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Note

Synthesis and reactions of uronic acid derivatives Part II[1]. β-Elimination reactions of some derivatives of methyl 3,4-*O*-isopropylidene-D-galacturonate

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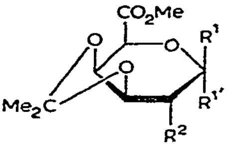
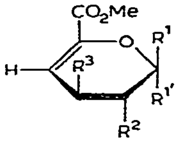
Because of the acidic nature of H-5, C-4 substituents (*e.g.*, alkyl- and arylsulfonyloxy[2,3], acyloxy[4,5], methoxy[5–7], hydroxy[6,8], and glycosyloxy[9]) in esterified uronic acid derivatives are easily eliminated. Degradation of acidic polysaccharides *via* a β-elimination reaction has also been described[10]. We now report on the formation of 4,5-unsaturated 4-deoxyhexopyranosiduronates formed by β-elimination reactions of model compounds substituted with an *O*-alkylidene group.

Derivatives of methyl 3,4-*O*-isopropylidene-D-galacturonate readily undergo base-catalyzed β-elimination reactions. The competing de-esterification reaction does not reduce the driving force for the elimination reaction to the same extent as in compounds where HO-4 is unsubstituted. Accordingly, the yields of the olefins **3**, **4**, and **5** from methyl (methyl 3,4-*O*-isopropylidene-α- and -β-D-galactopyranosid)uronate (**1** and **2**) and methyl (methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-galactopyranosid)uronate (**9**), respectively, on treatment with sodium methoxide in methanol containing 2,2-dimethoxypropane[10], are high.

McCleary[10] and others[7,11] have suggested that 4,5-unsaturated 4-deoxyhexuronates are not the final products of this type of reaction, as indicated by the

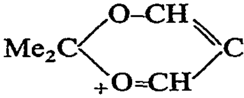


	R^1	R$^{1'}$	R^2
1	H	OMe	OH
2	OMe	H	OH
9	H	OMe	OMe
10	H	O CMe$_2$ O	



	R^1	R$^{1'}$	R^2	R^3
3	H	OMe	OH	OH
4	OMe	H	OH	OH
5	H	OMe	OMe	OH
6	H	O CMe$_2$ O		OH
7	OMe	H	OMe	OMe
8	H	OMe	OMe	OMe

presence of several olefinic components in the reaction mixtures[5,7]. Treatment of the olefin **3** with sodium hydride in dry 1,2-dimethoxyethane gave a crystalline diene (*A*, $C_8H_8O_5$). Although the structure of *A* has not been fully defined, its formation confirms that the product of β-elimination of **1** can undergo a further elimination reaction.

Olefin **6**, obtained from methyl 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranuronate, is also degraded (more rapidly than **3**) under the conditions of its formation. The best yield of **6** (based on the amount of the reacted starting-material) obtainable was 89.6%. The mass spectrum of **6** could be interpreted by using the scheme for the fragmentation of methyl derivatives of methyl 4-deoxy-β-L-*threo*-hex-4-enopyranosiduronate[12], taking into account the mode of fragmentation of *O*-isopropylidene derivatives of carbohydrates[13,14]. The 70-eV spectrum contained the following peaks (*m/e*): M^+ (230); $(M-Me)^+$ (215); $(M-Me-H_2O)^+$ (197, m^* 180.5); $(M-Me-AcOH)^+$ (155);  $Me_2C\langle{}^{O-CH}_{\overset{+}{O}=CH}\rangle CH$ (113); H_1 (100); H_2, *i.e.* $(H_1-Me)^+$, (85); H_2' (71); $Me\overset{+}{C}OMe$ with $\underset{H}{|}$ below C, $\underset{\;\;H}{Me\overset{+}{C}OMe}$ (59); $Me\overset{+}{C}O$ (43).

EXPERIMENTAL

M.p.s. were determined on a Kofler hot-stage. Optical rotations were measured by using a Bendix–Ericsson automatic polarimeter. Mass spectra were obtained at 70 and 12 eV with a MCh-1306 (U.S.S.R.) mass spectrometer. Exact mass measurements for substance *A* were determined with an MS 902 S instrument with the accuracy of 5 p.p.m. N.m.r. spectra were measured in chloroform-*d* (internal Me_4Si) with a Tesla BS 487 B spectrometer. The proton-signal assignments were made by the INDOR technique. Thin-layer chromatography (t.l.c.) was performed on Silica Gel G and column chromatography on silica gel (0.05–0.1 mm) with *A*, carbon tetrachloride–acetone (9:2); *B*, chloroform–acetone (4:1); *C*, benzene–acetone (5:1); *D*, carbon tetrachloride–acetone (9:1); and *E*, benzene–acetone (12:1). Detection was effected by charring with 5% sulphuric acid in ethanol. Olefinic components were located by spraying with 0.1% potassium permanganate in acetone. Solutions were concentrated under diminished pressure at <40°.

