SYNTHESIS OF METHYL 2,6-DIDEOXY-α-D-XYLO- AND α-D-LYXO-HEXOPYRANOSIDE*

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Synthesis of the title glycosides from methyl 3,4-anhydro-6-deoxy-α-D-galactopyranoside and 2-deoxy-D-*lyxo*-hexopyranose is described.

In previous papers of this series we studied the reactivity of hydroxy groups in methyl 4,6-dideoxyglycosides of the *arabino*[1], *xylo* and *lyxo*[2] configuration and methyl 2,6-dideoxyglycosides of the *ribo*[3] and *arabino*[4] configuration in methylation with methyl iodide and sodium hydroxide in acetonitrile. In the present communication we describe the preparation of the remaining two isomers (*xylo* and *lyxo*) of methyl 2,6-dideoxy-α-D-hexopyranoside.

Methyl 2,6-dideoxy-α-D-lyxo-hexopyranoside[5,6] (*I*) was synthesized analogously to the *ribo*[3] and *arabino*[7] isomers. D-Galactose was converted *via* the D-galactal into 2-deoxy-D-*lyxo*-hexopyranose[8,9] (*II*) which by a modified procedure (treatment with an ion exchanger (H^+ form) in methanol) afforded a mixture of anomeric methyl 2-deoxy-D-*lyxo*-hexopyranosides *III* and *IV*. The α-anomer *III* was isolated from this mixture as methyl 4,6-O-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside[9-11] (*V*). Benzoylation of *V* with benzoyl chloride in pyridine afforded methyl 3-O-benzoyl--4,6-O-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside (*VI*) which on reaction with N-bromosuccinimide was converted to methyl 3,4-di-O-benzoyl-6-bromo-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (*VII*). Catalytic hydrogenolysis of the compound *VII* over Raney nickel led into methyl 3,4-di-O-benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (*VIII*) which was debenzoylated with sodium methoxide to give the dihydroxy derivative *I*.

In the preparation of methyl 2,6-dideoxy-α-D-*xylo*-hexopyranoside[12] (*IX*) we made use of the described[13] synthesis of methyl 3,4-anhydro-6-deoxy-α-D-galactopyranoside (*X*). This intermediate on treatment with dilute sodium hydroxide at 42°C afforded

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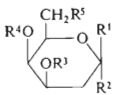
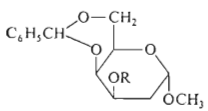
a mixture of the compound *X* and methyl 2,3-anhydro-6-deoxy-α-D-gulopyranoside (*XI*). From this mixture the compound *XI* was obtained as methyl 4-O-acetyl-2,3-anhydro-6-deoxy-α-D-gulopyranoside[13] (*XII*) by crystallisation.

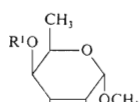
Reduction of *XII* with lithium aluminium hydride yielded a mixture consisting of methyl 2,6-dideoxy-α-D-*xylo*-hexopyranoside (*IX*) and methyl 3,6-dideoxy-α-D-*xylo*-hexopyranoside[14] (*XIII*) in the ratio 2·5 : 1, as determined by gas–liquid chromatography. However, preparative gas–liquid chromatography did not separate these isomers satisfactorily, even in the form of their di-O-acetyl derivatives *XIV* and *XV*. Therefore the mixture of *IX* and *XIII* was benzoylated with benzoyl chloride in pyridine to give methyl 3,4-di-O-benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside (*XVI*) and methyl 2,4-di-O-benzoyl-3,6-dideoxy-α-D-*xylo*-hexopyranoside (*XVII*) which were separated by high pressure liquid chromatography. Treatment of *XVI* with sodium methoxide afforded the dihydroxy derivative *IX*.



