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Note

Interconversion of methyl 2,3-*O*-isopropylidene-β-D-*ribo*- and α-L-*lyxo*-pentofuranosiduronate methyl esters

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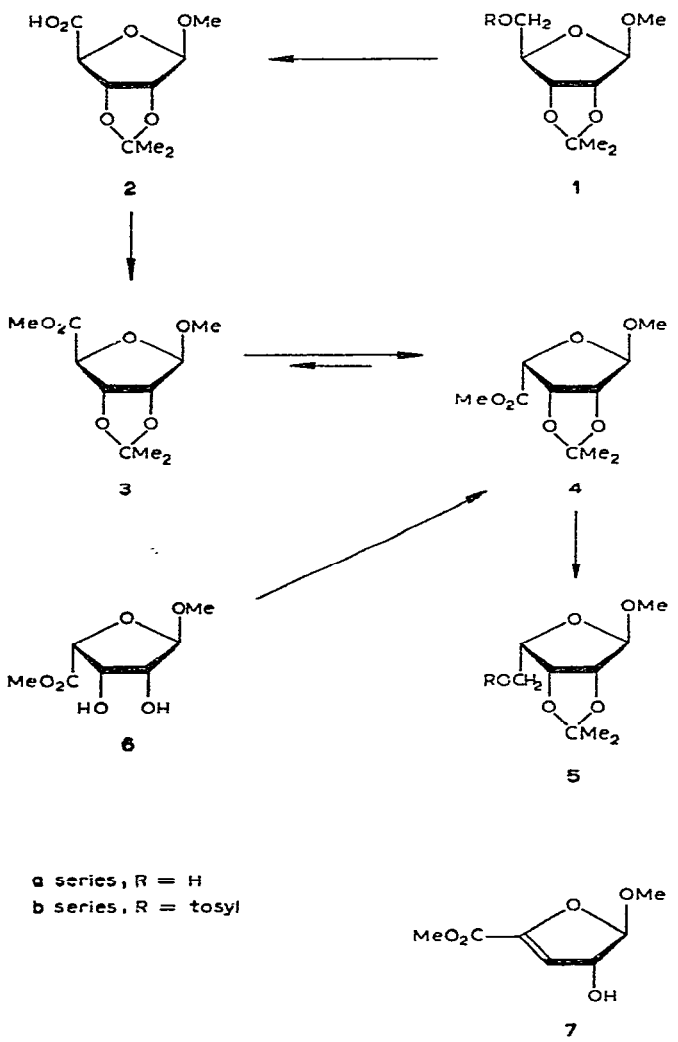
The formation of 4,5-unsaturated 4-deoxyhexopyranosiduronates from uronic acid derivatives having a leaving group β to the carbonyl function, by enzymic or alkali-catalyzed reactions, is well known[1]. In pentofuranuronates, base-catalyzed reaction of compounds having a mesyloxy or diphenyl phosphate leaving-group (*cis* or *trans*) in the 3-position yields 3,4-unsaturated 3-deoxypentofuranuronates[2]. The unsaturated carbohydrate products formed in these reactions are useful for structural as well as for synthetic studies.

It has been reported[3] that hexuronate derivatives substituted with 3,4-*O*-alkylidene groups undergo β-elimination on treatment with sodium methoxide in methanol containing 2,2-dimethoxypropane. This is in agreement with observations reported some time ago for 2′,3′-acetal-substituted pentofuranosylnucleoside-5′-carboxylic acid esters and the corresponding 5′-aldehydes. Nagpal and Horwitz reported that 9-(methyl 2,3-*O*-isopropylidene-β-D-ribofuranosyluronate)adenine reacts with sodium isopropoxide to cause loss of the acetal group with concurrent β-elimination and transesterification to yield isopropyl 3′-deoxy-3′-enoadenosine-5′-carboxylate[4]. Treatment of 2′,3′-*O*-benzylideneuridine-5′-aldehyde with base likewise yields a 3′,4′-unsaturated nucleoside[5]. In accord with these results, Schmidt and co-workers[6] have recently reported that treatment of methyl 2,3-*O*-isopropylidene-β-D-ribofuranosiduronic acid methyl ester (**3**) with a large excess of methoxide in methanol results in expulsion of the acetal group with elimination between C-3 and C-4 to give the unsaturated pentofuranuronate derivative, 4-hydroxy-5-methoxy-4,5-dihydro-2-furancarboxylic acid methyl ester (**7**).

