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2,5-ANHYDRO-D-HEXITOLS: SYNTHESES OF 2,5-ANHYDRO-D-ALTRITOL AND 2,5-ANHYDRO-D-IDITOL

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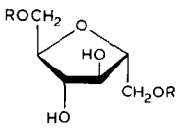
ABSTRACT

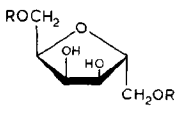
2,5-Anhydro-D-altritol (**2a**) and the previously-unknown 2,5-anhydro-D-iditol (**3a**) have been prepared from 2,5-anhydro-D-mannitol (**1a**). The preparation of **3a** from the intermediate epoxide **7b** is particularly sensitive to pH, and a mechanism is proposed to explain this. Attention is drawn to the limitations of the trifluoroperacetic acid–disodium hydrogenphosphate procedure for the epoxidation of alkenes of diminished reactivity.

INTRODUCTION

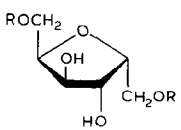
2,5-Anhydro-D-hexitols and their derivatives have recently attracted considerable interest, both as synthetic intermediates[1a–i] and because of some interesting biochemical observations, including reports that 2,5-anhydro-D-mannitol (**1a**, as its 1,6-bisphosphate) inhibits rabbit[2] and bovine[3] liver fructose-1,6-biphosphatase and glycogenolysis (in isolated hepatocytes[4] and in mice[5]) while activating yeast[6] and rabbit liver[5] pyruvate kinase. As part of our interest in studying the effects of analogs of **1a** on the foregoing systems and in the potential application of such compounds to the treatment of diabetes, we required practical quantities of **1a**, 2,5-anhydro-D-altritol (**2a**), and 2,5-anhydro-D-iditol (**3a**). We describe herein further modifications of Horton and Philips' much-improved synthesis[7] of **1a**, a new route to **2a**, and a stereospecific synthesis of the previously-undescribed **3a**.



1a,b
a, R = H
b, R = Bz



2a,b

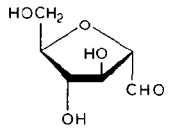


3a,b

0008-6215/84/$ 03.00

RESULTS AND DISCUSSION

2,5-Anhydro-D-*mannitol* (**1a**). — *(a) Preparation of 2,5-anhydro*-D-*mannose* (**4**). Early in our program it became apparent that relatively large quantities of **1a** would be required, both for pharmacological testing and as an intermediate in the syntheses of, for instance, **2a** and **3a**. The intermediate **4** was prepared largely according to the procedure of Horton and Philips[7], with changes as described in the Experimental section. The modifications were introduced because of, in our hands, serious limitations in the foregoing procedure[7] (attributed to, for instance, difficulties in complete removal of inorganic salts, the pH and temperature sensitivity of **4** and substantial loss of product on resins) experienced when working on a 25–100 g scale.



4

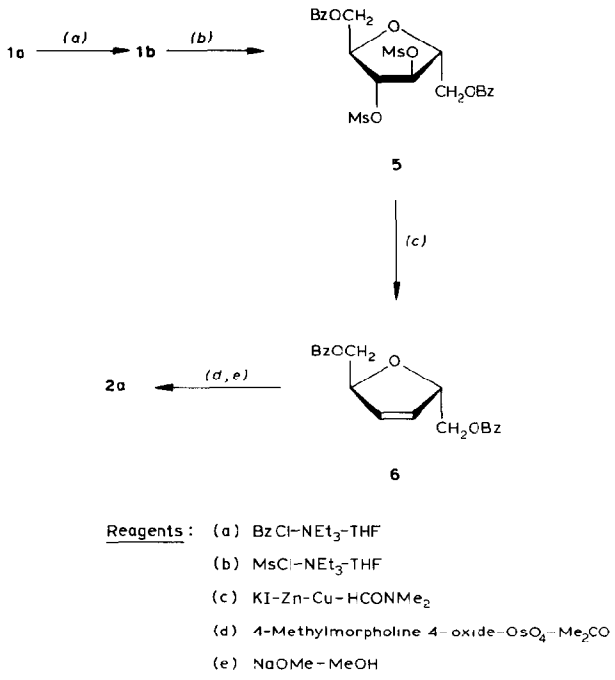
(b) Reduction of **4**. Problems encountered in the exhaustive removal of sodium borate and in maintaining an appropriate pH in the published borohydride reduction[7] led us to examine catalytic hydrogenation. Of the systems tried (Raney nickel, palladium-, ruthenium-, and platinum-on-carbon), by far the most effective was 5% platinum-on-carbon at 60 lb.in^{-2}. The procedure, which requires complete removal of inorganic salts prior to hydrogenation, affords pure **1a** in ~55% yield from 2-amino-2-deoxy-D-glucose hydrochloride. Crude material, 90–95% pure and generally suitable for further transformations, is formed in ~80% yield.