I, $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = OCH_3$
II, $R^1, R^2 = OH, H$, $R^3 = R^4 = H$, $R^5 = OH$
III, $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$, $R^5 = OH$
IV, $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$, $R^5 = OH$
VII, $R^1 = H$, $R^2 = OCH_3$, $R^3 = R^4 = Bz$, $R^5 = Br$
VIII, $R^1 = R^5 = H$, $R^2 = OCH_3$, $R^3 = R^4 = Bz$



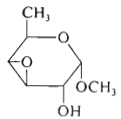
V, R = H
VI, R = Bz



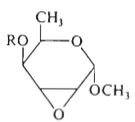
IX, $R^1 = R^3 = H$, $R^2 = OH$
XIII, $R^1 = R^2 = H$, $R^3 = OH$
XIV, $R^1 = Ac$, $R^2 = OAc$, $R^3 = H$
XV, $R^1 = Ac$, $R^2 = H$, $R^3 = OAc$
XVI, $R^1 = Bz$, $R^2 = OBz$, $R^3 = H$
XVII, $R^1 = Bz$, $R^2 = H$, $R^3 = OBz$

High efficiency of the employed liquid chromatography made possible to prepare the compound *IX* without isolating the pure 4-O-acetyl derivative *XII*. The

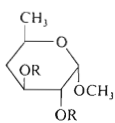
mixture of anhydro derivatives *X* and *XI* was directly reduced with lithium aluminium hydride to a mixture of *IX*, *XIII* and methyl 4,6-dideoxy-α-D-*xylo*-hexopyranoside[14] (*XVIII*) which on benzoylation with benzoyl chloride in pyridine was converted into the corresponding benzoyl derivatives *XVI*, *XVII* and *XIX*. Compound *XVI* was then isolated by the above-mentioned high pressure liquid chromatography.



X



XI, R = H
XII, R = Ac



XVIII, R = H
XIX, R = Bz

Ac = acetyl
Bz = benzoyl

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured at 20°C on an Opton photoelectric polarimeter. Solvents were evaporated at 40°C on a rotatory evaporator under reduced pressure (water pump). Analytical samples were dried at 20°C and 3 Pa, liquids were distilled at 1·3 Pa. Thin-layer chromatography (TLC) was performed on Silica gel G (according to Stahl, 10—40 μm; Merck, Darmstadt) on 25 × 75 mm plates, layer thickness 0·2—0·3 mm; detection by spraying with conc. sulfuric acid and subsequent mineralisation. The high-pressure liquid chromatography was carried out on a Varian 8500 instrument, using a preparative Micro Pak Si 5500 × 8 mm column; flow rate of the mobile phase (dichloromethane with 0·1% of 2-propanol) 150 ml/h at 14 MPa. ^{1}H-NMR spectra were measured in deuteriochloroform on a Varian XL-100-15 instrument (internal standard tetramethylsilane, δ-scale in ppm, coupling constants in Hz). Gas–liquid chromatography was performed on a Varian — Aerograph 2100 instrument combined with a Hewlett–Packard 3380 A integrator (flame-ionisation detector, carrier gas helium).

Methyl 4,6-O-Benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside (*V*)

A solution of 2-deoxy-D-*lyxo*-hexopyranose[9,8], m.p. 102—104°C (*II*; 11 g; 67·1 mmol), in methanol (300 ml) was mixed with Dowex 50 W (50 ml; H^+ form) and the mixture was set aside at 40°C for 24 h. After filtration and washing the ion exchanger with methanol, the combined filtrates were taken down and the residue dried *in vacuo* (oil pump), affording 11·5 g (96%) of a syrupy mixture of the anomeric methylglycosides *III* and *IV*. A part of this mixture (6 g; 33·7 mmol) was shaken with benzaldehyde (40 ml) and anhydrous zinc chloride (6 g) for 24 h, mixed with chloroform and washed with water and ice (3×) and then with saturated sodium hydrogen carbonate solution. The organic layer was dried over magnesium sulfate, filtered, taken down and the unreacted benzaldehyde was driven off *in vacuo* (oil pump). The residue was dissolved in ethanol, the solution concentrated and the compound *V* (2·8 g) obtained by crystallisation from ethanol on addition of acetone and ether; m.p. 179—181°C. The mother liquors were diluted with chloroform, washed with 1M sodium carbonate and water (3×), dried over magnesium sulfate, filtered, taken down and crystallized from ethanol–acetone–ether, yielding another portion (0·8 g) of the product *V* (40% total). Reported melting points are 179—180°C (ref.[9]), 178—179°C (ref.[10]) and 184—185°C (ref.[11]).