In contrast to these reports, we have observed that treatment, for a short time, of the methyl ester **3** with an equimolar or a slight excess of sodium methoxide in methanol does not yield unsaturated products. This treatment with base instead causes an epimerization about the penultimate carbon atom of **3** to yield the α-L-lyxose derivative **4**. Evidently, the acidic proton at C-4 of the uronic acid ester is abstracted by base to give an intermediate carbanion having sp^2-p geometry because of the conjugative delocalizing effects of the adjacent carbonyl group[7]. Reprotonation of the nearly planar carbanion, which can occur from either face of the molecule, is



controlled by the stereochemical and electronic environment. Abstraction of H-4 was demonstrated by conducting the equilibration experiments in CD_3OD–CD_3ONa; the n.m.r. spectra of these mixtures after processing indicated by integration the loss of one proton resonating in the δ 4.5–5.0 region.

Several related isomerizations have been reported. Treatment of 3-deoxy-1,2-*O*-isopropylidene-L-*threo*-pentodialdo-1,4-furanose with methoxide, followed by borohydride reduction, yields a 4 to 1 mixture of the corresponding D-*erythro* and L-*threo* alcohols[8]. Acid-catalyzed equilibration of 4′-methoxyuridine gives the more stable α-L-*lyxo* nucleoside[9]. Recent observations on the base-catalyzed anomerization of *C*-glycofuranosyl derivatives[10] indicates that products having contiguously disposed *O*-isopropylidene and bulky anomeric substituents are the thermodynamically more-favored isomers.

Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[11] (**1a**) was most conveniently oxidized with potassium permanganate under the basic conditions of Hampton[12] to give the acid **2** in good yield. Treatment with diazomethane gave ester **3** as a homogenous syrup whose n.m.r. parameters were in agreement with those reported[6]. Acid **2** could also be prepared by oxidation with acidic permanganate[13], but the material so obtained contained traces of starting material, which made purification by column chromatography at the stage of ester **3** mandatory.

Treatment of **3** with a slight excess of methoxide in methanolic solution for several h at room temperature readily yielded a major new product, as indicated by t.l.c. This product was isolated by column chromatography and identified as methyl (methyl 2,3-*O*-isopropylidene-α-L-lyxofuranosid)uronate (**4**) by n.m.r. spectroscopy and by direct comparison with material prepared by an alternative route[14]. It was also observed that similar methoxide treatment of **4** resulted in a low conversion into the *ribo* uronic ester **3**. Further confirmation of structures **3** and **4** was demonstrated by reduction of the ester group of **3** and **4** with lithium aluminum hydride, followed by conversion into the known[11,14] crystalline 5-*p*-toluenesulfonates, **1b** and **5b**. The sulfonates prepared by isomerization were identical in all respects to those obtained by direct tosylation of alcohols **1a** and **5a**.

The α-L-*lyxo* ester **4** proved to be the thermodynamically more-stable isomer. Equilibration of the *ribo* ester **3** yielded a 2.3 to 1 mixture of **4** and **3**; from the *lyxo* ester **4**, the ratio of **4** to **3** was 3.3 to 1. No extensive effort was made to determine the exact equilibrium point, as we observed (after several h of reaction) some decomposition to acidic products, as indicated by the presence of material at the origin on t.l.c. plates. In some experiments, a trace of an ultraviolet-absorbing component of intermediate R_F value, possibly the unsaturated[6] ester **7**, was observed.

We have also attempted the base-catalyzed isomerization of methyl 1,2:3,4-di-*O*-isopropylidene-β-D-galactopyranuronate and methyl 2′,3′-*O*-isopropylideneuridine-5′-carboxylate, but were unable to demonstrate clearly any isomerization about the penultimate carbon atoms in these instances.

EXPERIMENTAL

General methods. — Melting points were determined on a Thomas–Hoover capillary apparatus and are not corrected. T.l.c. was performed on microscope slides coated with Silica Gel GF-254 (EM Reagents) using the solvent systems indicated. Compounds were detected by spraying with 20% (v/v) sulfuric acid in ethanol followed by charring. Column chromatography was performed with Silica Gel G (EM Reagents) by a described procedure[15]. All evaporations were conducted *in vacuo* below 40°. Organic solutions were dried over anhydrous magnesium sulfate. Methanol was distilled from magnesium turnings and kept over 4 Å molecular sieves.

