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BRANCHED-CHAIN SUGARS VIA THE HYDROBORATION–OXIDATION OF UNSATURATED SUGAR DERIVATIVES*

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ABSTRACT

Hydroboration–oxidation of 5-*O*-benzyl-1,2-*O*-isopropylidene-3-deoxy-3-*C*-methylene-α-D-ribofuranose (**2**) afforded 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-ribofuranose (**3**), 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-xylofuranose (**4**), and 5-*O*-benzyl-1,2-*O*-isopropylidene-3-deoxy-3-*C*-hydroxymethyl-α-D-ribofuranose (**5**), in the ratio of 5:7:88. The minor *ribo*-isomer **3** was also synthesized (in 71% yield) by application of a Grignard synthesis to the ketose **1**. The oxymercuration–demercuration reaction of the unsaturated sugar derivative **2** failed. The structures of the isomeric branched-chain sugars **3**, **4**, and **5** were proved by chemical and physical means.

In continuation of our studies on the synthesis of branched-chain sugars via the hydroboration–oxidation reaction[1] in the sugar series[2] we now to report an extension of this reaction to a 3-*C*-methylene pentose derivative to afford novel, isomeric, branched-chain sugars. Previously we have reported[2] that hydroboration, followed by oxidation with alkaline hydrogen peroxide, of 1,2:5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*ribo*-hexofuranose yielded 3-deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose stereoselectively in 88% yield. Other workers[3,4] have also reported the stereoselective, anti-Markovnikov hydration of unsaturated carbohydrates in low yields (about 25%). Hydroboration–oxidation of olefins according to the H. C. Brown procedure[5] sometimes affords Markovnikov products, as well as the preponderantly anti-Markovnikov products. It seemed of interest to determine whether unsaturated sugar derivatives, in general, reacted stereoselectively in this reaction[1]. Moreover, the utilization of a 3-*C*-methylene pentose derivative as a substrate in the hydroboration–oxidation reaction might afford a direct route to a *ribo* branched-chain sugar without need for the subsequent degradation step in the procedure reported previously[2].

The starting material for this research was 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose[6] (**1**), obtained in 90% yield by oxidation of 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose with ruthenium tetraoxide[7].

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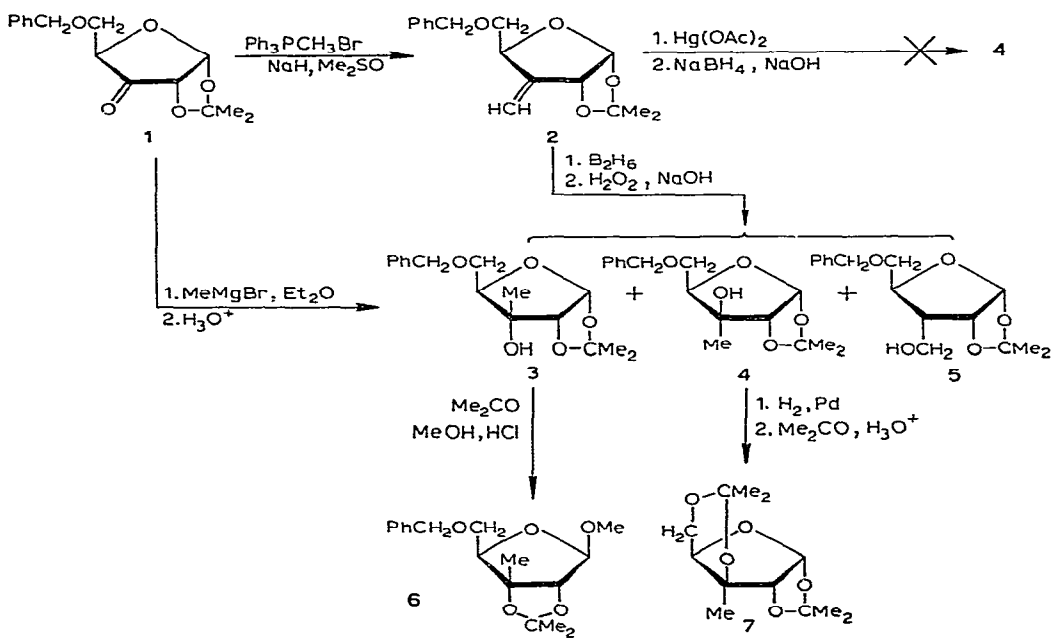
Ruthenium tetraoxide gave a much higher yield of the ketose **1** than did methyl sulfoxide–phosphorus pentaoxide[6]. The ketose required no purification and could be used directly in the Wittig reaction. Condensation of triphenylphosphinemethylene (Wittig reagent) with **1** according to a previous procedure[8] afforded 5-*O*-benzyl-1,2-*O*-isopropylidene-3-deoxy-3-*C*-methylene-α-D-ribofuranose (**2**) in 36% yield. Hydroboration of **2**, followed by oxidation with alkaline hydrogen peroxide, according to a previous procedure[2] yielded 87% of a mixture of three isomeric branched-chain sugar derivatives **3**, **4**, and **5** in the ratio of 5:7:88. The isomers were separated by silica gel column and thin-layer chromatography. The configuration at C-3 in compounds **3** and of **4** was assigned by chemical means and is also supported strongly by physical measurements. Conversion of **3** (with acetone and acidified methanol) into a 2,3-cis acetal, namely, methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-3-*C*-methyl-β-D-ribofuranoside (**6**), strongly indicated the *cis*-disposition of the hydroxyl groups at C-2 and C-3, and confirmed the *ribo* configuration of **3**. The assignment of the β-configuration to **6** was made on the basis of the low $J_{1,2}$ value ($\sim OH_2$) observed in its n.m.r. spectrum. Interestingly, reaction of the ketose **1** with methylmagnesium iodide in ether afforded the *ribo* branched-chain sugar **3** in 71% yield.

