SYNTHESIS OF METHYL ETHERS OF URONIC ACIDS.

III. SYNTHESIS OF METHYL (METHYL α-D-MANNOPYRANOSID)URONATE AND ITS 2- AND 4-O-METHYL ETHERS

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The synthesis of methyl (methyl α-D-mannopyranosid)uronate and its 2- and 4-O-methyl ethers has been effected by the chromium trioxide oxidation of the corresponding O-benzyl and O-benzylidene derivatives of methyl α-D-mannopyranoside, esterification with diazomethane, and subsequent elimination of the protective benzyl or benzylidene groups by catalytic hydrogenolysis.

Continuing work on the synthesis of methyl ethers of uronic acid [1], we have performed the directed synthesis of methyl (methyl **α-D-mannopyranosid)uronate** and its 2- and 4-O-methyl ethers.

Methyl (methyl α-D-mannopyranosid)uronate (I) was obtained by the oxidation of methyl 2,3,4-tri-O-benzyl-α-D-mannopyranoside with chromium trioxide in acetone followed by esterification of the carboxy group with diazomethane and elimination of the protective benzyl groups by catalytic hydrogenolysis. Compound (I) has been obtained previously by the oxidation of methyl 2,3,4-tri-O-benzoyl-α-D-mannopyranoside with potassium permanganate [2] and by the methanolysis of D-mannofuranurono-6,3-lactone [3].

Methyl (methyl 2-O-methyl-α-D-mannopyranosid)uronate (II) was synthesized from the following scheme: the hydrogenolysis of methyl exo-2,3:4,6-di-O-benzylidene-α-D-mannopyranoside by the $LiAlH_4$-$AlCl_3$ complex [4] led to methyl 3-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (III). The methylation of (III) followed by the hydrogenolysis of the 4,6-O-benzylidene groups [5] gave methyl 3,4-di-O-benzyl-2-O-methyl-α-D-mannopyranoside. Its oxidation with chromium trioxide, esterification with diazomethane, and hydrogenolysis of the benzyl groups led to (II).

Methyl (methyl-4-O-methyl-α-D-mannopyranosid)uronate (IV) was obtained by the benzylation of (III), acid debenzylidenation, tritylation of the primary alcoholic 6-OH group, methylation of the 4-OH group, detritylation, oxidation with chromium trioxide, esterification with diazomethane, and hydrogenolysis of the protective benzyl groups. Compound (IV) has been obtained previously in low yield from methyl α-D-mannopyranosiduronamide via the 2,3,-O-isopropylidene derivative [2].

EXPERIMENTAL

Melting points were determined on a heated stage, refractive indices on a IRF-22 refractometer, and specific rotations on SM-1 polarimeter (Na lamp). The refractive indices and specific rotations were determined at 20°C. Column chromatography was performed on silica gel L (100-250 μ), and thin-layer chromatography on silica gel Woelm TLC. The spots of the sugars on the plates were visualized with the aid of a 5-10% alcoholic solutions of H_2SO_4 followed by heating. The results of the analyses of all the compounds corresponded to the calculated figures. A series of general methods was used in the investigation.

Alkylation. A solution of the substance in dimethylformamide (10 ml/g) was placed in a flask fitted with a caustic potash tube. With stirring, three equivalents of sodium hydride per hydroxy group was added in portions, the mixture was stirred for an hour, and 1.1 equivalents of methyl iodide or benzyl bromide per hydroxy group were added in portions. After 1 h, the excess of sodium hydride was decomposed with methanol. The reaction mixture was poured

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into water and extracted with chloroform, and the chloroform extract was washed with water, dried with anhydrous sodium sulfate, and evaporated.

Oxidation. A solution of the substance in acetone (16 ml/g) was cooled to 5°C, and, with vigorous stirring, a 30% solution of chromium trioxide in 3.5 M sulfuric acid (3.5 ml of solution per 1 g) was added without the temperature being permitted to rise above 10°C. After the whole amount of oxidant had been added, the reaction mixture was stirred with cooling for another 10 min, and at room temperature for 60 min, and was poured into water and carefully extracted with chloroform. The chloroform extract was washed with a small amount of water, dried with anhydrous sodium sulfate, and evaporated to dryness.

Esterification. An ethereal solution of diazomethane was added to a solution of the acid in methanol or ether until a permanent yellow coloration remained. After 20 min, the excess of diazomethane was decomposed with acetic acid, and the solution was evaporated.