Methyl (methyl 3,4-O-isopropylidene-α- and -β-D-galactopyranosid)uronate (**1** *and* **2**). — Isopropylidenation[15] of methyl (methyl αβ-D-galactopyranosid)uronate[16] (4 g) gave two products (R_F 0.15 and 0.3, solvent *A*) which were separated on a column (3.5 × 50 cm) of silica gel. The faster moving component was the known acetal **1** (2.5 g, 52.7%), m.p. 112–114°; lit.[15] m.p. 113–114°.

The slower moving component was the hitherto unknown β anomer **2** (0.8 g, 17%), m.p. 137° (from chloroform–heptane), $[\alpha]_D^{25}$ −28° (*c* 0.9, chloroform) (Found: C, 50.16; H, 6.76; OMe, 24.00. $C_{11}H_{18}O_7$ calc.: C, 50.38; H, 6.91; OMe, 23.67%).

N.m.r. data: δ 4.41 (1-proton doublet, $J_{1,2}$ 2.5 Hz, H-1), 4.48 (1-proton quartet, H-2), 4.15 (1-proton quartet, H-3), 3.63 (1-proton quartet, H-4), 4.14 (1-proton doublet, H-5), 3.56 (3-proton singlet, OMe), 3.82 (3-proton singlet, COMe), 1.34 and 1.5 (two 3-proton singlets, CMe_2). The mass spectra of **1** and **2** were identical with the published[17] spectrum of **1**.

Hydrolysis of the *O*-isopropylidene group in **2** gave methyl (methyl β-D-galactopyranosid)uronate, m.p. 194–196°, $[\alpha]_D^{25}$ $-49°$ (*c* 1, methanol); lit.[18] m.p. 193–194°, $[\alpha]_D^{25}$ $-45.6°$ (*c* 1.06, water). Its mass spectrum was identical with the published spectrum[13] of methyl (methyl α-D-galactopyranosid)uronate.

*Methyl (methyl 4-deoxy-β-*L-threo-*hex-4-enopyranosid)uronate* (**3**). — (*a*) To a solution of **1** (5.25 g) in a mixture of dry 1,2-dimethoxyethane (100 ml) and 2,2-dimethoxypropane (5 ml), sodium hydride (1.7 g) was added at 0°. The mixture was stirred with the exclusion of atmospheric moisture and carbon dioxide at room temperature for 1 h. T.l.c. (solvent *B*) then showed complete disappearance of the starting material. Methanol (50 ml) was added and, with cooling, the solution was deionized with Dowex-50W(H^+) resin and concentrated. The residue was redissolved in a little methanol and excess diazomethane in ether was added. T.l.c. (solvent *B*) showed the presence of a small amount of **1** and two olefinic products (R_F 0.3 and 0.55, *cf.* 0.65 for the starting material). The component having R_F 0.55 was not detected by charring with sulphuric acid. Concentration gave a syrup (4.4 g) which partially crystallized. Crystallization from methanol gave 0.2 g of the component (*A*) having R_F 0.55, m.p. 185–187° (sublimation), $[\alpha]_D^{25}$ 0° (*c* 1, methanol) (Found: C, 51.76; H, 4.26; OMe, 33.85%). The mother liquor was concentrated and the residue was eluted from a column (3.7 × 50 cm) of silica gel, using solvent *B*, to give a further crop (0.05 g) of *A*.

The slower moving component **3** (3 g, 73.5%) had $[\alpha]_D^{25}$ $+192.5°$ (*c* 1.65, methanol), λ_{max}^{MeOH} 239 nm (ε 8300); lit.[6] $[\alpha]_D^{23}$ $+184°$ (*c* 1, methanol), λ_{max}^{MeOH} 238 nm (ε 4600); lit.[19] $[\alpha]_D$ $+203°$ (*c* 1.7, methanol), λ_{max}^{MeOH} 238 nm (ε 6400); lit.[20] $[\alpha]_D^{20}$ $+165.8°$ (*c* 1.78, methanol), λ_{max}^{MeOH} 235 nm. The i.r. and n.m.r. data agreed with those reported[6] for **3**, and the mass spectra (70 and 12 eV) confirmed the molecular weight (M^+ 204).

