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Note

Methyl α- and β-L-gulofuranosidurono-6,3-lactone*

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Methods previously described for the preparation of L-guluronic acid and its lactone, generally called L-gulurone, either employ a laborious separation of alginic acid hydrolysates[3] or a sodium amalgam reduction[4] of D-glucaro-6,3-lactone. Both procedures give syrupy L-guluronic acid, from which crystalline L-gulurone can be obtained in only very low overall yield. Apart from this and the still pending structural assignment for L-gulurone, its glycosidation with methanol–hydrochloric acid produces[5] a mixture of at least five chromatographically distinguishable products.

Because of this situation, we have devised a synthesis of both methyl L-gulofuranosidurono-6,3-lactones in gram quantities needed for comprehensive investigations of structure–reactivity relationships in hexofuranurono-6,3-lactones. Thus, D-glucofuranurono-6,3-lactone, the synthesis potential of which has been amply demonstrated[6], is converted into 1,2-*O*-benzylidene-α-D-glucofuranurono-6,3-lactone (**1**) followed by treatment with benzyl bromide–silver oxide to give the 5-*O*-benzyl derivative **2**. With di-isobutyl aluminium hydride, **2** readily yielded 5-*O*-benzyl-1,2-*O*-benzylidene-α-D-*gluco*-hexodialdodifuranose-(1,4:6,3) (**3**). In order to avoid over-reduction in this transformation, protection of the hydroxyl group at C-5 was found to be essential, in contrast to previous results[7]. Glycosidation of **3** with methyl iodide–silver oxide gave a 4:1 mixture of the *exo* methyl (**4**) and *endo* methyl glycoside (**5**), whereas the anomeric ratio was 1:1 when glycosidation was effected with trimethyl orthoformate–boron trifluoride etherate. Non-crystalline **4** was isolated by chromatography, whereas **5** could be obtained by crystallisation; the structures were assigned on the basis of n.m.r. data. Hydrogenolysis of **4** or **5** over palladium gave methyl (6*S*)- (**6**) or (6*R*)-D-*gluco*-hexodialdofuranose-(1,4)-furanoside-(6,3) (**7**) which, on catalytic oxidation over Adams' catalyst, yielded methyl β- (**8**) or α-L-gulofuranosidurono-6,3-lactone (**9**).

Because **4** was not obtained crystalline, an alternative route was investigated. Treatment of 1,2-*O*-benzylidene-5-*O*-toluene-*p*-sulphonyl-α-D-glucofuranurono-6,3-lactone (**10**) with di-isobutyl aluminium hydride gave 1,2-*O*-benzylidene-5-*O*-toluene-

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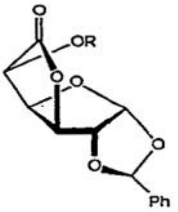
*Reactions of D-Glucuronic Acid: Part XII. For Part XI, see Ref. 1.

**Part of the doctor's thesis of I. Macher[2].



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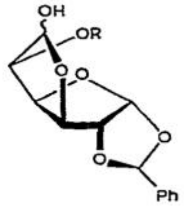
10 R = Ts



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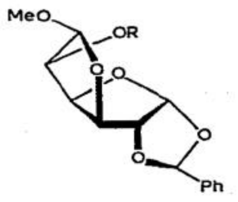

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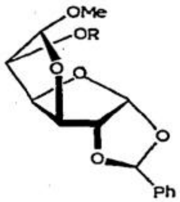

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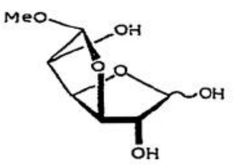

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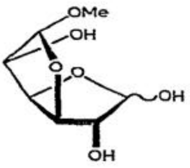

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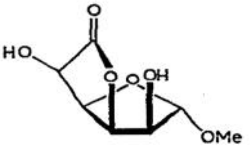

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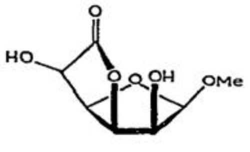

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p-sulphonyl-α-D-*gluco*-hexodialdodifuranose-(1,4:6,3) (**11**) in yields equal to those obtained for the conversion **2**→**3**. With methyl iodide–silver oxide, **11** gave exclusively the *exo* methyl glycoside **12**, readily isolated in crystalline form, whereas, with trimethyl orthoformate–boron trifluoride etherate, a 4:1 mixture of **12** and its anomer **13** was formed. Detosylation of **12** with lithium aluminium hydride in tetrahydrofuran at elevated temperature gave methyl 1,2-*O*-benzylidene-(6*S*)-α-D-*gluco*-hexodialdofuranose-(1,4)-furanoside-(6,3) (**14**), the catalytic hydrogenolysis of which yielded **6**.

