## Note

# A convenient synthesis of 1-deoxy-D-tagatose\*

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1-Deoxy-D-tagatose (1-deoxy-D-*ly:vo*-hexulose) (4) has been previously synthesized by the diazoketone method of Wolfrom and Bennett<sup>1</sup>. The reaction sequence involves six steps from the ultimate starting material, D-galactose, and overall yields<sup>1-3</sup> are of the order of 10%. Other synthetic pathways have thus far not proved useful<sup>4</sup>. The utility of transamination-type. oxidative-deamination reactions, originally used by Corey and Achiwa<sup>5</sup> in sugar syntheses. has recently been demonstrated by syntheses of D-glucosone derivatives<sup>6,7</sup> and of 1-deoxy-D-fructose<sup>8,9</sup>. Herein, we report the synthesis of 4, in good yields, by a new three-step synthesis which employs as the key step the oxidative deamination of 2-amino-1,2-dideoxy-D-galactitol (3).

сно	CH(SEt)₂	ÇH₃	ÇH₃
нсһн₃⁺сі⁻	H¢NH₃⁺CI⁻	HCNH2	င္ငံဝ
носн	носн	носн	носн
носн	носн	носн	носн
нсон	нсон	нсон	нсон
н₂сон	н₂сон	н₂сон	н₂сон
1	2	З	4

Treatment of (1) with ethanethiol in saturated hydrogen chloride gave crystalline 2-amino-2-deoxy-D-galactose diethyl dithioacetal hydrochloride (2) in yields of up to 70%. Performing the reaction for 24 h gave the greatest yields of product, and longer times resulted in the appearance of two side-products, probably the anomeric forms of ethyl 2-amino-2-deoxy-1-thio-D-galactopyranoside.

Reductive desulfurization of 2 with Raney nickel resulted in the formation of 3 in yields of up to 72%. The oxidative deamination of 3 with 3,5-di-*tert*-butyl-

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benzoquinone gave 4 in 70% yield as measured from 3, and 35% as measured from 1. The ease and overall yields of this synthesis are similar to those reported for 1-deoxy-D-fructose<sup>9</sup>.

The <sup>1</sup>H-n.m.r. spectrum of 4 showed the expected signals for the methyl protons of the ring forms of the sugar at  $\delta$  2.27 which, by analogy to 1-dec.xy-D-fructose<sup>4</sup>, could be attributed to the methyl protons of the open-chain form. It is therefore probable that 4, like the other 1-deoxy-2-hexuloses<sup>4,10</sup>, exists, to some extent, in the open-chain form in aqueous solution.

### EXPERIMENTAL

General. - 2-Amino-2-deoxy-D-galactose hydrochloride (1) was obtained from Sigma Chemical Co., St. Louis, MO 63178, and 3,5-di-tert-butylbenzoquinone and ethanethiol from Aldrich Chemical Co., Metuchen, NJ 08840. Raney nickel was generated from Raney nickel-aluminum alloy obtained from Apache Chemical Co., Seward, IL 61077, by previously described methods<sup>9,11</sup>. All other chemicals were standard laboratory reagents. Thin-layer chromatography was performed on Eastman silica gel plates without fluorescent indicator, previously treated with 0.08M sodium acetate in 90% ethanol and dried before use. Solvent systems used were 7:2:2 (v/v) acetone-2-propanol-water (Solvent A), and 6:1 (v/v) 2-propanol-water (Solvent B). Ascending paper chromatography was performed on Whatman No. 1 paper (0.016 mm) in 5:5:1:3 (v/v) pyridine-ethyl acetate-acetic acid-water (Solvent C), and 10:3:3 (v/v) 1-butanol-pyridine-water (Solvent D). Spray reagents for detection were as follows: acidic ninhydrin for amino sugars and derivatives<sup>12</sup>, alkaline methanolic triphenyltetrazolium chloride for reducing sugars<sup>12</sup>, and N-bromosuccinimidefluorescein for sulfur containing compounds<sup>13</sup>. All evaporations were performed in a rotary evaporator with the water-bath temperature maintained below 45°. <sup>1</sup>H-N.m.r. spectrometry was performed with a Varian CFT 20, 80-MHz n.m.r. spectrometer. Melting points were determined with an Electrothermal melting-point apparatus and are uncorrected. Optical rotations were measured with a Kern full-circle polarimeter.

2-Amino-2-deoxy-D-galactose diethyl dithioacetal hydrochloride (2). — The synthesis of 2 was accomplished by a variation of the method of Wolfrom and Onodera<sup>1+</sup>. To a solution of concentrated hydrogen chloride (15 mL) saturated with hydrogen chloride gas on ice was added 1 [5 g; m.p. 178–180°;  $R_F$  0.05 (A), 0.06 (B), 0.20 (C), and 0.13 (D)] followed by ethanethiol (16 mL). The reaction vessel was sealed and the mixture stirred vigorously for 24 h at room temperature. After this period, nitrogen gas was passed through the solution and subsequently bubbled through a 1-L column of 5% sodium hypochlorite to oxidize the excess of ethanethiol. The mixture was placed on a 20 × 5-cm column of Dowex 1-X8 (OH<sup>-</sup>, 200–400 mesh) anion-exchange resin and eluted with 50% aqueous ethanol. The eluate was concentrated to a mobile syrup, which was taken up in 95% ethanol and placed in a refrigerator. The crystalline product was isolated as white needles, which were recrystallized

from 95% ethanol. It was chromatographically pure in all four solvent systems, m.p. 157°,  $[\alpha]_D^{23} + 29°$  (c 0.86, H<sub>2</sub>O), identical to lit.<sup>13</sup>;  $R_F$  0.59 (A), 0.78 (B), 0.65 (C), and 0.77 (D). Further crops of crystals were obtained from the mother liquor, giving an overall yield of 3.8 g.