N.m.r. spectra were obtained with a Varian T-60A spectrometer in chloroform-*d* solutions, with tetramethylsilane as the internal standard. Chemical shifts are reported in p.p.m. (δ) and coupling constants are first order. Microanalyses were made by Research Division Analytical Services, Miles Laboratories.

Methyl (methyl 2,3-O-isopropylidene-β-D-ribofuranosid)uronate (**3**). — To a stirred solution of **1a** (8.25 g) in acetone (120 ml) and acetic acid (120 ml) was added potassium permanganate (9.60 g). Two additional charges of permanganate (9.60 g) were added at hourly intervals; the dark mixture was then stirred overnight at room temperature. Sodium hydrogen sulfite (10 g) was then added to the mixture and, after stirring for 15 min, the suspension was filtered through Celite and the filtrate evaporated to a thick syrup. The syrup was dissolved in water, the solution decolorized by the addition of sodium hydrogen sulfite (5 g), and the aqueous phase was extracted with three portions of dichloromethane. The organic phase was dried, filtered, and evaporated to a syrup that gave crystals of **2** (4.75 g, 54%) upon further evaporation in a high vacuum; n.m.r.: δ 8.80 (s, 1 H, CO_2H, exchanges with D_2O), 5.20 (d, 1 H, $J_{2,3}$ 6 Hz, H-3), 5.05 (s, 1 H, H-1), 4.65 (s, 1 H, H-4), 4.58 (d, 1 H, H-2), 3.42 (s, 3 H, OCH_3), 1.48, 1.33 (6 H, CMe_2). This crystalline residue was dissolved in methanol (80 ml), and the solution was cooled in ice and then treated with an excess of ethereal diazomethane for 10 min. After decomposition of the excess diazomethane with acetic acid, the mixture was evaporated to give 4.85 g (52%) of material that was purified by chromatography over silica gel (250 g) with 10:1 benzene–ethyl acetate as the eluent, to give 3.36 g of homogeneous (t.l.c.) **3**; n.m.r.: δ 5.22 (d, 1 H, $J_{2,3}$ 6 Hz. H-3), 5.01 (s, 1 H, H-1), 4.60 (s, 1 H, H-4), 4.53 (d, 1 H, H-2), 3.76 (s, 3 H, CO_2Me), 3.38 (s, 3 H, OMe), 1.45, 1.30 (6 H, CMe_2).

Alternatively, compound **2** (8.0 g)[12] in ether (125 ml) was treated with ethereal diazomethane as before to give chromatographically homogeneous **3** (8.5 g), identical by n.m.r. spectroscopy and t.l.c. to material obtained as just described.

Epimerization of **3**. — To a solution of **3** (3.00 g) in dry methanol (35 ml) was added a freshly prepared solution of sodium (300 mg) in methanol (25 ml), and the mixture was stirred at room temperature. T.l.c. in 6:1 benzene–ethyl acetate indicated the formation of a major component migrating slower than the starting material, together with faint traces of other, slower-migrating spots. After 3 h, the mixture was neutralized by the addition of Dowex-50 (H^+) (previously washed with methanol). After removal of the resin, the filtrate was evaporated to dryness to give 2.88 g (96%) of a syrup that was chromatographed over silica gel (200 g) with 8:1 benzene–ethyl acetate as the eluent. Fractions containing the faster-migrating component were combined and evaporated to give unchanged starting material **3** (681 mg, 23%).

Fractions containing the slower-migrating component were pooled and evaporated to give **4** (1.557 g, 52%). The combined yield of **3** and **4** was 75%, with the ratio of products (**3**:**4**) being 1:2.3.

Epimerization of **4**. — To a solution of **4** (5.00 g) in methanol (50 ml) was added a freshly prepared solution of sodium (710 mg) in methanol (25 ml). Examination of the mixture by t.l.c. in 4:1 benzene–ethyl acetate indicated the slow formation of **3**, together with **4** and a trace of material at the origin. After 4 h, the mixture was processed as before to give a yellow syrup (4.71 g, 94%), which was chromatographed over silica gel (250 g) with 6:1 benzene–ethyl acetate as the eluent. Fractions containing

the faster-migrating component were combined and evaporated to give 810 mg (16%) of **3**.