EXPERIMENTAL

General methods. — Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. T.l.c. was performed on silica gel 60 F_{254} (Merck, 5554). N.m.r. spectra (internal Me_4Si) were recorded in the pulsed Fourier-transform mode with a Bruker WH-90 DS instrument.

*1,2-*O*-(S)-Benzylidene-α-D-glucofuranurono-6,3-lactone*[8] (**1**). — A mixture of D-glucurono-6,3-lactone (17.6 g, 0.1 mol), zinc chloride (20 g, 0.15 mol), and benzaldehyde (150 ml) was stirred for 2–4 days, until a clear, yellow-orange solution was formed. The mixture was diluted with ether (250 ml), repeatedly extracted with water (total vol., 500 ml), and then concentrated, ultimately at 0.5 Torr to remove most of the benzaldehyde. Trituration of the residue with water (250 ml) gave a semicrystalline solid, which was dried, triturated with ether, and crystallised from ethyl acetate–light petroleum (b.p. 60–80°) to yield **1** (10.6 g, 40%), m.p. 146.5–148.5°, $[\alpha]_D^{20}$ +67° (*c* 1, acetone), R_F 0.38 (chloroform–methanol, 97:3); lit.[8] m.p. 140–145°, $[\alpha]_D$ +46.9° (pyridine). N.m.r. data (acetone-d_6): δ 2.96 (d, 1 H, $J_{5,HO-5}$ 2.0 Hz, HO-5), 4.73 (dd, 1 H, $J_{4,5}$ 3.9 Hz, H-5), 4.98 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-2), 5.0–5.22 (m, 2 H, H-3,4), 6.13 (s, 1 H, PhCH), 6.16 (d, 1 H, H-1), and 7.45 (m, 5 H, Ph).

From the mother liquors, a mixture of **1** and its (*R*)-isomer was obtained (8.4g, 32%), R_F 0.38 and 0.48 (chloroform–methanol, 97:3). All subsequent reactions can also be performed with this mixture.

5-O-Benzyl-1,2-O-(S)-benzylidene-α-D-glucofuranurono-6,3-lactone (**2**). — Benzylation of **1**, as described[9] for 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone, with crystallisation of the product from ether–light petroleum and then ethanol, gave **2** (57%), m.p. 123.5–124.5°, $[\alpha]_D^{20}$ +58° (*c* 1, chloroform), R_F 0.62 (chloroform). N.m.r. data (chloroform-*d*): δ 4.27 (m, 1 H, H-5), 4.78–4.92 (m, 2 H, H-3,4), 4.92 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 4.92 (s, 2 H, PhCH_2), 6.0 (s, 1 H, PhCH), 6.17 (d, 1 H, H-1), and 7.41 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.62; H, 5.22.