Based on t.l.c. (A and B), a significant proportion of 2 remained in the syrup along with two other less-mobile components. These components were separated in a 90  $\times$  2.5-cm column of Dowex 50W-4X (H<sup>+</sup>, 200–400 mesh) cation-exchange resin. Elution was achieved with a linear 400-mL gradient from 0.3 to 1.6M hydrochloric acid. The first component was eluted after 1880 mL. After concentration, neutralization with Dowex 1-X8 (OH<sup>-</sup>) anion-exchange resin, filtration, and evaporation to dryness, crystals were obtained (yield 0.4 g), m.p. 145-146°. The compound was chromatographically pure  $[R_F 0.64 (A), 0.41 (B), 0.50 (C), and 0.59 (D)]$  and contained sulfur and a free amino group as judged by the N-bromosuccinimide-fluorescein and ninhydrin tests, respectively: <sup>1</sup>H-n.m.r.:  $\delta$  2.94–2.65 (single ethyl group with the methylene quartet) and 1.38-1.19 (methyl triplet). The second component was eluted at 2050 mL and was processed as just described to give a crystalline product (0.3 g), m.p. 120–121°, chromatographically pure  $\lceil R_F 0.61 (A), 0.45 (B),$ 0.50 (C), and 0.54 (D)] that contained sulfur and a free amino group; <sup>1</sup>H-n.m.r.:  $\delta$  2.85–2.56 (single ethyl group with the methylene quartet) and at  $\delta$  1.38–1.20 (methyl triplet). Both components are probably ethyl 2-amino-2-deoxy-1-thio-a- and  $-\beta$ -D-galactopyranoside hydrochloride, by analogy with byproducts formed in the reaction of 2-acetamido-2-deoxy-D-glucose with ethanethiol<sup>14</sup>.

The desired product 2 was eluted at 3060 mL and, following processing, gave 1.2 g of crystals identical to those isolated earlier (overall yield of 2, 5.0 g, 70%).

2-Amino-1,2-dideoxy-D-galactitol (3). — This compound was prepared from 2 by reductive desulfurization with Raney nickel in a manner analogous to the synthesis of 2-amino-1,2-dideoxy-D-glucitol9. Compound 2 (3.5 g) in distilled water (300 mL) was treated with Raney nickel prepared from Raney nickel-aluminum alloy (150 g) for 16 h. After filtration, the nickel was washed once with 0.1M hydrochloric acid (300 mL) and three times with distilled water (300 mL). The combined filtrates and washings were concentrated and filtered again. The product was purified by treatment with a cation-exchange column as described for 2-amino-1,2-dideoxy-Dglucitol<sup>9</sup>. Following elution and concentration, a mobile syrup (2.25 g) was obtained. As judged by t.l.c.:  $[R_F 0.10 (A), 0.04 (B), 0.31 (C),$  extensive streaking, and 0.32 (D, extensive streaking)] preparations of 3 sometimes were contaminated with a second component which contained sulfur and is probably 2-amino-2-deoxy-1-Sethyl-1-thio-D-galactitol, [syrup,  $R_F$  0.36 (A), 0.04 (B), 0.31 (C, extensive streaking), and 0.32 (D, extensive streaking)]. The appearance of this compound could be reduced by using fresh Raney nickel that had been prepared with the temperature maintained  $<20^{\circ}$  and by the use<sup>8.9</sup> of 40 g or more of nickel-aluminum alloy for catalyst generation for every 1.0 g of 2.

*l-Deoxy-D-tagatose* (4). — A variation of the method used for l-deoxy-D-fructose<sup>9</sup> was used to synthesize 4 from 3. Dried 3 (0.5 g) was dissolved in methanol

(25 mL), and the solution was dried over anhydrous sodium sulfate. Following filtration, 3,5-di-tert-butylbenzoquinone (0.73 g) was added, and the mixture was kept for 2.5 h at room temperature. Tetrahydrofuran (25 mL), water (25 mL), and enough glacial acetic acid to lower the pH of the solution to 4.0 were added. After 18 h, the mixture was extracted three times with ether. The aqueous phase was evaporated to 30 mL, and the pH was adjusted to 6.0 with Dowex 1-X8 ( $OH^{-}$ ) anion-exchange resin. Following filtration, the solution was evaporated and the residue dried by successive additions and evaporations of absolute ethanol. The mobile syrup crystallized on being kept, and the crystals were recrystallized from absolute ethanol-2-propanol (yield 0.36 g, 70%), m.p. 130° (lit.<sup>1</sup> m.p. 121-123°); single component in t.l.c. and p.c.:  $R_{\rm F}$  0.66 (A), 0.50 (B), 0.57 (C), and 0.45 (D); <sup>1</sup>H-n.m.r.:  $\delta$  3.90–3.20 (H-1, -2, -3, -4, and -5), 1.47, 1.40 and 1.38 (CH<sub>3</sub>): ratio  $CH_3 - H-1 - 5$ , 3:5; small signal at  $\delta$  2.27 probably due to  $CH_3$  of the open chain. A further indication of the identity of 4 synthesized by this method was the formation of a fluorescent product upon heating in phosphoric acid with 3,5-diaminobenzoic acid, a reaction previously observed with 1-deoxy-D-fructose<sup>16</sup>.

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