydroxyl group at C-3 position had been substituted with benzyl group. The mixture of thus produced α- and β-anomers of methyl furanosides of 3-*O*-benzyl-5-*O*-methyl-D-xylose was resolved by chromatography on a silica gel column. The faster moving component was methyl 3-*O*-benzyl-5-*O*-methyl-α-D-xylofuranoside and the slower moving component was methyl-3-*O*-benzyl-5-*O*-methyl-β-D-xylofuranoside. Methyl furanosides of 5-*O*-methyl-D-xylose were then readily obtained (Chart 1) by the following reductive debenzylation of the isolated anomers.

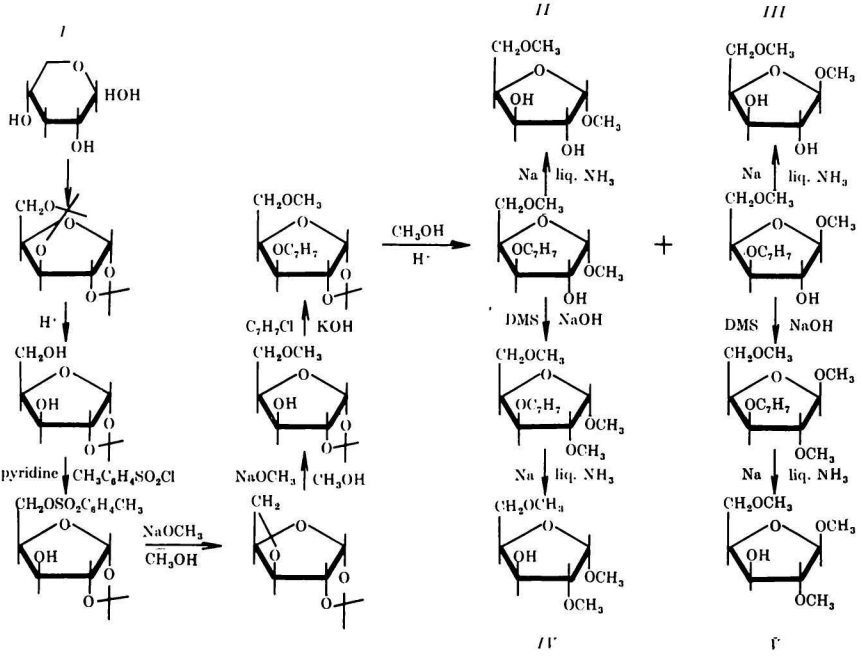

Chart 1. Synthesis of methyl furanosides of 5-*O*- and 2,5-di-*O*-methyl-D-xylose.
I. D-Xylose.
II. Methyl 5-*O*-methyl-α-D-xylofuranoside.
III. Methyl 5-*O*-methyl-β-D-xylofuranoside.
IV. Methyl 2,5-di-*O*-methyl-α-D-xylofuranoside.
V. Methyl 2,5-di-*O*-methyl-β-D-xylofuranoside.

Levene and *Raymond*'s procedure [7] could be successfully extended to the 2,5-di-*O*--methyl substituted methyl furanosides of D-xylose by methylation of C-2 hydroxyl group of individual intermediates leading to methyl furanosides of 5-*O*-methyl-D--xylose (Chart 1). It was observed, by monitoring this synthetic step by TLC that, like in the case of the synthesis of methyl furanosides of 2,3-di-*O*-methyl-D-xylose [2], substitution of the C-2 hydroxyl group with a methoxyl group reversed the mobility of the anomers *i.e.* of the two anomers with the hydroxyl group on C-2 free the α-anomer was the faster moving component. This one became the slower moving of the two as soon as the hydroxyl group on C-2 had been methylated. Following the last step in the synthesis of methyl furanosides of 2,5-di-*O*-methyl-D-xylose by TLC showed that these two separate excellently on silica gel. Thus, when the whole synthesis was repeated without isolation of the intermediates, separation of the final products on a column of silica gel afforded almost quantitative yield of methyl furanosides of 2,5-di-*O*-methyl-D-xylose.

Small scale experiments on the synthesis of methyl furanosides of 3,5-di-*O*-methyl--D-xylose showed that these can be easily separated by column chromatographyt The synthesis of methyl furanosides of 3,5-di-*O*-methyl-D-xylose as well as tha- of 2,3,5-tri-*O*-methyl-D-xylose could therefore be readily accomplished by metha. nolysis of 1,2-*O*-isopropylidene-3,5-di-*O*-methyl-D-xylofuranose [8] followed by

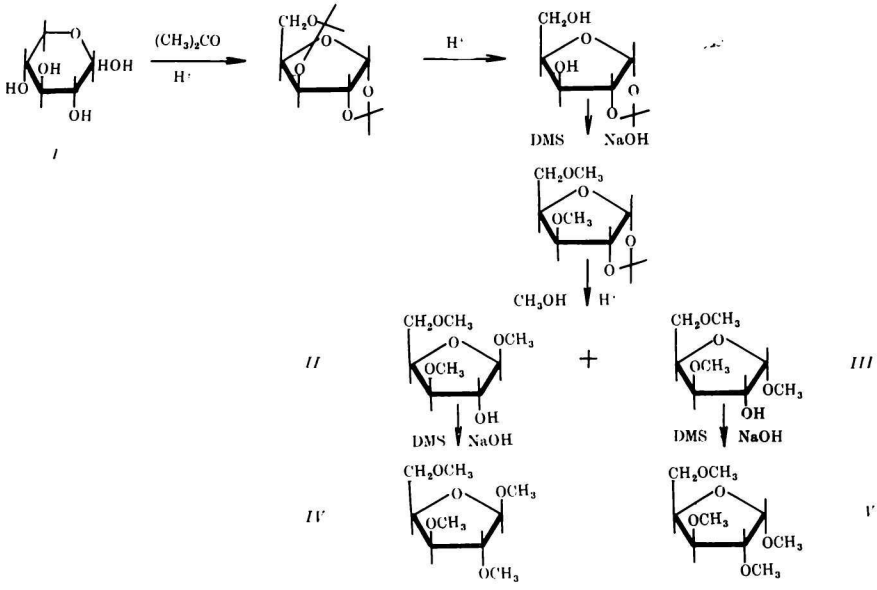

Chart. 2. Synthesis of methyl furanosides of 3,5-di-*O*- and 2,3,5-tri-*O*-methyl-D-xylose.
I. D-Xylose.
II. Methyl 3,5-di-*O*-methyl-β-D-xylofuranoside.
III. Methyl 3,5-di-*O*-methyl-α-D-xylofuranoside.
IV. Methyl 2,3,5-tri-*O*-methyl-β-D-xylofuranoside.
V. Methyl 2,3,5-tri-*O*-methyl-α-D-xylofuranoside.

chromatography, and by methylation of the remaining free hydroxyl group of the isolated methyl furanosides of 3,5-di-*O*-methyl-D-xylose, respectively (Chart 2).

Throughout the synthesis of the last four methyl furanosides there was again observed that the α-anomer was the faster moving component of the two when the C-2 hydroxyl group was free, whereas in the case of furanosides with the C-2 hydroxyl group substituted with a methoxyl group the mobility was reversed. As the same results were obtained when the respective mobilities were examined by gas—liquid chromatography [5], referring to our previous works [1—3], it can be concluded that for the order in which a pair of methyl *O*-methyl-D-xylofuranosides is eluted the same rule can be applied as for methyl *O*-methyl-D-glycopyranosides [4].

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