The structure of the branched-chain sugar **4** was determined as follows. Debenzylation of **4** with hydrogen over palladium readily afforded a sugar derivative having free hydroxyl groups at C-3 and C-5. Treatment of the latter compound with acidified acetone gave a diisopropylidene acetal **7** in almost quantitative yield, thus confirming that **4** must have the *xylo*-configuration. The structure is, therefore, 5-*O*-benzyl-1,2-isopropylidene-3-*C*-methyl-α-D-xylofuranose.



The configuration at C-3 in **5** was readily deduced from its n.m.r. spectrum. The H-2 signal of **5** appears at τ 5.32 as a triplet showing that H-2 is coupled to H-3 and to H-1. On the other hand, in the gluco-(and xylo)-furanose series[9] there is no coupling between H-2 and H-3, thus leading to a doublet for H-2. Therefore, the only possible configuration for 5 is *ribo*. This assignment was further proved by spin–spin decoupling experiments. Irradiation of the H-2 signal at τ 5.32 of **5** collapsed the H-1 signal into a singlet and altered the H-3 signals. Therefore, **5** is undoubtedly 5-*O*-benzyl-1,2-*O*-isopropylidene-3-deoxy-3-*C*-hydroxymethyl-α-D-ribofuranose.

Although the oxymercuration–demercuration reaction[10] provides a convenient, mild method for achieving the Markovnikov mode of hydration of carbon–carbon double bonds of olefins, this reaction has been applied successfully[11] to only one unsaturated (exocyclic ene) carbohydrate. When this reaction was applied to the unsaturated sugar **2**, the starting material, surprisingly, underwent no reaction.

EXPERIMENTAL

General considerations. — N.m.r. spectra were obtained in chloroform-*d* solution (unless otherwise stated) with tetramethylsilane as the internal standard (set at τ 10) by using a Jeolco 60, or Varian HA-100 spectrometer (peak multiplicities, s, singlet; d, doublet; t, triplet; m, multiplet). I.r. spectra were obtained with a Perkin–Elmer Model 457 spectrophotometer. All melting points (micro hot-stage) are corrected. Silica gel G was used for t.l.c. and Silica gel Woelm (100–200 mesh, activity grade II) for column chromatography. Elemental analyses were performed by the microanalytical laboratory, University of British Columbia.

5-O-Benzyl-1,2-O-isopropylidene-α-D-erythro-pentofuranos-3-ulose (**1**). — To a solution of 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranose[7] (5.6 g) in carbon tetrachloride (100 ml) was added water (15 ml), sodium hydrogen carbonate (1 g), and ruthenium dioxide (80 mg). Sodium metaperiodate (1.2 equivalents of 5% aqueous solution) was added dropwise in small aliquots to the vigorously stirred mixture (it is important to avoid adding excess of the oxidant and to add the oxidant only when the color of the solution changes). After decomposition of excess oxidant by the addition of a few drops of isopropyl alcohol, the ruthenium dioxide precipitated was removed by filtration. The water layer was then extracted with chloroform (6 × 50 ml). These extracts were added to the carbon tetrachloride layer and the solution was evaporated to a syrup. Xylene (2 × 50 ml) was distilled from the residue to yield the ketose **1** (5.1 g, 90%), having the same constants as those reported previously[6] (prepared by oxidation with methyl sulfoxide).

