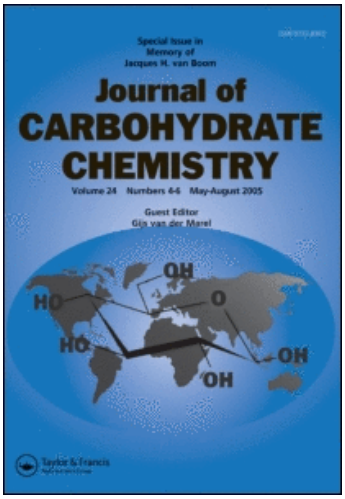

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Jarosz, Slawomir and Zamqjski, Aleksander(1993) 'A Facile Synthesis of 1,2:3,4:5,6-Tri-*O*-Isopropylidene-D-Gluconate-A Convenient Precursor of the Open Chain form of D-Glucose', Journal of Carbohydrate Chemistry, 12: 8, 1223 — 1228
To link to this Article: DOI: 10.1080/07328309308020130
URL: http://dx.doi.org/10.1080/07328309308020130

J. CARBOHYDRATE CHEMISTRY, 12(8), 1223-1228 (1993)

COMMUNICATION

A FACILE SYNTHESIS OF 1,2:3,4:5,6-Tri-*O*-ISOPROPYLIDENE-D-GLUCONATE - A CONVENIENT PRECURSOR OF THE OPEN CHAIN FORM OF D-GLUCOSE

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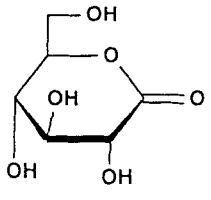
Received September 1, 1992 - Final Form August 11, 1993

Condensation of D-glucono-1,5-lactone (1) with acidified acetone yields in low yield, among other products, 1,2:3,4:5,6-tri-*O*-isopropylidene-D-gluconate (2).[1,2] Reaction of 2 with sodium methoxide in methanol gives methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate[3] (3); this compound was prepared recently by Chittenden and co-workers[3] directly from 1 (by reaction of 1 with acetone and dimethoxypropane). It is easily transformed[3] into 2,3:4,5-di-*O*-isopropylidene-D-arabinose (4).



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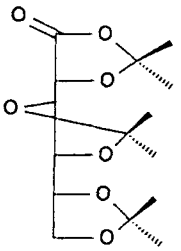

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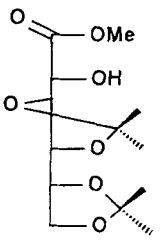

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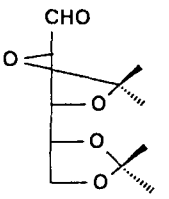
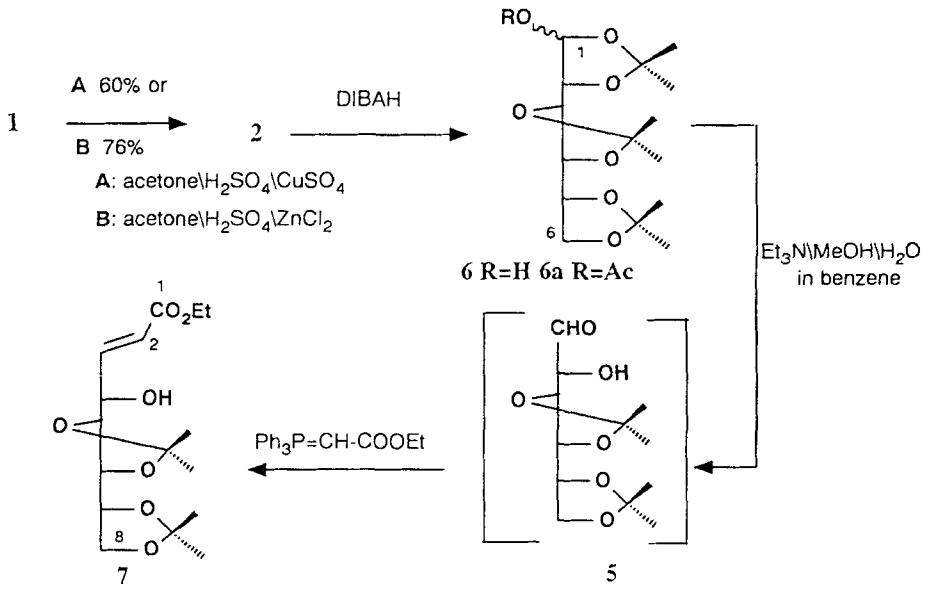