Hydrogenolysis. The substance was dissolved in a 10% methanolic solution of formic acid (50 ml/g) and subjected to hydrogenolysis with gaseous hydrogen in the presence of a palladium catalyst (10% Pd/C, Merck, 0.1-0.2 g/g of substance). The catalyst was filtered off and the filtrate was evaporated under reduced pressure with the periodic addition of water and ethanol to eliminate formic acid.

Methyl (Methyl α-D-Mannopyranosid)uronate (I). The oxidation of 4.4 g of methyl 2,3,4-tri-O-benzyl-α-D-mannopyranoside [6] followed by esterification gave methyl (methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosid)uronate (V) with a yield of 2.6 g (56%) after purification on SiO_2 [benzene → benzene–acetone (15:1)] $[\alpha]_D$ +28° (c 1.4; chloroform), n_D 1.547.

The hydrogenolysis of 2.5 g of (V) gave, after purification on SiO_2 [benzene–acetone (1:1)], 1.09 g (80%) of the desired product; $[\alpha]_D$ +75° (c 2.5; water), n_D 1.489. According to the literature [2, 3]: $[\alpha]_D$ +80°, n_D 1.4842; $[\alpha]_D$ +78.8°, n_D 1.4812.

Methyl (Methyl 2-O-Methyl-α-D-Mannopyranosid)uronate (II). With stirring, 1.5 g (0.04 mole) of $LiAlH_4$ and 5.4 g (0.04 mole) of $AlCl_3$ were added to a solution of 14.8 g (0.04 mole) of methyl exo-2,3:4,6-di-O-benzylidene-α-D-mannopyranoside [7] in 200 ml of ether–dichloromethane (1:1). After 10 min, the excess of reagents was decomposed with 20 ml of ethyl acetate, and the reaction mixture was diluted with dichloromethane and carefully washed with water. The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness. After separation of the resulting mixture on SiO_2 [chloroform–acetone (50:1) → chloroform–acetone (20:1)], (III) was isolated with a yield of 12.3 g (83%); $[\alpha]_D$ +46° (c 2.1; chloroform). According to the literature [4]: $[\alpha]_D$ +47°.

The methylation of 5.7 g of (III) led to methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-mannopyranoside (VI) with a yield after purification on SiO_2 [chloroform–acetone (50:1)] of 4.7 g (79%); $[\alpha]_D$ +59° (c 2.0; chloroform). According to the literature [4]: $[\alpha]_D$ +60.5°.

With stirring 2.05 g (0.054 mole) of $LiAlH_4$ was added in three portions to a solution of 4.6 g (0.012 mole) of (VI) in 70 ml of ether–dichloromethane (1:1), and the reaction mixture was heated to the boil. Then a solution of 6.4 g (0.048 mole) of $AlCl_3$ in 50 ml of ether was added to it in portions over 30 min and it was boiled for 1.5-2 h. After the end of the reaction (monitored by TLC), the excess of reagents was decomposed with 15 ml of ethyl acetate, and the mixture was diluted with dichloromethane and washed with water. The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness. After purification on SiO_2 [chloroform–acetone (50:1) → chloroform–acetone (25:1)], 3.7 g (80%) of methyl 3,4-di-O-benzyl-2-O-methyl-α-D-mannopyranoside (VII) was obtained; $[\alpha]_D$ +50° (c 1.7; chloroform). n_D 1.539.

The oxidation of 3.1 g of (VII) followed by esterification gave methyl (methyl 3,4-di-O-benzyl-2-O-methyl-α-D-mannopyranosid)uronate (VIII) in a yield of 2.2 g (66%) after purification on SiO_2 [benzene → benzene–acetone (20:1)]; $[\alpha]_D$ +55° (c 1.7; chloroform), n_D 1.527.

The hydrogenolysis of 2.0 g of (VIII) led, after purification on SiO_2 [chloroform–acetone (5:1) → chloroform–acetone (2:1)], to 0.8 g (71%) of (II); $[\alpha]_D$ +36° (c 1.6; chloroform), n_D 1.477.

Methyl (Methyl 4-O-Methyl-α-D-Mannopyranosid)uronate (IV). The benzylation of 7.6 g of (III) yielded, after purification on SiO_2 (benzene), 8.2 g (86%) of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside (VI); $[\alpha]_D$ +30° (c 2.2; chloroform), n_D 1.564.

