SYNTHESES OF METHYL ETHERS OF URONIC ACIDS.

IV. SYNTHESIS OF THE 3-O-, 2,3-, 2,4-, and 3,4-DI-O-, AND 2,3,4-TRI-O-METHYL ETHERS OF METHYL (METHYL α-D-MANNOPYRANOSID)URONATE

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The synthesis is described of methyl O-benzyl-O-methyl-α-D-mannopyranosides and their oxidation by chromium trioxide, leading, after catalytic hydrogenolysis, to the 3-O, 2,3-, 2,4-, and 3,4-di-O-, and 2,3,4-tri-O-methyl ethers of methyl (methyl α-D-mannopyranosid)uronate.

The methyl ethers of uronic acids are of considerable interest for the structural investigations of acidic oligo- and polysaccharides. In view of this, we have proposed the directed synthesis of the 3-O, 2,3-, 2,4-, and 3,4-di-O, and 2,3,4-tri-O-methyl ethers of methyl (methyl α-D-mannopyranosid)uronate.

Methyl (methyl 3-O-methyl-α-D-mannopyranosid)uronate was synthesized by the exhaustive benzylation of methyl 3-O-methyl-6-O-trityl-α-D-mannopyranoside, followed by detritylation, oxidation with chromium trioxide in acetone, esterification of the carboxy group with diazomethane, and catalytic hydrogenolysis of the protective benzyl groups.

Methyl (methyl 2,3-di-O-methyl-D-mannopyranosid)uronate has been obtained previously in the form of a mixture of anomers from natural alginic acid [1], by its exhaustive methylation followed by methanolysis. We have effected the synthesis of the α anomer of this compound from methyl 2,3-di-O-methyl-6-O-trityl-α-D-mannopyranoside. Its benzylation and the subsequent course of the operations, similar to that described above, led with a high yield to methyl (methyl 2,3-di-O-methyl-α-di-O-mannopyranosid)uronate.

Methyl (methyl 2,4- and 3,4-di-O-methyl-α-D-mannopyranosid)uronates were obtained with high yields from methyl 2,4- and 3,4-di-O-methyl-6-O-trityl-α-D-mannopyranosides, respectively by their benzylation, detritylation, oxidation with chromium trioxide, esterification with diazomethane, and hydrogenolysis of the protective benzyl groups.

Methyl (methyl 2,3,4-tri-O-methyl-α-D-mannopyranosid)uronate was obtained by the detritylation of methyl 2,3,4-tri-O-methyl-6-O-trityl-α-D-mannopyranoside, followed by oxidation with chromium trioxide and esterification with diazomethane. This product had been obtained previously by the permanganate oxidation and esterification of methyl 2,3,4-tri-O-methyl-α-D-mannopyranoside [2].

EXPERIMENTAL

Melting points were obtained on a heated stage, refractive indices on a IRF-22 refractometer, and specific rotations on a SM-1 polarimeter (Na lamp). The refractive indices and specific rotations were determined at 20°C. Column chromatography was performed on silica gel L (200-250 μ) and thin-layer chromatography on Woelm TLC silica gel. The spots of the sugars on the plates were detected with the aid of a 5-10% ethanolic solution of H_2SO_4 followed by heating. The analyses of all the compounds corresponded to the calculated figures.

A number of general methods was used in the work.

Benzylation. A solution of the substance in dimethyl sulfoxide (10 ml/g) was placed in a flask fitted with a caustic potash tube. With stirring, three equivalents of sodium

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hydride for each hydroxy group was added in portions, the mixture was stirred for 1 h, and 1.1 equivalents of benzyl bromide per hydroxy group was added in portions. After 1 h, the excess of sodium hydride was decomposed with methanol. The reaction mixture was poured into water and extracted with chloroform, and the chloroform extract was washed with water, dried with anhydrous sodium sulfate, and evaporated.