4

Triacetonide **2** may be regarded as a precursor of the open-chain form of D-glucose; reduction of the ester function in **2** with diisobutylaluminum hydride (DIBAH) should afford aldehyde **5**, which is, to the best of our knowledge, the first example of an open-chain form of the D-glucose with a free 2-OH. This compound is properly functionalized for an efficient chain elongation at *C*-1 and, therefore, may serve as a convenient precursor of higher carbon sugars in which the presence of the free hydroxyl group at *C*-2 allows manipulation at the chiral center (*e.g.*, OH ---> NH_2).

Being interested in the synthesis of higher carbon sugars, we decided to elaborate an easy and efficient route to 1,2:3,4:5,6-tri-*O*-isopropylidene-D-gluconate (**2**) and to 3,4:5,6-di-*O*-isopropylidene-D-glucose (**5**) (Scheme).

SCHEME



We have found that a modification of the original[1,2] procedure significantly increased the yield of triacetonide **2**. Lactone **1** was allowed to react with acetone/H_2SO_4 in the presence of anhydrous $CuSO_4$ for 2 days, which increased the yield of **2** from 23%[2] to 64% (on a 10 g scale, method A). The product could be easily purified by simple crystallization from toluene/methanol. The reaction can be easily scaled up. On a 40 g scale we obtained 60% of crystalline **2**.

Reaction of D-glucono-1,5-lactone (**1**) with acetone/zinc chloride (method **B**) improved the yield of **2** to 76% (on a 10 g scale). This method is, according to our experience, more convenient than method **A**.

Reduction of **2** with diisobutylaluminum hydride afforded hemiacetal **6** (protected form of **5**). This compound may be used as the aldehyde equivalent in the reactions with nucleophiles. However, since hemiacetals are much less reactive than free aldehydes,[4] reaction of hemiacetal **6** with (ethoxycarbonylmethyl)triphenylphosphorane (Ph_3P=CH-COOEt) did not yield any adduct (substrate **6** remained unchanged).

We have found that compound **6** was partially hydrolyzed to **5** during purification by flash chromatography.[5] To achieve the complete conversion of **6** into **5**, the hemiacetal was treated with a catalytic amount of sodium ethoxide in ethanol (5 min at 0 °C) or potassium carbonate in methanol (30 min at room temperature). The hydrolysis of the 1,2-*O*-isopropylidene ring led to **5** but, the free aldehyde was too unstable to survive even these slightly basic conditions.

A convenient method for conversion of triacetonide hemiacetal **6** into the free aldehyde **5** was found when *ca.* 3% solution of **6** in benzene was treated with methanol/triethylamine/water for 2-3 hours at room temperature.

The free aldehyde **5** was too unstable for purification, but the crude product was pure enough for the reactions. The latter reacted readily (contrary to hemiacetal **6**) with Ph_3P=CH-COOEt (2 hours, at room temperature) furnishing precursor of octoses, ethyl 2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-D-gluco-oct-2-enoate (**7**) (E/Z *ca.* 9:1; ^1H NMR estimation) in 73% yield .