2,5-Anhydro-D-*altritol* (**2a**). — This material, first synthesized and characterized by Defaye[8], was prepared as outlined in the Scheme. The semi-crystalline, crude 2,5-anhydro-D-mannitol (**1a**) obtained from the reduction of **4** was selectively transformed into the 1,6-dibenzoate **1b** which, after purification, was treated with methanesulfonyl chloride and triethylamine in oxolane (tetrahydrofuran, THF) to give the dimethanesulfonate **5** in 51% overall yield, based upon 2-amino-2-deoxy-D-glucose hydrochloride. Reductive elimination of **5** using zinc–copper couple[9] gave the desired intermediate alkene **6** as the only isolated product in 74% yield. Transformation of **6** into **2a**, via *cis*-hydroxylation[10] and subsequent base-catalyzed hydrolysis was uneventful, proceeding in 75% yield.

Synthesis of 2,5-anhydro-D-*iditol* (**3a**). — This compound has not previously been described. The L-enantiomer has been prepared by Vargha, Puskás, and Nagy[11] and by Dekker and Hashizume[12], although neither synthesis could be applied to the formation of **3a**.

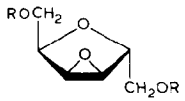
Having alkene **6** in hand, an appealing strategy for the synthesis of **3a** would

Scheme 1



Reagents: (a) BzCl–NEt_3–THF
(b) MsCl–NEt_3–THF
(c) KI–Zn–Cu–$HCONMe_2$
(d) 4-Methylmorpholine 4-oxide–OsO_4–Me_2CO
(e) NaOMe–MeOH

involve regiospecific *trans*-opening of the derived epoxide **7b**. In principle, steric considerations suggest that intermolecular nucleophilic attack on **7b** should give products having the *manno* configuration, whereas intramolecular epoxide opening, via participation of the neighboring benzoate carbonyl group, should favor the desired regiochemistry. In fact, somewhat surprisingly, oxidation of **6** under the "buffered" conditions of Emmons and Pagano[13] (trifluoroperacetic acid–disodium hydrogenphosphate–dichloromethane) led directly to a 1:4 mixture of **2b** and **3b** within 1 h at room temperature (The reaction failed when *m*-chloroperoxybenzoic acid was used). Base-catalyzed hydrolysis of the major product-component led to the desired **3a** in 58% yield from **6**.



7 a,b

The unexpected lability of the presumed intermediate epoxide led us to re-examine this reaction. In a second experiment, with conditions similar to the foregoing, t.l.c. after 30 min at 0° showed a 1:1 mixture of **6** and a new product,

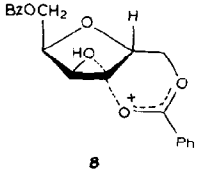
presumably the epoxide **7b**. Processing of an aliquot of the mixture after 45 min at 0° afforded a 2:3 mixture of **6** and **7b** (identified by comparison with authentic **7b**, see later). The balance of the mixture was again kept for 1 h at room temperature after which time t.l.c. indicated essentially quantitative formation of the same mixture of products as in the initial experiment. *Despite the presence of an excess of disodium hydrogenphosphate, the pH* (pH paper) *of the mixture remained below 1 throughout the experiment. Clearly this salt has little effectiveness as a buffer when used under the conditions described.*

A more direct, stereospecific route to 2,5-anhydro-D-iditol (**3a**) was found as follows: Successive treatment of pure 2,5-anhydro-D-mannitol (**1a**) with triphenylphosphine–diethyl azodicarboxylate in *N,N*-dimethylformamide[14] and benzoyl chloride in THF–triethylamine at 0° gave the epoxy dibenzoate **7b** in 61% yield. Treatment of **7b** with 0.7 equivalents of 60% aqueous perchloric acid in boiling ethanol (1 h), followed by basic hydrolysis (methanolic sodium methoxide) gave **3a** as the sole product in 84% yield from **7b**. Opening of the epoxide **7b** is particularly sensitive to the relative concentration of acid used–when the reaction was repeated using 2–3 mol equivs of perchloric acid, significant quantities of the altritol derivative **2b** (up to 40%) were formed in addition to **3b**.

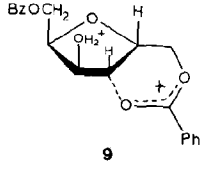
The absence of **1b** from the foregoing product-mixtures strongly suggests that epoxide opening occurs exclusively via the desired benzoate participation, namely, without any unimolecular (unstabilized carbonium ion) contribution to the reaction pathway. A possible explanation of the effects of varying acid concentration could be:

(i) In weakly acidic media, epoxide hydrolysis proceeds through the oxonium ion **8**. Here steric crowding would ensure that attack of water is only at the participating benzoate carbonyl group, allowing transfer of the carbonyl oxygen atom to the developing carbinol and necessarily producing a *trans* diol.

