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SYNTHESIS OF METHYL DERIVATIVES OF URONIC ACIDS. I. SYNTHESIS OF METHYL (METHYL α-D-GALACTOPYRANOSID)-URONATE AND ITS 2-, 3-, AND 4-O-METHYL ETHERS

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Alternative unidirectional methods for synthesizing methyl (methyl α-D-galactopyranosid)uronate and its mono-O-methyl ethers by the oxidation (with CrO_3—H_2SO_4—acetone) of the corresponding methyl O-benzyl-O-methyl-α-D-galactopyranosides having unsubstituted 6-OH groups to the corresponding methyl O-benzyl-O-methyl-α-D-galactouronic acids followed by esterification with CH_2N_2 and the catalytic hydrogenolysis of the benzyl groups are proposed.

Methyl derivatives of uronic acids are used in establishing the structures of acidic glycosides and oligo- and polysaccharides by the methylation method. However, their synthesis encounters certain difficulties. In the first place, the corresponding uronic acids are comparatively difficultly accessible. In the second place, under strongly alkaline conditions (typical methylation conditions), methyl uronates, especially those with the trans-diaxial position of a hydroxyl at C_4 and a hydrogen atom at C_5, undergo a number of destructive transformations, β-elimination with the formation of 4,5-unsaturated sugars [1], and epimerization at C_5 with the formation of derivatives of a different uronic acid [2]. Consequently, the most suitable starting materials are the methyl ethers of the corresponding methyl hexosides, which are then oxidized to uronic acids. The greatest interest from the point of view of synthesis is presented by the selective oxidation of the primary hydroxy group with oxygen in the presence of platinum catalysts [3], since under these conditions no protection of the secondary hydroxy groups is required. However, in spite of the broad development and the advantages of this method, it cannot be regarded as universal because, in a number of cases, the yields of uronic acids do not exceed 10-20%. Other methods of oxidation [4] have likewise not found wide use in sugar chemistry.

The most convenient and unambiguous method of oxidation is the use of chromium trioxide and dilute sulfuric acid in acetone [5]. Methyl O-benzyl-O-methylhexopyranosides having unsubstituted 6-OH groups are most frequently oxidized by this method to methyl O-benzyl-O-methylhexosiduronic acids. Their subsequent esterification with diazomethane gives methyl (methyl O-benzyl-O-methylhexopyranosid)uronates, and the elimination of the protective benzyl

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groups by catalytic hydrogenolysis leads to the corresponding methyl (methyl O-methylhexopyranosid)uronates, which are the final synthetic products. The use of this method for the synthesis of methyl derivatives of glucuronic acids [6] and of a number of other products has shown its high efficiency.

It must be mentioned that because of the substantial difficulties arising in the synthesis of convenient intermediate compounds, for the single case of the 2-O-methyl ether of D-galacturonic acid directed syntheses have been proposed [7-9] using methyl (methyl 3,4-O-isopropylidene-α-D-galactopyranosid)uronate. In addition, a method of obtaining the 2-, 3-, and 4-O-methyl ethers of D-galacturonic acid has been proposed [10] which is based on the partial benzoylation of methyl (methyl α-D-galactopyranosid)uronate followed by methylation with diazomethane in the presence of boron trifluoride etherate and the elimination of the benzoate groups. However, a serious disadvantage of these methods of synthesis is the formation of unsaturated compounds under the conditions of methylation or of the alkaline hydrolysis of the benzoyl groups.

We suggest alternative unidirectional methods of synthesizing methyl (methyl α-D-galactopyranosid)uronate and its mono-O-methyl ethers starting from D-galactose derivatives and using the method of oxidation described above (CrO_3—H_2SO_4—acetone) under the optimum conditions for it [11]. In this way we have synthesized all the possible mono-O-methyl ethers of galacturonic acid, the constants of the products agreeing with those given in the literature. The starting materials used were methyl 3-O-benzyl-2-O-methyl-, 2-O-benzyl-3-O-methyl-, and 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranosides, which are readily obtainable by the alkylation of methyl 4,6-O-benzylidene-α-D-galactopyranoside [12]. The debenzylidenation of these compounds followed by the tritylation of the primary hydroxy group, methylation or benzylation of the 4-OH group, detritylation, and oxidation leads to the methyl O-benzyl-O-methylgalactosiduronic acids. Their esterification with diazomethane followed the hydrogenolysis of the protective benzyl groups with final chromatographic purification on silica gel led to the required methyl (methyl O-methyl-α-D-galactopyranosid)uronates.