(*b*) Methanolic M sodium methoxide (22 ml) was added with stirring to a solution of **1** (5.25 g) in methanol (100 ml) containing 2,2-dimethoxypropane (5 ml), and the reaction mixture was kept at 50° for 30 min, after which time t.l.c. (solvent *B*) showed complete disappearance of the starting material. The solution was cooled, neutralized with Dowex-50W(H^+) resin, and concentrated, and ethereal diazomethane was added to the residue. T.l.c. then showed the presence of trace amounts of **1** and *A*, and another, fast-moving, olefinic component (R_F 0.6, not further examined). The major reaction product **3** (3.85 g, 95%), isolated as described above, had $[\alpha]_D^{25}$ $+229°$ (*c* 1.7, methanol).

To a cooled (~0°) solution of **3** (1.5 g) in 1,2-dimethoxyethane (30 ml), sodium hydride (0.3 g) was added with stirring. The mixture was then stirred at room temperature for 24 h, after which time only traces of **3** were present. The reaction mixture was worked-up as described in (*a*) above to give a product which contained (t.l.c., solvent *B*) *A*, several faster moving, minor products (not further examined), and a large proportion of **3**. Compound *A* (65 mg) was obtained by crystallization from methanol and the residue was chromatographed on a column of silica gel to give **3** (1.25 g) and a further crop of *A* (31 mg; total yield 43%, based upon the amount of reacted **3**).

*Methyl (methyl 4-deoxy-α-*L-threo-*hex-4-enopyranosid)uronate* (**4**). — Compound **2** (5.2 g) was treated as described in (*b*) above to give **4** (3.9 g, 95.5%), $[\alpha]_D^{25}$ $-67°$ (*c* 1.15, methanol); lit.[8] $[\alpha]_D^{27}$ $-66°$ (*c* 1.16, methanol). The mass spectrum of **4** was qualitatively identical to that of **3**.

*Methyl (methyl 4-deoxy-2-*O*-methyl-β-*L-threo-*hex-4-enopyranosid)uronate* (**5**). — A solution of chromatographically pure methyl (methyl 3,4-*O*-isopropylidene-2-*O*-methyl-α-D-galactopyranosid)uronate (**9**) (4 g, obtained by purification of the crude product[15] by column chromatography using solvent *E*) in dry methanol (80 ml) containing 2,2-dimethoxypropane (4 ml) was treated with methanolic M sodium methoxide (17 ml) at 50° for 30 min. T.l.c. (solvent *C*) then showed that no starting material was present and the mixture was worked-up as described in (*b*) above. Traces of the starting material (R_F 0.4) were detected together with **5** (R_F 0.2) which was isolated, after chromatography on a column (3 × 30 cm) of silica gel, as a syrup (2.8 g, 88.5%), b.p. 140–160° (bath)/0.02 torr, $[\alpha]_D^{27}$ $+198.5°$ (*c* 2, methanol), λ_{max}^{MeOH} 233 nm (ε 7100) (Found: C, 49.70; H, 6.41; OMe, 42.03. $C_9H_{14}O_6$ calc.: C, 49.54; H, 6.47; OMe, 42.67%). N.m.r. data: δ 5.15 (1-proton doublet, $J_{1,2}$ 2.6 Hz, H-1), 3.46 (1-proton quartet, H-2), 4.49 (1-proton quartet, H-3), 6.08 (1-proton doublet, H-4), 3.52 and 3.55 (two 3-proton singlets, 2OMe), 3.80 (3-proton singlet, COMe). The mass spectrum confirmed the molecular weight (M^+ 218) of **5**.

*Methyl (methyl 2-*O*-methyl-α-*D*-galactopyranosid)uronate.* — A solution of **9** (2 g) in 90% methanol (40 ml) containing methanol-washed, air-dry Dowex-50W(H^+) resin (4 g) was heated at 60° with stirring for 1 h, whereafter the reaction was complete (t.l.c., solvent *B*). The mixture was filtered and concentrated to give the title compound (1.45 g, 85%; R_F 0.3, *cf.* 0.9 for the starting material), b.p. 190–200° (bath)/0.02 torr), m.p. 77–79° (from butanone–ether, 1:1), $[\alpha]_D^{25}$ $+140°$ (*c* 0.7, methanol); lit.[15] $[\alpha]_D$ $+97°$ and $+105°$ (*c* 0.7, methanol) for the amorphous compound. N.m.r. data: δ 5.05 (1-proton doublet, $J_{1,2}$ 3.1 Hz, H-1), 3.59 (1-proton quartet, H-2), 4.0 (1-proton quartet, H-3), 4.34 (1-proton quartet, H-4), 4.46 (1-proton doublet, H-5), 3.82 (3-proton singlet, COMe), 3.50 and 3.46 (two 3-proton singlets, 2OMe), 3.03 (1-proton singlet, OH).