Detritylation. A solution of the substance in acetic acid (10 ml/g) was heated to boiling, and water (4 ml/g of substance) was added in portions. After it had been boiled for 20-30 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, extracted with chloroform, dried, 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 of substance) was added in portions without the temperature being allowed to rise above 10°C. After the addition of the whole amount of oxidant, the reaction mixture was stirred for another 10 min with cooling and for 60 min at room temperature, and was then 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 a uronic acid in methanol or ether until a permanent yellow coloration arose. 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 mg/g) and subjected to hydrogenolysis with gaseous hydrogen in the presence of a palladium catalyst (Merck 10% Pd/C; 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 3-O-Methyl-α-D-mannopyranosid)uronate (I). The benzylation of 5 g of methyl 3-O-methyl-6-O-trityl-α-D-mannopyranoside [3] led to methyl 2,4-di-O-benzyl-3-O-methyl-6-O-trityl-α-D-mannopyranodie in a yield of 5.7 g (84%) after purification on silica gel (hexane—chloroform (2:1)→chloroform); $[\alpha]_D$ +27° (c 1.8; chloroform), glass.

The detritylation of 5.5 g of (II) gave methyl 2,4-di-O-benzyl-3-O-methyl-α-D-mannopyranoside (III) with a yield of 2.35 g (69%) after purification on silica gel (hexane—chloroform (1:1)→chloroform); $[\alpha]_D$ +47° (c 1.5; chloroform), n_D 1.538.

The oxidation of 1.8 g of (III) with subsequent esterification gave methyl (methyl 2,4-di-O-benzyl-3-O-methyl-α-D-mannopyranosid)uronate (IV) in a yield of 1.05 g (54%) after purification on silica gel (chloroform→chloroform—acetone (15:1); $[\alpha]_D$ +38° (c 1.4; chloroform), n_D 1.527.

The hydrogenolysis of 1.0 g of (IV) led to 0.45 g (79%) of (I) after purification on silica gel (chloroform—acetone (5:1)→chloroform—acetone (2:1); $[\alpha]_D$ +64° (c 1.4; chloroform), n_D 1.477.

Methyl (Methyl 2,3-Di-O-methyl-α-D-mannopyranosid)usonate (V). The benzylation of 5.7 g of methyl 2,3-di-O-methyl-6-O-trityl-α-D-mannopyranoside [3, 4] gave methyl 4-O-benzyl-2,3-di-O-methyl-6-O-trityl-α-D-mannopyranoside (VI) in a yield of 6.5 g (96%) after purification on silica gel (chloroform—hexane (3:2)→chloroform); $[\alpha]_D$ +45° (c 1.4; chloroform), n_D 1.557.

The detritylation of (VI) gave methyl 4-O-benzyl-2,3-di-O-methyl-α-D-mannopyranoside (VII) in a yield of 3.5 g (97%) after purification on silica gel (chloroform—hexane (2:1)→chloroform); $[\alpha]_D$ +73° (c 1.4; chloroform), n_D 1.508.

The oxidation of 3.4 g of (VII) followed by esterification led to methyl (methyl 4-O-benzyl-2,3,3-O-methyl-α-D-mannopyranosid)uronate (VIII) in yield of 2.7 g (73%) after purification on silica gel (benzene—acetone (15:1)); $[\alpha]_D$ +61° (c 1.5; chloroform), n_D 1.4985.

The hydrogenolysis of 2.6 g of (VIII) gave (V) in a yield of 1.7 g (89%) after purification on silica gel (chloroform—hexane (2:1); $[\alpha]_D$ +37° (c 1.8; chloroform), n_D 1.4635. On standing it crystallized; mp 92-93°C (ether), $[\alpha]_D$ +31° (c 2.0; water). According to the literature [1], for a mixture of anomers: $[\alpha]_D$ +59° (water), n_D 1.4650.