Application of the Wittig reaction to **1** *to yield 5-O-benzyl-1,2-O-isopropylidene-3-deoxy-3-C-methylene-α-D-ribofuranose* (**2**). — Sodium hydride (1 g) was suspended in anhydrous methyl sulfoxide (50 ml) and the mixture was heated for 45 min at 75° in a dry box having an atmosphere of anhydrous nitrogen. After the solution had been cooled to 20° methyltriphenylphosphonium bromide (15 g) was added, and the mixture stirred for 30 min. To the resulting mixture was added dropwise with stirring

a solution of compound **1** (4.5 g) in methyl sulfoxide (25 ml). The mixture was then stirred for an additional 2 h and worked-up by a procedure previously described[8] to yield 2.4 g of a syrup, which was chromatographed on a column of silica gel[8] to afford 1.8 g (36%) of pure **2**, $[\alpha]_D^{22}$ +63° (*c* 1, chloroform).

Anal. Calc. for $C_{16}H_{20}O_4$: C, 69.60; H, 7.26. Found: C, 70.02; H, 7.15.

Hydroboration of **2** *followed by oxidation with alkaline hydrogen peroxide to yield 5-O-benzyl-1,2-O-isopropylidene-3-C-methyl-α-*D*-ribo-pentofuranose* (**3**), *5-O-benzyl-1,2-O-isopropylidene-3-C-methyl-α-*D*-xylo-pentofuranose* (**4**), *and 5-O-benzyl-1,2-O-isopropylidene-3-deoxy-3-C-hydroxymethyl-α-*D*-ribo-pentofuranose* (**5**). — Into a solution of compound **2** (2.8 g, mmoles) in anhydrous tetrahydrofuran (20 ml) was slowly bubbled a large excess of commercial diborane for 4 h at room temperature. It is essential that the tetrahydrofuran be saturated with diborane. After the reaction mixture had been cooled to 0° a 1:1 water–tetrahydrofuran mixture (10 ml) was added dropwise with vigorous stirring, followed by 2M sodium hydroxide (30 ml) and then 30% hydrogen peroxide (15 ml). The reaction mixture was allowed to warm to room temperature and was stirred for a further 0.5 h. After removal of the solvent under diminished pressure the residue was dissolved in water (50 ml) and the solution extracted with 4×20 ml of ether. The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated under diminished pressure to afford 2.6 g (87%) of a syrup. This syrup was chromatographed on silica gel (160 g in a column having a 30:1 length to diameter ratio) with 400 ml of 10:1 benzene–ethyl acetate followed by 1800 ml of 5:1 benzene–ethyl acetate as developer. Fractions (10 ml) were collected mechanically. The faster-moving zone (0.291 g), which consisted of compounds **3** and **4**, was separated by preparative t.l.c. on silica gel G with 4:1 chloroform–ether as developer to afford 0.110 g (5%) of a crystalline compound, R_F 0.35 (ethyl acetate), which was recrystallized from petroleum ether (b.p. 60–90°) to give pure 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-*ribo*-pentofuranose (**3**), m.p. 111–112°; $[\alpha]_D^{22}$ +15° (*c* 0.5, chloroform); ν(mM CCl_4) 3620 (OH); τ^{CDCl_3} 4.25 (d, $J_{1,2}$ 4 Hz, H-1), 5.54 (d, OCH_2Ph), 5.9 (d, $J_{1,2}$ 4 Hz, H-2), 6.0 (m, H-4), 6.35 (m, H-5), 7.1 (s, disappears with addition of D_2O, OH), 8.43, 8.66, 8.88 (s, CH_3 groups).

Anal. of **3**. Calc. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.39; H, 7.49.

The second zone on the t.l.c. plate, R_F 0.40, yield 0.154 g (6%), was recrystallized from petroleum ether (b.p. 60–90°) to give pure 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-*xylo*-pentofuranose (**4**), m.p. 94–95°, $[\alpha]_D^{22}$ +46° (*c* 0.5, chloroform); τ^{CDCl_3} 4.05 (d, $J_{1,2}$ 4 Hz, H-1), 5,4 (d, OCH_2Ph), 5.75 (d, $J_{1,2}$ 4 Hz, H-2), 6.1 (m, H-4, H-5).

Anal. of **4**. Calc. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.42; H, 7.38.

The slower-moving zone on the column (1.848 g, 76%), was recrystallized from petroleum ether (b.p. 60–90°) to afford pure 5-*O*-benzyl-1,2-*O*-isopropylidene 3-deoxy-3-*C*-hydroxymethyl-α-D-ribofuranose (**5**), m.p. 69–70°; $[\alpha]_D^{22}$ +37° (*c* 2, chloroform); τ^{CDCl_3} 4.25 (d, $J_{1,2}$ 4 Hz, H-1), 5.32 (t, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 4.0 Hz, H-2), 5.47 (s, CH_2Ph), 5.7 (m, H-4), 6.23 (d, *J* 6 Hz, CH_2OH), 6.40 (d, H-5), 7.30

(s, disappears on addition of D_2O, OH), 7.80 (m, H-3), 8.52 and 8.72 (two s, CMe_2). Irradiation of **5** at τ 4.25 collapsed the triplet at τ 5.32 into a doublet. Irradiation at τ 5.32 collapsed the doublet at τ 4.25 into a singlet and altered the H-3 resonance.

