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Carbohydrate Research 260 (1994) 155–158

CARBOHYDRATE
RESEARCH

Note

A facile isolation of 2,5-anhydro-L-iditol

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(Received December 13th, 1993; accepted January 26th, 1994)

During the course of an ongoing analytical project, multigram quantities of several anhydrohexitols, including 2,5-anhydro-L-iditol (**3**), were required. Although preparations of **3** are known [1–8], all proceed in poor yield and require multiple synthetic and/or separation steps. Presented below is a three-step (5.2% overall yield) modification of Bock and co-workers method [3] for isolation of 2,5-anhydro-L-iditol from a mixture of dehydration products of D-glucitol (see Scheme 1). Purification is readily effected using continuous extraction and obviates the need for high vacuum distillation or column chromatography.

Acid-catalyzed dehydrations of D-glucitol are known to produce complex mixtures of mono- and di-anhydrohexitols [3,9–11]; major reaction products include 1,4-anhydro-D-glucitol and 1,4:3,6-dianhydro-D-glucitol. Smaller proportions of 1,5-, 2,5-, 2,6-, and 3,6-anhydrohexitols are formed concomitantly. Our separation method was based on the observation that a relatively small subset of the dehydration products is able to form di-*O*-isopropylidene acetals.

D-Glucitol was dehydrated using methanesulfonic acid in refluxing xylenes. Upon cooling and decanting of the solvent, the syrupy residue was isopropylidenated, processed, and subjected to continuous extraction into hexane. The major dehydration products, 1,4-anhydro-D-glucitol (~60% as the 5,6-acetal) and 1,4:3,6-dianhydro-D-glucitol (~25%), remained in the aqueous phase. The resulting hexane extract was concentrated and the residue recrystallized from hexane to produce 2,5-anhydro-1,3:4,6-di-*O*-isopropylidene-L-iditol (**2**, 5.7%). Deprotection of **2** using IR-120 (H^+) resin afforded **3** in 91.1% yield (5.2% overall).

Numerous experiments were performed in an attempt to increase the very modest yield of **2**. Maximum isolated yields of **2** were obtained when the dehydration reactions were continued until ~1.1 equiv of water had been removed. Removal of less water (0.75 equiv) led to mixtures of anhydrohexitols containing a

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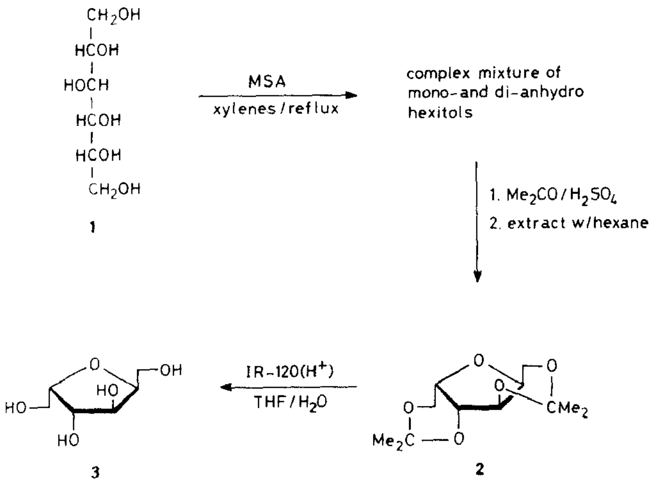
SSDI 0008-6215(94)00056-L



Scheme 1.

marginally higher proportion of crude **2** (HPLC assay). However, these product mixtures also contained a significant proportion of residual D-glucitol which, upon isopropylidenation, was converted into 1,2:3,4:5,6-tri-*O*-isopropylidene-D-glucitol and extracted into the hexane. Crystallization of **2** was inhibited, and lower isolated yields were obtained in these cases. Removal of 1.5 equiv or more of water left no residual D-glucitol, but slightly decreased the recovery of **2** (typically 4–4.5%) and afforded a highly colored product.

TLC analysis of the chromatographically complex mother liquor indicated the presence of 1,2:3,4:5,6-tri-*O*-isopropylidene-D-glucitol, residual **2**, and several additional, poorly resolved components. Subsequent fractionation on silica gel afforded additional **2** (0.9%) *. The co-products remain to be resolved and identified.

1. Experimental

General methods.—Melting points were obtained on a Thomas–Hoover capillary apparatus and are uncorrected. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter at 589 nm. Infrared spectra were obtained on a Nicolet 510 FT-IR instrument using the DRIFTS method. NMR spectra were run on a Bruker AM-300 instrument. Thermogravimetric analyses were performed on a Perkin–Elmer TGS-II. High-resolution mass spectra were obtained using a Kratos profile mass spectrometer. HPLC analyses were performed using a Dionex

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* The overall yield of **2** (6.6%) is in accord with the results of Bock and co-workers [3]. Their ^{13}C NMR data on the dehydration of D-glucitol (3 M H_2SO_4 at 104°C) indicated a 7% concentration of **3** between 70 and 172 h (6% calculated for T_{∞}).