Methyl (methyl α-D-galactopyranosid)uronate has been synthesized from natural D-galacturonic acid and from D-galactose [7, 8, 13]. We suggest one of the possible variants of obtaining this compound by the oxidation and subsequent hydrogenolysis of methyl 2,3,4-tri-O-benzyl-α-D-galactopyranoside, which permits a high anomeric purity to be achieved.

EXPERIMENTAL

Melting points were determined 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 of the substances were determined at 20°C. Column chromatography was performed on silica gel L/40-100 μ (Czechoslovakia). The results of the microanalysis of all the compounds synthesized coincided with the calculated figures.

A number of general methods was used in the investigation.

Debenzylidenation. A solution of 0.02 mole of the substance in 150 ml of a mixture of dioxane and water (2:1) containing 0.005 M sulfuric acid was kept at 100°C until the reaction was complete, after which the acid was neutralized with barium carbonate, the precipitate was filtered off, and the filtrate was evaporated to dryness.

Tritylation. A solution of the substance in pyridine (10 ml/g) was treated with 1.1 equivalents of chlorotriphenylmethane and the mixture was kept at 80°C until the reaction was complete, after which the pyridine was distilled off under reduced pressure, the residue was dissolved in chloroform, and the solution was washed with water, sulfuric acid solution, water, sodium bicarbonate solution, and water again. Then it was dried with anhydrous sodium sulfate and evaporated, and the product was freed from the excess of chlorotriphenylmethane by chromatography on silica gel with elution by benzene and by benzene—acetone (15:1).

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, stirring was continued for 1 h, and 1.1 equivalents of methyl iodide or benzyl bromide for each hydroxy group was added in portions. After another hour, 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 glacial acetic acid (10 ml/g) was heated to the boil and was added in portions to water (40 ml/g of substance). After being heated for 20-30 min, the solution was cooled and the triphenyl carbinol that had deposited was filtered off. The filtrate was diluted with water and extracted with chloroform, and the extract was washed with sodium bicarbonate solution and with water and was 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/g) was added in portions in such a way that the temperature did not rise above 10°C. After the addition of the whole amount of oxidant, the reaction mixture was stirred with cooling for an additional 10 min and at room temperature for 60 min and was poured into water. The aqueous layer was treated with hexane to eliminate small amounts of the initial substance and other impurities and was then 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 had been obtained. After 20 min, the excess of diazomethane was decomposed by the addition of acetic acid, and the solution was evaporated.

Hydrogenolysis. The substance was dissolved in a 10% methanolic solution of formic acid (50 ml/g) and was 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 the formic acid.

Methyl (Methyl α-D-Glactopyranosid)uronate (V). The benzylation of 5.2 g of methyl 6-O-trityl-α-D-galactopyranoside (I) [14] led to methyl 2,3,4-tri-O-benzyl-6-O-trityl-α-D-galactopyranoside (II); 7.1 g (84%), mp 125°C (from ethanol, $[\alpha]_D$ +25° (c, 1.8; chloroform). According to the literature [15]: mp 126-127°C, $[\alpha]_D$ +26°.

The detritylation of 6.5 g of (II) gave a quantitative yield of methyl 2,3,4-tri-O-benzyl-α-D-galactopyranoside (III), $[\alpha]_D$ +57° (c, 1.5, chloroform). According to the literature [16]: $[\alpha]_D^{25}$ + 59.4°.

The oxidation of 3.6 g of (III) followed by esterification with diazomethane yielded 3 g (78%) of methyl (methyl 2,3,4-tri-O-benzyl-α-D-galactopyranosid)uronate (IV), $[\alpha]_D$ +22° (c, 2.1; chloroform); n_D 1.554.

The hydrogenolysis of 2.4 g of (IV) gave 1.0 g (92%) of methyl (methyl α-D-galactopyranosid)uronate. Crystallization from ethanol yielded a hydrate with the composition $C_8H_{16}O_7 \cdot H_2O$, mp 147°C $[\alpha]_D$ +126° (c, 0.9; water). According to the literature [7, 8]: mp 147°C $[\alpha]_D$ +128°; mp 145°, $[\alpha]_D$ +121°.

Methyl (Methyl 2-O-methyl-α-D-galactopyranosid)uronate (XII). The debenzylidenation of 17.5 g of methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside (VI) [12] gave 12.6 g (93%) of methyl 3-O-benzyl-2-O-methyl-α-D-galactopyranoside (VII), $[\alpha]_D$ +100° (c, 2.0; chloroform). According to the literature [17]: $[\alpha]_D^{22}$ +105°.