Anal. of **5**. Calc. for $C_{16}H_{22}O_5$: C, 65.28; H, 7.53. Found: C, 65.39; H, 7.47.

Reaction of methylmagnesium iodide with **1** *to yield* **3**. — To a stirred solution of methylmagnesium iodide (from 1.59 g of magnesium and 7.3 g of methyl iodide) in ether (70 ml) was added dropwise a solution of **1** (1.8 g) in ether (20 ml). After stirring for an additional 10 min the reaction mixture was poured with stirring into an ice-cold mixture of ether (200 ml) and 20% aqueous ammonium chloride solution (300 ml). The water layer was separated and extracted with ether (3 × 100 ml). The combined ether extracts were dried with magnesium sulfate, filtered, and evaporated. The residue was recrystallized from petroleum ether (b.p. 60–90°) to give 1.35 g (71%) of pure **3**, m.p. 110–111°, mixed m.p. with **3** from the former procedure, 110–111°. The n.m.r. spectra of the two products were identical.

Attempted oxymercuration–dermercuration[10,11] *of* **2**. — The unsaturated sugar **2** (0.11 g) in anhydrous tetrahydrofuran (1 ml) was added to a mixture of mercuric acetate (0.138 g) in water (2 ml) and tetrahydrofuran (1 ml). The unsaturated sugar **2** was unchanged (after work-up) after 30 min at room temperature or at 60°, as evidenced by its i.r. and n.m.r. spectra. The reaction mixture was subsequently treated with 3M sodium hydroxide followed by sodium borohydride according to a previously reported procedure[10], but only starting material was obtained.

*Methyl 5-*O*-benzyl-2,3-*O*-isopropylidene-3-*C*-methyl-β-*D*-ribofuranoside* (**6**). — To a solution of **3** (0.150 g) in anhydrous acetone (3 ml) was added a 3% solution of anhydrous hydrogen chloride in absolute methanol (3 ml). After the reaction mixture had been kept for 24 h at room temperature, solid sodium hydrogen carbonate (0.5 g) was added, and the mixture was stirred for 15 min. The solids were removed by filtration, the filtrate was evaporated to dryness, and the residue extracted with dichloromethane (3 × 10 ml). Evaporation of the solvent gave a syrup that was distilled at 125–135° at 0.05 torr to afford 0.120 g (73%) of pure **6**, $[\alpha]_D^{22}$ −38° (*c* 1, chloroform); R_F 0.8 (10:1 benzene–ethyl acetate); τ^{CDCl_3} 5.13 (s, H-1), 5.47 (s, CH_2Ph), 5.65 (m, H-4), 5.85 (s, H-2), 6.5 (d, $J_{4,5}$ 5 Hz, H-5), 6.72 (s, OCH_3), 8.52 and 8.62 (CMe_2 and CH_3).

Anal. Calc. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.78. Found: C, 65.98; H, 7.60.

*1,2:3,5-Di-*O*-isopropylidene-3-deoxy-3-*C*-methyl-α-*D*-xylofuranose* (**7**). — The branched-chain sugar **4** (20 mg) was dissolved in a solution of methanol (10 ml) and 1 drop of conc. acetic acid, and was debenzylated with hydrogen over palladium on calcium sulfate. The catalyst was removed by filtration and the solvent evaporated under diminished pressure to give 15 mg of 1,2-*O*-isopropylidene-3-*C*-methyl-α-D-xylofuranose, $[\alpha]_D^{22}$ +65° (*c* 0.50, chloroform); τ^{CDCl_3} (60 MHz), 4.15 (d, H-1), 5.8 (d, H-2), 6.05 and 6.25 (H-4 and H-5), 6.9 (s, OH), 8.6 and 8.8 (CMe_2 and CMe).

The monoisopropylidene acetal was treated with anhydrous acetone (1 ml) containing concentrated sulfuric acid (0.03 ml) and anhydrous copper sulfate (20 mg) for 2 days at room temperature. The mixture was filtered, and then neutralized with

concentrated ammonium hydroxide, evaporated to dryness, and the residue was extracted with chloroform (2×2 ml). The solvent was evaporated off to give 13 mg of chromatographically pure 7; $[\alpha]_D^{22} + 52°$ (c 0.5, chloroform); R_F 0.65 (10:1 benzene–ethyl acetate); τ^{CDCl_3} (60 MHz) 4.1 (d, $J_{1,2}$ 4 Hz, H-1), 5.8, 6.2, 6.4 (H-2, H-4, H-5), 8.4–8.8 (CMe_2, C–Me = 15 H).

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