Carbopac MA1 (4 × 250 mm) column and a Dionex MA1 (4 × 50 mm) guard column. The mobile phase was 0.75 M aq NaOH. Detection was performed using a Dionex pulsed amperometric detector. TLC analyses were performed on Merck silica gel plates and developed using 10:1:0.1 hexane–acetone–MeOH.

Procedure.—D-Glucitol (Aldrich, 100.0 g, 0.55 mol) was suspended in xylenes (500 mL). Methanesulfonic acid (0.1 mL, 1.54 mmol) was added and the mixture heated to reflux under N_2. Water (11 mL, 1.1 equiv) was collected in a Dean–Stark trap over 2.5 h. The mixture was cooled to 55° C and the solvent decanted; subsequent HPLC analysis indicated the xylenes contained only 1,4:3,6-dianhydro-D-glucitol.

The syrupy yellow residue was treated with molecular sieve-dried, reagent-grade acetone (4.0 L) and H_2SO_4 (1 mL); warming the mixture to 45° C enhanced dissolution. After stirring under N_2 for 16 h at ambient temperature, the mixture was quenched with an excess of $KHCO_3$ (8 g dissolved in 100 mL of water) and concentrated in vacuo. One portion of water was added and evaporated to remove residual acetone.

The light-yellow residue was partially dissolved in hexane (500 mL) and water (500 mL) then subjected to continuous extraction using hexane (1.0 L) overnight. Concentration of the hexane solution afforded a semi-crystalline mass (17.75 g). Recrystallization from refluxing hexane (50 mL) afforded 2,5-anhydro-1,3:4,6-di-*O*-isopropylidene-L-iditol (**2**, 7.65 g, 5.7% from D-glucitol); mp 128.5–130° C (lit. [2] 130–131° C, lit. [7] 128–129° C). An analytical sample of **2** was prepared by recrystallization from refluxing hexane; mp 130–131° C; $[\alpha]_D$ +20.3° (*c* 0.4, $CHCl_3$), [lit. [2] +23.6° (*c* 3.7, $CHCl_3$)]; IR (KBr) 2992, 2930, 2883, 1452, 1376, 1198, 1167, 1129, 1099, 983, 919, 839, 708, 525, and 504 cm^{-1}. NMR data (C_6D_6): ^1H δ 3.61 (dd, 2 H, $J_{1,1a} = J_{6,6b} = 13.7$, $J_{1a,2} = J_{6a,5} = 3$ Hz, H-1a and H-6a), 3.92–3.99 (m, 4 H, H-1b, H-2, H-5, H-6b), 4.12 (d, 2 H, $J_{2,3} = J_{4,5} = 2.1$ Hz, H-3 and H-4); ^{13}C δ 96.86 (isopropylidene), 75.34 (C-3 and 4), 72.75 (C-2 and 5), 61.14 (C-1 and 6), 28.84, 19.15 (isopropylidene methyls).

Additional **2** (1.23 g, 0.9%) was obtained by purification of the mother liquor on a dry-packed silica gel column using 10:1:0.1 hexane–acetone–MeOH. Deisopropylidenation of **2** (6.5 g, 26.6 mmol) was effected using IR-120 (H^+) resin (13 g) in a mixture of THF (100 mL) and water (50 mL) at ambient temperature. The product was recrystallized from refluxing EtOH (20 mL) to afford **3** (3.44 g). Concentration of the resulting mother liquor afforded additional **3** (0.54 g, 91.1% overall yield).

Compound **3** (first crop) melted at 118.5–119.5° C (lit. [6,13] 117–118° C); $[\alpha]_D$ +6.5° (*c* 0.4, H_2O); [lit. [4] +6.4° (*c* 1.1, H_2O), lit. [6] +9.7° (*c* 2.5, H_2O), lit. [12] +9° (H_2O)]; HPLC peak area, 100%; IR (KBr) 3444, 3330, 3223, 2962, 2923, 1442, 1406, 1265, 1080, 1041, 991, 899, 852, 744, 674, and 582 cm^{-1}; ms calcd: (M + H) = 165.0763; obsd = 165.0765; TGA (0.1% loss at 120.1° C): ^1H and ^{13}C NMR data were in accord with the literature [1,3,4] values. A second crop of **3** melted at 118–119.5° C; the HPLC peak area, 99.3%.

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