The tritylation of (VII) gave 19.5 g (85%) of methyl 3-O-benzyl-2-O-methyl-6-O-trityl-α-D-galactopyranoside (VIII), $[\alpha]_D$, +50° (c, 1.0; chloroform). According to the literature [17]: mp 104-106°C, $[\alpha]_D^{22}$ +54°.

The benzylation of 9.4 g of (VIII) led to methyl 3,4-di-O-benzyl-2-O-methyl-6-O-trityl-α-D-galactopyranoside (IX); 9.2 g (84%), $[\alpha]_D$ +51° (c, 1.8; chloroform), n_D 1.578.

The detritylation of 8.7 g of (IX) gave 5.1 g (95%) of methyl 3,4-di-O-benzyl-2-O-methyl-α-D-galactopyranoside (X), $[\alpha]_D$ +56° (c, 1.7; chloroform), n_D 1.541.

The oxidation of 4.5 g of (X) followed by esterification yielded 3.6 g (74%) of methyl (methyl 3,4-di-O-benzyl-2-O-methyl-α-D-galactopyranosid)uronate (XI), $[\alpha]_D$ +78° (c, 1.0; chloroform), n_D 1.5305.

The hydrogenolysis of 2.7 g of (XI) gave 1.3 g (85%) of (XII), $[\alpha]_D$ +126° (c, 1.7; methanol), n_D 1.472. According to the literature [8, 10]: $[\alpha]_D$ = 105°, n_D^{17} 1.468; mp 77-79°C, $[\alpha]_D^{25}$ +140°.

Methyl (Methyl 3-O-Methyl-α-D-galactopyranosid)uronate (XIX). The debenzylidenation of 8.0 g of methyl 2-O-benzyl-4,6-O-benzylidene-3-O-methyl-α-D-galactopyranoside (XIII) [12] gave 5.9 g (96%) of methyl 2-O-benzyl-3-O-methyl-α-D-galactopyranoside (XIV), $[\alpha]_D$ +70° (c, 4.6; chloroform), n_D 1.526.

The tritylation of 5.5 g of (XIV) led to 8.1 g (81%) of methyl 2-O-benzyl-3-O-methyl-6-O-trityl-α-D-galactopyranoside (XIV), $[\alpha]_D$ +34° (c, 1.2; chloroform), glass.

The benzylation of 8.1 g of (XV) led to methyl 2,4-di-O-benzyl-3-O-methyl-6-O-trityl-α-D-galactopyranoside (XVI); 8.1 g (93%), $[\alpha]_D$ +20° (c, 2.4; chloroform), glass.

The detritylation of 8.5 g of (XVI) gave 5.0 g (96%) of methyl 2,4-di-O-benzyl-3-O-methyl-α-D-galactopyranoside (XVII), $[\alpha]_D$ +19° (c, 3.3, chloroform), n_D 1.530.

The oxidation of 4.5 g of (XVII) followed by esterification yielded 3.5 g (72%) of methyl (methyl 2,4-di-O-benzyl-3-O-methyl-α-D-galactopyranosid)uronate (XVIII), $[\alpha]_D$ +19° (c, 3.2; chloroform), n_D 1.533.

The hydrogenolysis of 2.8 g of (XVIII) gave 1.3 g (82%) of (XIX). Crystallization from ether yielded pure (XIX) with mp 101-102°C, $[\alpha]_D$ +150° (c, 1.7; chloroform). According to the literature [10]: mp 102-103°C, $[\alpha]_D^{22}$ +151°.

Methyl (Methyl 4-O-Methyl-α-D-galactopyranosid)uronate (XXVII). The debenzylidenation of 12 g of methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside (XX) [12] gave 8.6 g (89%) of methyl 2,3-di-O-benzyl-α-D-galactopyranoside (XXI), $[\alpha]_D$ +47° (c, 3.7; chloroform), n_D 1.553. According to the literature [18]: mp 87-88°C, $[\alpha]_D$ +45.4°.

The tritylation of (XXI) and crystallization from methanol of the methyl 2,3-di-O-benzyl-6-O-trityl-α-D-galactopyranoside (XXII) so obtained gave 10.5 g (74%) of pure (XXII), mp 75-77°C, $[\alpha]_D$ +20° (c, 2.1; chloroform).

The methylation of 10.5 g of (XXII) led to methyl 2,3-di-O-benzyl-4-O-methyl-6-O-trityl-α-D-galactopyranoside (XXIII); 10.1 g (94%), $[\alpha]_D$ +14° (c, 2.0; chloroform), n_D 1.574.