Homogeneous fractions containing the slower-migrating component were pooled and evaporated to give 2.69 g (54%) of **4**. The combined recovery of **3** and **4** was 70%, with the ratio of **3** to **4** being 1:3.3.

Methyl (methyl 2,3-O-isopropylidene-α-L-lyxofuranosid)uronate (**4**). — Crystalline methyl (methyl α-L-lyxofuranosid)uronate (**6**, 7.50 g), m.p. 83–85° (lit.[14] m.p. 85°), was dissolved in a mixture of acetone (50 ml) and 2,2-dimethoxypropane (25 ml). *p*-Toluenesulfonic acid monohydrate (500 mg) was added and the mixture stirred for 2 h at room temperature. The mixture was evaporated to a syrup, which was dissolved in dichloromethane (100 ml) and the organic layer was washed three times with brine (75 ml). The organic phase was dried, filtered, and evaporated to give **4** (9.00 g, quantitative yield) as a homogeneous (t.l.c.) light-yellow syrup; n.m.r.: δ 5.05 (s, 1 H, H-1), 4.95–4.50 (3 H; 4.95, apparent doublet; 4.87, small singlet; 4.59, large apparent singlet; 4.50, apparent doublet; both doublets, J 2 Hz), 3.80 (s, 3 H, ester Me), 3.34 (s, 3 H, OCMe), 1.42, 1.30 (6 H, CMe_2).

Methyl 2,3-O-isopropylidene-5-O-p-tolylsulfonyl-β-D-ribofuranoside (**1b**). — A solution of **3** (744 mg) obtained from **4**, in ether (20 ml), was added dropwise to a stirred suspension of lithium aluminum hydride (91 mg) in ether (15 ml). After several min of stirring, the excess of hydride was quenched with ethyl acetate, with subsequent addition of brine. The ether layer was decanted off, washed once with brine, dried, filtered, and evaporated to give **1a** (556 mg, 85%), whose n.m.r. spectrum was identical both to that of an authentic sample of purified **1a** and to that previously reported[11].

Tosylation followed by recrystallization from 95% ethanol gave pure **1b**, m.p. 81.5–82.5° (lit.[11] m.p. 83–84°); n.m.r. spectrum previously reported[11].

Direct tosylation of **1a** yielded **1b**, m.p. 81.5–83°.

Methyl 2,3-O-isopropylidene-6-O-p-tolylsulfonyl-α-L-lyxofuranoside (**5b**). — A solution of **4** (1.00 g), obtained from **3**, in ether (20 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (106 mg) in ether (15 ml). Processing as before gave syrupy methyl 2,3-*O*-isopropylidene-α-L-lyxofuranoside (**5a**, 700 mg, 80%); n.m.r.: δ 4.93 (1 H, s, H-1), 4.90–4.50 (2 H, m, H-2, H-3), 4.23–3.80 (3 H, m, 2 H-5, H-4), 3.35 (3 H, s, OCMe), 2.60 (1 H, broad, OH), 1.47, 1.32 (6 H, CMe_2).

The alcohol **5a** (640 mg) thus obtained was similarly converted into the *p*-toluenesulfonate **5b**. Recrystallization from 95% ethanol gave analytically pure **5b** (820 mg, 73%), m.p. 76.5–78° (lit.[14] m.p. 76–77°); n.m.r.: δ 7.83, 7.57 (4 H, AB pattern, J 8 Hz, aromatic), 4.85 (1 H, s, H-1), 4.76–4.03 (5 H), 3.28 (3 H, s, OMe), 2.43 (3 H, s, Ts-Me), 1.32, 1.23 (6 H, CMe_2).

Anal. Calc. for $C_{16}H_{22}O_7S$: C, 53.63; H, 6.19. Found: C, 53.65; H, 6.29.

In a similar manner, reduction of **4** (1.00 g, prepared from **6**), gave the alcohol in 92% yield. Tosylation and recrystallization gave 1.12 g (78%) of **5b**, m.p.77–78.5 identical with material already prepared.

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