Methyl 3-O-Benzoyl-4,6-O-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside (*VI*)

Benzoyl chloride (2·7 ml) was added at about —10°C to a solution of the compound *V* (5·5 g; 20·7 mmol) in pyridine (45 ml) and the mixture was allowed to stand for 48 h at 20°C. After evaporation of the solvent, the residue was mixed with water (10 ml) and extracted three times with chloroform. The combined chloroform extracts were washed with 0·5M sulfuric acid, water, saturated sodium hydrogen carbonate solution and again with water (3×). After drying over magnesium sulfate and filtration, the solution was taken down and the product *VI* obtained by crystallisation from ether–light petroleum, m.p. 103—105·5°C; yield 7·3 g (95%); $[\alpha]_D^{20}$ +199° (*c* 0·6, chloroform). For $C_{21}H_{22}O_6$ (370·4) calculated: 68·11% C, 5·98% H; found: 68·41% C, 6·14% H.

Methyl 3,4-Di-O-benzoyl-6-bromo-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (*VII*)

A mixture of the compound *VI* (3·5 g; 9·5 mmol), tetrachloromethane (100 ml), barium carbonate (3·72 g) and N-bromosuccinimide (1·86 g) was refluxed and the reaction was monitored by TLC (benzene, containing 6% of acetone). After completion of the reaction the mixture was filtered, the precipitate washed with boiling tetrachloromethane and the combined filtrates were taken down. The residue was dissolved in chloroform, the solution washed three times with water, dried over magnesium sulfate, filtered and taken down. The obtained crude *VII* (4·5 g) was purified by chromatography on an alumina column (15 g) in benzene, affording 3·9 g (91%) of a syrupy, not completely pure, compound *VII*, $[\alpha]_D^{20}$ +134° (*c* 0·7, chloroform). For $C_{21}H_{21}$·BrO_6 (449·3) calculated: 56·13% C, 4·71% H, 17·79% Br; found: 56·66% C, 4·95% H, 16·96% Br. ^{1}H-NMR spectrum: 2·13 (1 H, m, $J_{2,2'} = 12{\cdot}0$, $J_{2,3} = 6{\cdot}0$, $J_{1,2} < 3{\cdot}0$, H—2); 2·38 (1 H, q, $J_{1,2'} = 3{\cdot}5$, $J_{2',3} < 2{\cdot}5$, H—2'); 3·38—3·50 (5 H, m, CH_3O, CH_2Br); 4·29 (1 H, m, $J_{5,6} = 6{\cdot}5$, $J_{4,5} < 3{\cdot}0$, H—5); 5·04 (1 H, m, H—1); 5·63 (1 H, m, $J_{3,4} = 3{\cdot}0$, H—3); 5·80 (1 H, m, H—4); 7·20—7·60 (6 H, m, H—Ar); 7·75—7·89 (2 H, m, H—Ar); 7·98—8·12 (2 H, m, H—Ar).

Methyl 3,4-Di-O-benzoyl-2,6-dideoxy-α-D-*lyxo*-hexopyranoside (*VIII*)

A solution of the bromo derivative *VII* (4 g; 8·92 mmol) in methanol (120 ml) was mixed with Raney nickel W—6 (15 ml) and a 20% solution (3 ml) of diethylamine in methanol and stirred