EXPERIMENTAL

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconate (2). *Method A:* To a suspension of D-glucono-1,5-lactone (**1**, 10.5 g, 59 mmol) in acetone (120 mL), sulfuric acid (2.0 g, 1.1 mL) was added dropwise, and the mixture was stirred at room temperature (<20 °C) for 3 h. Anhydrous cupric sulfate (15 g) was added and the mixture was stirred at room temperature (<20 °C) for 48 hours, filtered with suction through Celite and poured into toluene/saturated sodium chloride (250/50 mL). The organic phase was washed 3-4 times (30 mL each) with saturated sodium chloride solution (until neutrality), dried, and concentrated to a thick syrup. Methanol (40 mL) was added and the mixture was left for crystallization at -20 °C for 3 h. The

crystals were collected and dried at room temperature at 0.2 torr to give 8.3 g of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-gluconate (**2**, mp 110 °C, lit: 111 °C[1] and 109 °C[2]). The mother liquors were concentrated again to a thick syrup and after addition of methanol (20 mL) left at -20 °C for 3 h; second crop of crystals, 2.3 g. This procedure was repeated 2 times to give third (0.8 g) and fourth (0.5 g) crops of crystalline **2**. Total yield, 11.9 g (37.7 mmol, 64%): $[\alpha]_D$ 37.5 ° (*c* 2, $CHCl_3$); [lit: 31 ° (EtOH)[1], 34 ° ($CHCl_3$)[2]]; IR (KBr): 1810 cm^{-1} (C=O); ^1H NMR (500 MHz, $CDCl_3$, for numbering of protons in **2**, **6a**, and **7** see Scheme) 4.61 (d, 1 H, $J_{2,3}$ 1.5 Hz, **H-2**), 4.27 (dd, 1 H, $J_{3,4}$ 8.3 Hz, **H-3**), 4.14 (dd, 1 H, $J_{5,6}$, 6.0, $J_{6,6'}$ 8.5 Hz, **H-6'**), 4.08 (m, 1 H, **H-5**), 3.98 (dd, 1 H, $J_{5,6}$ 4.0 Hz, **H-6**), 3.94 (t, 1 H, $J_{4,5}$ 8.5 Hz, **H-4**), 1.65, 1.58, 1.41, 1.39, 1.38, and 1.33 (6s, 3xCMe_2).

Anal. Calcd for $C_{15}H_{24}O_7$: C, 56.95; H, 7.65. Found: C, 57.00; H, 7.54.

Method B: To freshly melted zinc chloride (23 g) in acetone (120 mL), sulfuric acid (0.4 g, *ca.* 0.2 mL) was added dropwise, and the mixture was stirred at room temperature (<20 °C) for 10 min. D-Glucono-1,5-lactone (**1**, 10.5 g, 59 mmol) was added in one portion, the mixture was stirred at room temperature (<20 °C) overnight, and then poured into toluene/saturated sodium chloride (250/50 mL). The organic phase was washed 3-4 times with saturated sodium chloride solution (30 mL each, until neutrality), dried, and concentrated to a thick syrup.

The pure product was isolated analogously as in method A (by crystallization from methanol); yield 14.2 g (first crop, 11.5 g, second 1.7 g, third, 1.0; 76% overall).

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-glucose (**6**). To a solution of **2** (5.7 g, 18.0 mmol) in methylene chloride (200 mL) at -78 °C under an argon atmosphere, diisobutylaluminum hydride (18 mL of a 1.2 M solution in toluene) was added dropwise and the resulting mixture was stirred for 1 h at -78 °C. The excess of DIBAH was decomposed by dropwise addition of ethyl acetate (20 mL). After 30 min the mixture was warmed to 0 °C, water (10 mL) was added, the mixture was allowed to reach the room temperature and partitioned between methylene chloride (100 mL) and water (50 mL). Inorganic salts were filtered off through Celite, the organic phase was separated, dried, and the solution was concentrated to dryness. Flash chromatography[5] of the crude material (ethyl acetate - hexane, 9:1 to 3:2) afforded:

- unreacted **2** (1.56 g, 4.93 mmol, 27%)