*5-O-Benzyl-1,2-O-(S)-benzylidene-α-D-*gluco*-hexodialdodifuranose*-(1,4:6,3) (**3**). — To a stirred solution of **2** (14.2 g, 0.04 mol) in tetrahydrofuran (150 ml) at —44°, a solution of di-isobutyl aluminium hydride in toluene (45 ml, 0.045 mol) was added slowly under argon. After completion of the reaction (~10 h, t.l.c.), methanol–water (40 ml, 9:1) was added slowly, and the mixture was allowed to attain room temperature, and was then diluted with ether (250 ml) and stored overnight. The precipitate was removed by centrifugation, the supernatant layer was concentrated, and the residue was crystallised from cyclohexane to yield **3** (11 g, 77.5%), m.p. 116–118°, $[\alpha]_D^{20}$ +48° (*c* 1, chloroform), R_F 0.35 (benzene–ethyl acetate, 5:1), HO-6 *endo,exo* ratio 6:4. N.m.r. data (chloroform-*d*): δ 3.35 [d, 0.6 H, $J_{6,HO-6}$ 4.2 Hz, HO-6 of (6*R*)-isomer], 3.87 [dd, 0.6 H, $J_{4,5}$ 4.7, $J_{5,6}$ 3.5 Hz, H-5 of (6*R*)-isomer], 3.88 [dd, 0.4 H, $J_{4,5} = J_{5,6}$ = 4.7 Hz, H-5 of (6*S*)-isomer], 3.88 [d, 0.4 H, $J_{6,HO-6}$ 7.7 Hz, HO-6 of (6*S*)-isomer], 4.49–4.98 (m, 5 H, H-2,3,4 and PhCH_2), 5.23 [dd, 0.4 H, H-6 of (6*S*)-isomer], 5.38 [dd, 0.6 H, H-6 of (6*R*)-isomer], 5.93 [s, 0.4 H, PhCH of (6*S*)-isomer], 5.94 [s, 0.6 H, PhCH of (6*R*)-isomer], 6.13 [d, 0.6 H, $J_{1,2}$ 3.7 Hz, H-1 of (6*R*)-isomer], 6.19 [d, 0.4 H, $J_{1,2}$ 3.7 Hz, H-1 of (6*S*)-isomer], and 7.39 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.32; H, 5.62.

Methyl 5-O-benzyl-1,2-O-(S)-benzylidene-(6S)- (**4**) and -(6R)-α-D-gluco-*hexodialdofuranose-(1,4)-furanoside-(6,3)* (**5**). — (*a*) A solution of **3** (25 g, 0.07 mol) and methyl iodide (50 ml, 115 g) in toluene (200 ml) was stirred with silver oxide (18 g, 0.08 mol) for 12 h at ambient temperature, filtered, and concentrated to yield a syrupy mixture of **4** and **5** (ratio 4:1), $[\alpha]_D^{20}$ +98° (*c* 1.6, chloroform). Elution of the mixture from silica gel with chloroform gave **4** as a colourless syrup, $[\alpha]_D^{20}$ +119° (*c* 0.9, chloroform), R_F 0.62 (benzene–ethyl acetate, 10:1). N.m.r. data (chloroform-*d*): δ 3.38 (s, 3 H, OMe), 3.92 (dd, 1 H, $J_{4,5}$ 4.5, $J_{5,6}$ 2.8 Hz, H-5), 4.64 and 4.78 (AB, 2 H, J_{AB} 11.6 Hz, PhCH_2), 4.71 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 4.82 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 4.93 (dd, 1 H, H-4), 4.96 (d, 1 H, H-6), 5.97 (s, 1 H, PhCH), 6.17 (d. 1 H, H-1), and 7.38 (m, 10 H, 2 Ph).

Anal. Calc. for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.20; H, 5.89.

Eluted second was **5**, m.p. 119–120°, $[\alpha]_D^{20}$ +37° (*c* 1.3, chloroform), R_F 0.36

(benzene–ethyl acetate, 10:1). N.m.r. data (chloroform-*d*): δ 3.42 (s, 3 H, OMe), 3.67 (dd, 1 H, $J_{4,5} = J_{5,6} = 4.5$ Hz, H-5), 4.70 and 4.84 (AB, 2 H, J_{AB} 12.5 Hz, PhC*H*$_2$), 4.70 (d, 1 H, $J_{3,4}$ 5 Hz, H-3), 4.72 (d, 1 H, $J_{5,6}$ 4.5 Hz, H-6), 4.77 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 4.87 (dd, 1 H, H-4), 5.93 (s, 1 H, PhC*H*), 6.23 (d, 1 H, H-1), and 7.39 (m, 10 H, 2 Ph).

Anal. Found: C, 68.14; H, 6.04.

(*b*) To an ice-cold solution of **3** (7.1 g, 0.02 mol) in trimethyl orthoformate (50 ml) was added boron trifluoride etherate (1 ml) slowly with stirring. After 1–2 h, the mixture was diluted with ether (50 ml), shaken successively with 10% aqueous sodium carbonate (20 ml) and water (2 × 20 ml), dried, and concentrated to give a quantitative yield of a 1:1 mixture of **4** and **5** from which **5** (2.2 g, 30%) was obtained by two crystallisations from ethyl acetate–light petroleum.