The detritylation of 10.1 g of (XXIII) gave 5.6 g (90%) of methyl 2,3-di-O-benzyl-4-O-methyl-α-D-galactopyranoside (XXIV), $[\alpha]_D$ +24° (c, 1.4; chloroform), n_D 1.539.

By the oxidation of 5.1 g of (XXIV) followed by esterification, 4.2 g (76%) of methyl (methyl 2,3-di-O-benzyl-4-O-methyl-α-D-galactopyranosid)uronate (XXV) $[\alpha]_D$ +39° (c, 1.6; chloroform), n_D 1.5335, was obtained.

The hydrogenolysis of 2.9 g of (XXV) gave 1.5 g (91%) of (XXVI). Crystallization from acetone–ether yielded pure (XXVI), mp 138-140°C, $[\alpha]_D$ +130° (c, 1.0; chloroform). According to the literature [10]: mp 140-141°C, $[\alpha]_D^{22}$ + 132.5°.

SUMMARY

Unambiguous syntheses of methyl (methyl α-D-galactopyranosid)uronate and its mono-O-methyl ethers have been proposed.

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SYNTHESIS OF METHYL DERIVATIVES OF URONIC ACIDS. II. SYNTHESIS OF THE 2,3-, 2,4-, AND 2,4-DI- AND 2,3,4-TRI-O-METHYL ETHERS OF METHYL (METHYL α-D-GALACTOPYRANOSID)URONATE

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Unidirectional methods are proposed for the synthesis of the 2,3-, 2,4-, and 3,4-di-, and 2,3,4-tri-O-methyl ethers of methyl (methyl α-D-galactopyranosid)uronate by the oxidation (CrO_3—H_2SO_4—acetone) of the corresponding methyl O-benzyl-O-methyl-α-D-galactopyranosides having unsubstituted 6-OH groups to the corresponding (methyl O-benzyl-O-methyl-α-D-galactosid)uronic acids followed by esterification with CH_2N_2 and catalytic hydrogenolysis of the benzyl groups.

Continuing work on the synthesis of methyl derivates of uronic acids, we have synthesized all the di-O- and tri-O-methyl ethers of D-galacturonic acid.

Methyl (methyl 2,3-di-O-methyl-D-galactopyranosid)uronate is one of the main products of the methanolysis of completely methylated pectic substances [1]. However, up to the present time no synthesis of the pure α anomer of this compound has been proposed. A number of authors have obtained the crytalline β anomer [2] and an anomeric mixture of the 2,3-di-O-methyl ethers [1, 3]. We propose a synthesis of methyl (methyl 2,3-di-O-methyl-α-D-galactopyranosid)uronate from methyl 4,6-O-benzylidene-2,3-di-O-methyl-α-D-galactopyranoside by the following method: debenzylidenation, tritylation of the primary alcoholic 6-OH group, benzylation of the 4-OH group, detritylation, oxidation with a solution of chromium trioxide in acetone, esterification with diazomethane, and hydrogenolysis of the protective benzyl group.

Methyl (methyl 2,4-di-O-methyl-α-D-galactopyranosid)uronate was synthesized by the method of Kovač and Brezný [4], but we obtained the intermediate product methyl 3-O-benzyl-4,6-O-benzylidene-2-O-methyl-α-D-galactopyranoside in a simpler manner [5].

In the syntheses of methyl (methyl 3,4-di-O-methyl-α-D-galactopyranosid)uronate described in the literature, the difficultly accessible methyl (methyl 3,4-O-isopropylidene-α-D-galactopyranosid)uronate is used as the starting material; and, moreover, the alkaline conditions of methylation lead to the formation of unsaturated compounds [6], while on detosylation [7] deesterification of the methyl uronate takes place, which requires subsequent re-esterification with diazomethane. In the synthesis of the 3,4-di-O-methyl ether we started from methyl 2-O-benzyl-3-O-methyl-6-O-trityl-α-D-galactopyranoside [8], the methylation of which, with subsequent detritylation, oxidation, esterification, and hydrogenolysis of the benzyl group, gave the required product.

The synthesis of methyl (methyl 2,3,4-tri-O-methyl-α-D-galactopyranosid)uronate presents no fundamental difficulties and has been proposed by a number of authors starting from D-galacturonic acid [2, 9] and from methyl 2,3,4-tri-O-methyl-α-D-galactopyranoside by permanganate oxidation [10]. We have performed an alternative synthesis of this compound, starting from methyl 6-O-benzyl-α-D-galactopyranoside using the following scheme: exhaustive methylation, hydrogenolysis of the benzyl group, oxidation, and esterification.

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