in a hydrogen atmosphere at 20°C and atmospheric pressure. The reaction was followed by TLC (benzene with 6% of acetone). After all the bromo derivative *VII* had reacted, the solution was filtered and taken down, the residue treated with water (about 15 ml) and the mixture extracted with chloroform. The combined extracts were washed with water, dried over magnesium sulfate, filtered and taken down, leaving 3·2 g (96%) of the syrupy deoxy derivative *VIII*, $[\alpha]_D^{20}$ +179° (*c* 0·6, chloroform). For $C_{21}H_{22}O_6$ (370·4) calculated: 68·10% C, 5·99% H; found: 68·17% C, 5·83% H; ^{1}H-NMR spectrum: 1·26 (3 H, d, $J_{5,6}$ = 7·0, CH_3C); 2·12 (1 H, m, $J_{2,2'}$ = 12·0, $J_{2,3}$ = 6·0, $J_{1,2}$ < 3·0, H—2); 2·37 (1 H, q, $J_{1,2'}$ = 3·5, $J_{2',3}$ < 3·0, H—2′); 3·40 (3 H, s, OCH_3); 4·22 (1 H, q, $J_{4,5}$ < 3·0, H—5); 4·97 (1 H, m, H—1); 5·58 (1 H, m, $J_{3,4}$ = 3·0, H—4); 5·67 (1 H, m, H—3); 7·20—7·60 (6 H, m, H—Ar); 7·78—7·90 (2 H, m, H—Ar); 8·02—8·17 (2 H, m, H—Ar).

Methyl 2,6-Dideoxy-α-D-*lyxo*-hexopyranoside (*I*)

A catalytic amount of sodium was added to a solution of the dibenzoyl derivative *VIII* (2·85 g; 7·7 mmol) in methanol and the mixture was kept at 40°C for 4 h. After all the compound *VIII* had reacted (TLC in benzene with 6% of acetone), the solution was saturated with carbon dioxide till it was no longer alkaline and the solvent was driven off. Methyl benzoate was removed by repeated evaporation with water. The thus-obtained residue was taken up in chloroform, the combined extracts were dried over magnesium sulfate, filtered and taken down. Crystallisation from benzene–light petroleum afforded 1·15 g (92%) of the glycoside *I*, m.p. 57—58·5°C, $[\alpha]_D^{20}$ +168° (*c* 0·6, chloroform). ^{1}H-NMR spectrum: 1·27 (3 H, d, $J_{5,6}$ = 6·8, CH_3C); 1·82 (2 H, m, H—2, H—2′); 3·33 (3 H, s, OCH_3); 3·62 (1 H, d, $J_{3,4}$ = 3·0, $J_{4,5}$ < 1·5, H—4); 3·89 (1 H, q, H—5); 3·99 (1 H, m, $J_{2,3}$ = 7·0, $J_{2',3}$ = 10·0, H—3); 4·77 (1 H, m, $J_{1,2}$ = 1·5, $J_{1,2'}$ = 2·5, H—1). For the compound *I* reported[5,6] m.p. 70—72°C. $[\alpha]_D^{16}$ +122° (*c* 2, chloroform); for its enantiomer[15] m.p. 58—59°C, $[\alpha]_D^{20}$ —173° (chloroform).

Methyl 4-O-Acetyl-2,3-anhydro-6-deoxy-α-D-gulopyranoside (*XII*)

To a solution of methyl 3,4-anhydro-6-deoxy-α-D-galactopyranoside[13] (*X*; 1·1 g; 6·9 mmol) in water (100 ml) 9·5M sodium hydroxide (0·1 ml) was added. After warming to 42°C for 2·5 h, the mixture was neutralized by addition of Dowex 50 W (H^+ form). After filtration and washing the ion exchanger with water, the combined filtrates were taken down and the obtained mixture of the anhydro derivatives *X* and *XI* was sublimed (900 mg) and acetylated with acetic anhydride in pyridine[13], affording 184 mg of the compound *XII*, m.p. 83—84°C. (Reported[13] m.p. 83·5 to 84·5°C).