A solution of 8 g of (IX) in 120 ml of dioxane–water (2:1) was treated with 8 ml of a N solution of H_2SO_4 and the mixture was kept at 100°C until the hydrolysis of the benzylidene group was complete (2-3 h). The acid was neutralized with barium carbonate, the precipitate was filtered off, the filtrate was evaporated, and the residue was purified on SiO_2 [benzene–acetone (15:1) → benzene–acetone (5:1)]. This gave 5.7 g (88%) of methyl 2,3-di-O-benzyl-α-D-mannopyranoside (X): $[\alpha]_D$ +3° (c 1.5; chloroform), n_D 1.4725.

To a solution of 5.5 g of (X) in 55 ml of pyridine was added 4.5 g of triphenylchloromethane, and the mixture was kept at 80°C for 20 h. Then it was poured into water and extracted with chloroform. The chloroform extract was washed with water, with sulfuric acid solution, with water, with sodium bicarbonate solution, and with water again. The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness. Purification on SiO_2 [benzene → benzene–acetone (30:1)] gave 5.7 g (63%) of methyl 2,3-di-O-benzyl-6-O-trityl-α-D-mannopyranoside (XI); $[\alpha]_D$ −2° (c 2.0; chloroform), glass.

The methylation of 5.3 g of (IX) led to methyl 2,3-di-O-benzyl-4-O-methyl-6-O-trityl-α-D-mannopyranoside (XII) with a yield of 4.8 g (89%) after purification on SiO_2 [chloroform–hexane (1:1) → chloroform] $[\alpha]_D$ +14.5° (c 1.4; chloroform), n_D 1.573.

A solution of 4.6 g of (XII) in 45 ml of acetic acid was heated to the boil, and 20 ml of water was added in portions. After being boiled for 15 min, the solution was cooled, and the triphenyl carbinol that had deposited was filtered off. The filtrate was diluted with water, neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulfate and evaporated to dryness. After purification on SiO_2 (benzene), 1.7 g (60%) of methyl 2,3-di-O-benzyl-4-O-methyl-α-D-mannopyranoside (XIII) was obtained with $[\alpha]_D$ +43° (c 1.5; chloroform), n_D 1.537.

The oxidation of 1.5 g of (XIII) followed by esterification led to methyl (methyl 2,3-di-O-benzyl-4-O-methyl-α-D-mannopyranosid)uronate (XIV) with a yield of 1.0 g (62%) after purification on SiO_2 [chloroform → chloroform–acetone (15:1)]; $[\alpha]_D$ +38° (c 1.3; chloroform), n_D 1.525.

The hydrogenolysis of 0.85 g of (XIV) gave after purification on SiO_2 [chloroform–acetone (5:1) → chloroform–acetone (2:1)], 0.4 g (83%) of (IV); $[\alpha]_D$ +82 (c 1.1; water, n_D 1.474. According to the literature [2]: $[\alpha]_D$ +84°, n_D 1.4727.

SUMMARY

Directed syntheses have been performed of methyl (methyl α-D-mannopyranosid)uronate and its 2- and 4-O-methyl ethers.

LITERATURE CITED

1. V. I. Grishkovets, A. E. Zemlyakov, and V. Ya. Chirva, Khim. Prir. Soedin., 279 (1982); V. I. Grishkovets, A. E. Zemlyakov, and V. Ya. Chirva, Khim. Prir. Soedin., 283 (1982).
2. R. A. Edington, E. L. Hirst, and E. E. Percival, J. Chem. Soc., 2281 (1955).
3. H. W. H. Schmidt, Tetrahedron Lett., 235 (1967).
4. A. Liptak, I. Gregeny, J. Harangi, and P. Nanasi, Carbohydr. Res., 73, 327 (1979).
5. A. Liptak, L. Jodal, and P. Nanasi, Carbohydr. Res., 44, 1 (1975).
6. H. B. Boren, K. Eklind, P. J. Caregg, B. Lindberg, and A. Pilotti, Acta Chem. Scand., 26, 4143 (1972).
7. V. I. Grishkovets, A. E. Zemlyakov, and V. Ya. Chirva, Khim. Prir. Soedin., 119 (1982).