*1,2-*O*-(*S*)-Benzylidene-5-*O*-toluene-*p*-sulphonyl-α-*D*-glucofuranurono-6,3-lactone* (**10**). — Conventional treatment of **1** with toluene-*p*-sulphonyl chloride–pyridine gave **10** (88%), m.p. 201–202° (from acetone–water), $[\alpha]^{20}_{D}$ +45° (*c* 1.3, chloroform), R_F 0.76 (chloroform–methanol, 97:3).

Anal. Calc. for $C_{20}H_{18}O_8S$: C, 57.41; H, 4.34; S, 7.66. Found: C, 57.27; H, 4.43; S, 7.78.

*1,2-*O*-(*S*)-Benzylidene-5-*O*-toluene-*p*-sulphonyl-α-*D*-*gluco*-hexodialdodifuranose-(1,4:6,3)* (**11**). — Reduction of **10** with di-isobutyl aluminium hydride, as described above, gave exclusively (n.m.r. data) **11** having HO-6 *endo* [75% after recrystallisation from ethyl acetate–light petroleum (b.p. 60–80°)], m.p. 138–142°, $[\alpha]^{20}_{D}$ +11°→ +16° (*c* 1.15, chloroform), R_F 0.45 (benzene–ethyl acetate, 5:1). N.m.r. data (chloroform-*d*): δ 2.44 (s, 3 H, Me of Ts), 3.64 (d, 1 H, $J_{6,HO-6}$ 7.8 Hz, HO-6), 4.65 (d, 1 H, $J_{3,4}$ 4.3 Hz, H-3), 4.66 (dd, 1 H, $J_{4,5}$ 4.3, $J_{5,6}$ 4.6 Hz, H-5), 4.85 (dd, 1 H, H-4), 4.90 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 5.24 (dd, 1 H, H-6), 5.89 (s, 1 H, PhC*H*), 6.18 (d, 1 H, H-1), and 7.22–8.0 (m, 9 H, aromatic, Ph and Ts). On addition of traces of acid, C-6-anomerisation occurs.

Anal. Calc. for $C_{20}H_{20}O_8S$: C, 57.13; H, 4.80; S, 7.63. Found: C, 57.00; H, 4.86; S, 7.76.

*Methyl 1,2-*O*-(*S*)-benzylidene-5-*O*-toluene-*p*-sulphonyl-(6*S*)-α-*D*-*gluco*-hexodialdofuranose-(1,4)-furanoside-(6,3)* (**12**). — Treatment of **11** with methyl iodide–silver oxide, as described above, gave, after recrystallisation from ethyl acetate–light petroleum, **12** as colourless needles (69%), m.p. 146–147°, $[\alpha]^{20}_{D}$ +89° (*c* 1.1, chloroform), R_F 0.72 (benzene–ethyl acetate, 5:1). N.m.r. data (chloroform-*d*): δ 2.44 (s, 3 H, Me of Ts), 3.29 (s, 3 H, OMe), 4.70 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 4.70 (dd, 1 H, $J_{4,5}$ 4.5, $J_{5,6}$ 1.8 Hz, H-5), 4.79 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 4.96 (d, 1 H, H-6), 4.98 (dd, 1 H, H-4), 5.89 (s, 1 H, PhC*H*), 6.06 (d, 1 H, H-1), and 7.22–7.96 (m, 9 H, aromatic, Ph and Ts).

Anal. Calc. for $C_{21}H_{22}O_8S$: C, 58.05; H, 5.11; S, 7.38. Found: C, 57.93; H, 5.02; S, 7.51.