- pure **6** (2.51 g, 7.85 mmol, 44%), which was characterized as acetate **6a** (*ca* 9:1 mixture of epimers at *C*-1 ^1H NMR estimation). ^1H NMR (500 MHz, $CDCl_3$) for the main isomer: 6.34 (d, 1 H, $J_{1,2}$ 2.7, **H-1**), 4.32 (dd, 1 H, $J_{2,3}$ 3.8 Hz, **H-2**), 4.13 (dd, 1 H, $J_{5,6}$, 6.0, $J_{6,6'}$, 8.5 Hz,

H-6'), 4.09 (dd, 1 H, $J_{3,4}$ 7.5 Hz, **H-3**), 4.07 (m, 1 H, **H-5**), 3.97 (dd, 1 H, $J_{5,6}$ 4.6 Hz, **H-6**), 3.94 (dd, 1 H, $J_{4,5}$ 8.5 Hz, **H-4**), 2.10 (s, 3 H, OAc), 1.52, 1.49, 1.42, 1.41, 1.38, and 1.35 (6s, 3 x CMe_2); for the minor isomer: 6.20 (d, 1H, **H-1**) and 2.04 (s, 3 H, OAc).

Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83. Found: C, 56.48; H, 7.85

- free aldehyde **5** (0.61 g 2.3 mmol, 13%), identical with the free aldehyde prepared below.

3,4:5,6-Di-*O*-isopropylidene-*aldehydo*-D-glucose (5). To a stirred solution of **6** (901 mg, 2.83 mmol) in benzene (30 mL), methanol (1 mL), triethylamine (1 mL), and water (1 mL) were added and the mixture was stirred at room temperature until TLC (ethyl acetate - hexane, 3:2) indicated disappearence of the starting material and formation of a more polar product (2 -3 h). This mixture was partitioned between toluene (50 mL) and water (10 mL). The organic phase was separated, dried, concentrated to *ca.* 10 mL, and the toluene solution of crude **5** was used directly for the next reaction.

Ethyl 2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-enoate (7). To a toluene solution of crude **5** (from the previous experiment) a solution of Ph_3P=CH-COOEt (1.2g, 3.4 mmol, 1.2 equiv) in dry benzene (10 mL) was added and the resulting mixture was stirred at room temperature until TLC (hexane - ethyl acetate, 3:2) indicated disappearence of starting material and formation of a new, less polar product that was visible under U.V. light (3 h). Chromatographic purification (hexane - ethyl acetate, 4:1) afforded **7** (mixture of ***E/Z*** isomers in the ratio *ca.* 9:1; ^{1}H NMR estimation) as an oil (680 mg, 2.06 mmol, 73% from **6**). ^{1}H-N.M.R. (500 MHz, $CDCl_3$) for the main ***E*** isomer of **7**: 7.09 (dd, 1 H, $J_{2,3}$ 15.7, $J_{3,4}$ 3.8 Hz **H-3**), 6.16 (dd, 1 H, $J_{2,4}$ 2.1 Hz, **H-2**), 4.52 (m, 1 H, **H-4**), 4.21 (q, 2 H, *J* 7.1, CH_2CH_3), 4.17 (dd, 1 H, $J_{4,5}$ 6.1, $J_{5,6}$ 8.7 Hz, **H-5**), 4.06 (d, 1 H, $J_{8',7}$ 3.2, $J_{8,8'}$ 7.8 Hz, **H-8'**), 4.03 (m, 1 H, **H-7**), 3.98 (dd, 1 H, $J_{5,6}$ 8.7, $J_{6,7}$ 4.0 Hz, **H-6**), 3.78 (dd, 1 H, $J_{8,7}$ 8.7 Hz, **H-8**), 3.76 (s, 3 H, OMe), 1.43, 1.41, 1.38, and 1.35 (4s, 12 H, 2 x CMe_2), 1.29 (t, 3 H, CH_2CH_3).

Anal. Calcd for $C_{17}H_{28}O_8$: C, 58.17; H, 7.93. Found: C, 58.09; H, 7.87.

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