The amide had m.p. 176–176.5°, $[\alpha]_D^{25}$ $+127°$ (*c* 1.27, water); lit.[15] m.p. 174–175°, $[\alpha]_D^{15}$ $+60°$ (*c* 1.3, water).

*Methyl 4-deoxy-1,2-*O*-isopropylidene-β-*L-threo-*hex-4-enopyranuronate* (**6**). — A solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranuronic acid[15] (10 g) in dry methanol (50 ml) was treated with excess of ethereal diazomethane to give the methyl ester **10** (11 g, ~100%), b.p. 110–111°/0.02 torr), m.p. 57–58° (from hexane), $[\alpha]_D^{25}$ $-70.5°$ (*c* 0.95, methanol). N.m.r. data: δ 5.65 (1-proton doublet, $J_{1,2}$ 4.9 Hz, H-1), 4.38 (1-proton quartet, H-2), 4.67 (1-proton quartet, H-3), 4.55 (1-proton quartet, H-4), 4.45 (1-proton quartet, H-5), 3.75 (3-proton singlet, COMe), 1.25–1.5 (four 3-proton singlets, $2Me_2C$).

To a solution of the ester **10** (15 g) in dry methanol (375 ml) and dry 2,2-dimethoxypropane (75 ml), methanolic M sodium methoxide (75 ml) was added at 40°. After 24 h at this temperature with the exclusion of atmospheric moisture and carbon dioxide, t.l.c. (solvent *A*) showed that ~50% of the starting material was still present. The reaction mixture was worked-up as described in (*b*) above, and t.l.c. showed then the presence of the olefin **6** (R_F 0.45), a small amount of *A* (R_F 0.2), and starting material (R_F 0.7). Substance *A* (0.25 g) was obtained by crystallization from methanol and the material in the mother liquor was eluted from a column (100 × 4.5 cm) of silica gel, using solvent *D*, to give starting material (8 g), **6** (5 g, 89.6% based on the amount of the reacted starting-ester), and *A* (0.05 g).

The olefin **6** had b.p. 160–180° (bath)/0.02 torr, $[\alpha]_D^{25}$ +103° (*c* 1, methanol), λ_{max}^{MeOH} 232 nm (ε 8700) (Found: C, 52.13; H, 6.03; OMe, 13.70. $C_{10}H_{14}O_6$ calc.: C, 52.17; H, 6.13; OMe, 13.48%). N.m.r. data: δ 5.61 (1-proton doublet, $J_{1,2}$ 2.8 Hz, H-1), 4.26 (1-proton octet, H-2), 4.41 (1-proton quartet, H-3), 6.18 (1-proton quartet, H-4), 3.81 (3-proton singlet, COMe), 1.45 and 1.47 (two 3-proton singlets, Me_2C).

More vigorous, basic, reaction conditions resulted in a lower yield of **6**.

*Methyl (methyl 4-deoxy-2,3-di-*O*-methyl-α- and -β-*L-threo-*hex-4-enopyranosid)-uronate) (7 and* **8**). — Compound **3** (2 g) was methylated with methyl iodide and silver oxide to give **8** (2 g, 88%), b.p. 89–90°/0.02 torr, $[\alpha]_D^{24}$ +241° (*c* 1.36, methanol), λ_{max}^{MeOH} 238 nm (ε 8100); lit.[6] b.p. 75–82°/0.03 torr, $[\alpha]_D^{23}$ +189° (*c* 1, methanol), λ_{max}^{EtOH} 238 nm (ε 5500). N.m.r. data agreed with those reported[6].

Similar methylation of **4** (2 g) gave **7** (2.2 g, 97%), m.p. 57.5–58.5°, $[\alpha]_D^{25}$ −34° (*c* 2, methanol), λ_{max}^{MeOH} 233 nm (ε 7100); lit.[5] m.p. 51–53°, $[\alpha]_D$ +48° (*c* 2, methanol), λ_{max} 236 (ε 6200). N.m.r. data: δ 4.49 (1-proton quartet, $J_{1,2}$ 4.4 Hz, H-1), 3.49 (1-proton octet, H-2), 3.8 (1-proton octet, H-3), 6.23 (1-proton quartet, H-4), 3.44–3.56 (three 3-proton singlets, 3OMe), 3.82 (3-proton singlet, COMe). The mass spectra of **7** and **8** were qualitatively identical and confirmed the molecular weight (M^+ 232). We are unable to explain the difference between the physical constants found for **7** and the values reported for this compound[5].

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