Methyl (Methyl 2,4-Di-O-methyl-D-mannopyranosid)uronate (IX). The benzylation of 5.9 g of methyl 2,4-di-O-methyl-6-O-trityl-α-D-mannopyranoside [3, 5] gave methyl 3-O-benzyl-2,4-di-O-methyl-6-O-trityl-α-D-mannopyranoside (X) in a yield of 6.8 g (97%) after purification on silica gel (chloroform—hexane (2:1)); $[\alpha]_D$ +40° (c 1.4; chloroform), n_D 1.564.

The detritylation of 6.7 g of (X) gave methyl 3-O-benzyl-2,4-di-O-methyl-D-mannopyranoside (XI) in a yield of 3.6 g (95%) after purification on silica gel (chloroform); $[\alpha]_D$ +69° [c 1.4; chloroform), n_D 1.506.

The oxidation of 3.4 g of (XI) followed by esterification led to methyl (methyl 3-O-benzyl-2,4-di-O-methyl-α-D-mannopyranosid)uronate (XII) in a yield of 2.85 g (77%) after purification on silica gel (benzene—acetone (25:1)); $[\alpha]_D$ +64° [c 1.5; chloroform), n_D 1.499.

The hydrogenolysis of 2.8 g of (XII) gave (IX) with a yield of 1.8 g (87%) after purification on silica gel (chloroform—hexane (2:1)→chloroform); $[\alpha]_D$ +44° (c 1.8; chloroform), n_D 1.4655.

Methyl (Methyl 3,4-Di-O-methyl-α-D-mannopyranosid)uronate (XIII). The benzylation of 3.4 g of methyl 3,4-di-O-methyl-6-O-trityl-α-D-mannopyranoside [4, 6] gave methyl 2-O-benzyl-3,4-di-O-methyl-6-O-trityl-α-D-mannopyranoside (XIV) in a yield of 3.9 g (96%) after purification on silica gel (chloroform—hexane (2:1)); mp 140°C (hexane—benzene); $[\alpha]_D$ +14° (c 1.4; chloroform).

The detritylation of 3.8 g of (XIV) led to methyl 2-O-benzyl-3,4-di-O-methyl-α-D-mannopyranoside (XV) with a yield of 2.05 g (96%) after purification on silica gel (chloroform), $[\alpha]_D$ +40° (c 1.4; chloroform), n_D 1.506.

The oxidation of 1.9 g of (XV) followed by esterification gave methyl (methyl 2-O-benzyl-3,4-di-O-methyl-α-D-mannopyranosid)uronate (XVI) in a yield of 1.7 g (82%) after purification on silica gel (benzene—acetone) (25:1)); $[\alpha]_D$ +24° (c 1.5; chloroform), n_D 1.497.

The hydrogenolysis of 1.6 g of (XVI) led to (XIII) in a yield of 0.95 g (81%) after purification on silica gel (chloroform—hexane (2:1)→chloroform; $[\alpha]_D$ +73° (c 2.3; chloroform), n_D 1.462.

Methyl (Methyl 2,3,4-tri-O-methyl-α-D-mannopyranosid)uronate (XVII). The detritylation of 7.4 g of methyl 2,3,4-tri-O-methyl-6-O-trityl-α-D-mannopyranoside [3, 7] led to methyl 2,3,4-tri-O-methyl-α-D-mannopyranoside (XVIII) in a yield of 2.5 g (68%) after purification on silica gel (chloroform→chloroform-acetone)(20:1)); $[\alpha]_D$ +66° (c 2.3; chloroform), n_D 1.461. According to the literature [7]: n_D 1.4605.

The oxidation of 2.3 g of (XVIII) followed by esterification gave (XVII) in a yield of 1.35 g (52%) after purification on silica gel (hexane—acetone (10:1); $[\alpha]_D$ +53° (c 1.8; chloroform); n_D 1.450. According to the literature [2]: $[\alpha]_D$ +45°, n_D 1.4515.

SUMMARY

Directed methods for the synthesis of the 3-O-, 2,3-, 2,4-, and 3,4-di-O-, and 2,3,4-tri-O-methyl ethers of methyl (methyl-α-D-mannopyranosid)uronate have been proposed.

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