*Methyl 1,2-*O*-(*S*)-benzylidene-(6*S*)-α-*D*-*gluco*-hexodialdofuranose-(1,4)-furanoside-(6,3)* (**14**). — To a stirred solution of **12** (2 g, 4.6 mmol) in tetrahydrofuran

(80 ml) was slowly added lithium aluminium hydride (2 g, 52 mmol). The mixture was boiled under reflux until the reaction was complete (t.l.c., 2–4 h), cooled to room temperature, and then treated with water (2 ml), 15% aqueous sodium hydroxide (2 ml), and water (6 ml). The precipitate was collected and washed with tetrahydrofuran (2 × 15 ml), and the combined filtrate and washings were concentrated to a syrup (1.7 g). To remove 4-methylthiophenol, a solution of the residue in ether (50 ml) was shaken with saturated lead acetate (4 × 20 ml) and water (20 ml), filtered through neutral aluminium oxide (5 g), and concentrated to dryness. A solution of the residue in methanol (50 ml) was treated with charcoal and concentrated, and the residue was crystallised from toluene–cyclohexane to give **14** (0.94 g, 73%), m.p. 78–80°, $[\alpha]_D^{20}$ +132° (*c* 0.9, chloroform), R_F 0.41 (benzene–ethyl acetate, 3:1). N.m.r. data (chloroform-*d*): δ 2.89 (d, 1 H, $J_{5,HO-5}$ 6.5 Hz, HO-5), 3.37 (s, 3 H, OMe), 4.12 (ddd, 1 H, $J_{4,5}$ 5.0, $J_{5,6}$ 1.7 Hz, H-5), 4.71 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 4.85 (d, 1 H, H-6), 4.89 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-2), 4.91 (dd, 1 H, H-4), 5.97 (s, 1 H, PhC*H*), 6.15 (d, 1 H, H-1), and 7.42 (m, 5 H, Ph).

Anal. Calc. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.76. Found: C, 60.08; H, 5.75.

Methyl β-L-gulofuranosidurono-6,3-lactone (**8**). — A solution of **4** or **14** (3 mmol) in methanol (50 ml) was hydrogenated at 4 atmos. in the presence of 10% palladium-on-charcoal (0.1 g) for 1–2 days. The catalyst was collected and washed with methanol (20 ml), and the combined filtrate and washings were concentrated to give syrupy methyl (6*S*)-D-*gluco*-hexodialdofuranose-(1,4)-furanoside-(6,3) (**6**) in quantitative yield, $[\alpha]_D^{20}$ +111.5° (*c* 3.7, water), R_F 0.46 (ethyl acetate).

A solution of **6** (1 g, 5.3 mmol) in water (100 ml) was oxidised by air in the presence of Adams' catalyst (hydrogenated platinum oxide, 0.3 g) with vigorous stirring at <20°. After completion of the reaction (20–60 min, t.l.c.), the mixture was filtered and concentrated to dryness. The residue was extracted with acetone (25 ml), and the extract was filtered and concentrated to yield syrupy **8** (90%), $[\alpha]_D^{20}$ +154° (*c* 1.9, methanol), R_F 0.78 (ethyl acetate). N.m.r. data (acetone-d_6/deuterium oxide): δ 3.32 (s, 3 H, OMe), 4.15 (d, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 4.42 (d, 1 H, $J_{4,5}$ 4.3 Hz, H-5), 4.63 (dd, 1 H, $J_{3,4}$ 7.3 Hz, H-4), 4.91 (s, 1 H, H-1), and 5.05 (dd, 1 H, H-3).

Methyl α-L-gulofuranosidurono-6,3-lactone (**9**). — Using the procedures described above, **5** was converted into methyl (6*R*)-D-*gluco*-hexodialdofuranose-(1,4)-furanoside-(6,3) (**7**), $[\alpha]_D^{20}$ −40.5° (*c* 1.6, water), R_F 0.16 (ethyl acetate), and thence into **9** (75%), m.p. 140–143°, $[\alpha]_D^{20}$ −27° (*c* 0.9, acetone), R_F 0.65 (ethyl acetate). N.m.r. data (acetone-d_6/deuterium oxide): δ 3.34 (s, 3 H, OMe), 4.13 (d, 1 H, $J_{4,5}$ 0.5 Hz, H-5), 4.16 (dd, 1 H, $J_{1,2}$ 4.5, $J_{2,3}$ 5.5 Hz, H-2), 4.64 (dd, 1 H, $J_{3,4}$ 5.5 Hz, H-4), 4.84 (d, 1 H, H-1), and 4.97 (dd, 1 H, H-3).

Anal. Calc. for $C_7H_{10}O_6$: C, 44.21; H, 5.30. Found: C, 44.19; H, 5.38.

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