Reduction of Methyl 4-O-Acetyl-2,3-anhydro-6-deoxy-α-D-gulopyranoside (*XII*)

A solution of the compound *XII* (750 mg; 3·7 mmol) in ether (30 ml) was added to lithium aluminium hydride (500 mg) in ether (50 ml). After end of the reaction (TLC in benzene with 10% of acetone), the mixture was decomposed by dropwise addition of water (0·5 ml), 15% sodium hydroxide solution (0·5 ml) and water (1·5 ml). The solids were filtered off and washed with ether. The combined filtrates were taken down, yielding 577 mg (96%) of a syrupy mixture of methyl 3,6-dideoxy-α-D-*xylo*-hexopyranoside (*XIII*) and the 2,6-dideoxyglycoside *IX*. According to gas–liquid chromatography (1 800 × 2 mm column packed with 5% Versamid 900 on Chromosorb T, 170°C, flow rate 20 ml He/min) the ratio *IX* (R_t = 489 s): *XIII* (R_t = 608 s) was 2·5 : 1.

Methyl 3,4-Di-O-benzoyl-2,6-dideoxy-α-D-*xylo*-hexopyranoside (*XVI*)

Benzoyl chloride (1·2 ml) was added at about —10°C to a solution of the mixture of *IX* and *XIII* from the preceding experiment (510 mg; 3·15 mmol) in pyridine (25 ml). Procedure, analogous to that described for the preparation of *VI*, led to a syrupy mixture of benzoyl derivatives *XVI* and *XVII* (1·04 g; 89%) from which *XVI* was isolated by liquid chromatography as a syrup, $[\alpha]_D^{20}$ +154° (*c* 0·9, chloroform). Under the given conditions the retention volume for *XVI* was 29·9 ml and for *XVII* 34·9 ml. For $C_{21}H_{22}O_6$ (370·4) calculated: 68·11% C, 5·98% H; found: 67·88% C, 6·15% H. ^{1}H-NMR spectrum: 1·27 (3 H, d, $J_{5,6}$ = 6·8, CH_3C); 2·09 (1 H, o, $J_{2,2'}$ = = 15·0, $J_{1,2}$ = 1·5, $J_{2,3}$ = 3·0, H—2); 2·30 (1 H, m, $J_{1,2'}$ = 4·0, $J_{2',3}$ = 3·5, H—2′); 2·42 (3 H, s, OCH_3); 4·58 (1 H, o, $J_{4,5}$ = 1·5, H—5); 4·89 (1 H, m, H—1); 5·15 (1 H, q, $J_{3,4}$ = 3·5, H—4); 5·30 (1 H, m, H—3); 7·32—7·60 (6 H, m, H—Ar); 8·00—8·16 (4 H, m, H—Ar). The dibenzoyl derivative *XVI* was obtained also by high pressure liquid chromatography of the benzoylated mixture of the reduced anhydro derivatives *X* and *XI*, without isolating the acetyl derivative *XII*. Reduction of the anhydro derivatives *X* and *XI*, as well as the subsequent benzoylation, was performed in the same manner as described for the preparation of *XVI* from the pure gulo-derivative *XII*.

Methyl 2,6-Dideoxy-α-D-*xylo*-hexopyranoside (*IX*)

The dibenzoyl derivative *XVI* (300 mg; 0·81 mmol) was converted into the syrupy glycoside *IX* (117 mg; 89%), $[\alpha]_D^{20}$ +128° (*c* 0·8, chloroform), as described for the preparation of *I*. For $C_7H_{14}O_4$ (162·2) calculated: 51·84% C, 8·70% H; found: 51·98% C, 8·92% H. ^{1}H-NMR spectrum: 1·27 (3 H, d, $J_{5,6}$ = 6·8, CH_3C); 1·79 (1 H, m, $J_{1,2}$ = 1·5, $J_{2,3}$ = 2·5, $J_{2,2'}$ = 15·0, H—2); 2·14 (1 H, dt, $J_{1,2'} = J_{2',3}$ = 3·4, H—2′); 3·37 (3 H, s, OCH_3); 3·46 (1 H, q, $J_{3,4}$ = 3·5, $J_{4,5} \leqq$ $\leqq$ 2·0, H—4); 3·86 (1 H, m, H—3); 4·22 (1 H, o, H—5); 4·77 (1 H, q, H—1). For *IX* reported[12] $[\alpha]_D^{20}$ +108·7 ± 2° (*c* 0·98, methanol).

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