(ii) In more-strongly acidic conditions, the dication **9** forms; the β face of the molecule is no longer protected and hydrolysis of **9** might be expected to give the observed mixtures of *cis* and *trans* diols.



8



9

EXPERIMENTAL

General methods. — All reactions described were performed in an atmosphere of nitrogen and solvents were removed *in vacuo* with a Büchi rotary evaporator. Solutions were dried with magnesium sulfate. Melting points were de-

termined in a Thomas–Hoover capillary apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. ^{1}H- and ^{13}C-n.m.r. spectra were recorded on Jeol FX90Q and JNM FX200 spectrometers. Microanalyses were determined by Mr. W. Bonkowski and his staff of our department.

2,5-Anhydro-D-*mannitol** (**1a**). — 2-Amino-2-deoxy-D-glucose hydrochloride (53.9 g, 0.25 mol) was dissolved in 375 mL of water and kept for 24 h at room temperature. Sodium nitrite 825.9 g, 0.375 mol) was added to the cooled (−5°) solution, followed by aq. hydrochloric acid [(2,5 mL, 3.2M) dropwise, maintaining the temperature below 0°]. After the resulting exotherm and evolution of nitrogen had subsided (0.5 h), further hydrochloric acid (30.5 mL, 3.2M) was added over 1 h. Stirring was continued at 0 to −5° for an additional 3 h, after which time the excess of nitrous acid was removed by flushing vigorously with nitrogen at ambient temperature. The pH was then brought to ~6 by stirring with poly(4-vinylpyridine) (18 g, Reilly Tar and Chemical, cross-linked LX-1) and the filtered solution was carefully evaporated (bath temp. <30°) to a syrup. After triturating thoroughly with acetone (5 × 100 mL), methanol (35 mL), and abs., ethanol (200 mL) were added and the resulting mixture was kept for 16 h at 0°. After filtration the combined filtrate and abs. ethanol washings were concentrated to low volume and again dissolved in methanol (25 mL) and abs. ethanol (75 mL), cooled and filtered (total wt. of inorganic solid, 20.8 g; theor., 21.9 g). The filtrate was passed through a resin column (40 mL, Amberlite IRN-150) and eluted with further methanol. The combined eluantes were carefully concentrated to 200 mL, 5% platinum-on-carbon (9 g) was added, and the mixture was shaken with hydrogen (60 lb.in^{-2}) for 2 days. The syrup which remained after filtration and concentration (33 g) crystallized on seeding [and was in general sufficiently pure (~90%) for use as a synthetic intermediate]. Trituration of the crude product with 30% methanol in acetonitrile (70 mL), cooling, and filtration afforded 24.2 g (59%) of **1a**; m.p. 96–98°. A sample, on recrystallization for methanol–acetonitrile had m.p. 100–101°, $[\alpha]_D^{23}$ +57.8° (*c* 1.73, water) [lit.[7] m.p. 101–101.5°, $[\alpha]_D^{25}$ +57° (*c* 1.2, water)].

2,5-Anhydro-1,6-di-O-*benzoyl*-D-*mannitol* (**1b**). — Triethylamine (59.6 g, 0.59 mol) and benzoyl chloride (82.9 g, 0.59 mol) were successively added to a suspension of crude **1** (36.9 g) in dry THF (450 mL) and the mixture was boiled under reflux for 24 h. The cooled mixture was treated with methanol (20 mL), concentrated to low volume, and partitioned between chloroform and water. After two further washings of the aqueous phase with chloroform, the combined organic extracts were dried and concentrated to a brown syrup. Chromatography of this product on silica gel and elution with 5% methanol in chloroform gave a total of 55.1 g (66%) of product, m.p. 100–102°. Recrystallization of a sample from dichloromethane–pentane gave m.p. 102–104°, $[\alpha]_D^{23}$ +31.4° (*c* 1.5, methanol).

*The conditions described allow the complete removal of sodium chloride with the minimal amount of resin. We consistently experienced substantial losses of product when using larger quantities of resin.

Anal. Calc. for $C_{20}H_{20}O_7$ (372.4): C, 64.5; H, 5.4. Found: C, 64.2; H, 5.4.

*2,5-Anhydro-1,6-di-*O*-benzoyl-3,4-di-*O*-(methylsulfonyl)-*D*-mannitol* (**5**). — A solution of **1b** (12.9 g, 34.5 mmol) in THF (100 mL) was successively treated with triethylamine (8.3 g, 82 mmol) and methanesulfonyl chloride (9.1 g, 80 mmol) at room temperature. After the marked exotherm had subsided (30 min), solvent was removed and the residue was partitioned between chloroform and water. The aqueous phase was extracted twice more with chloroform and the dried combined chloroform extracts, after filtration through a bed of silica gel and eluting with chloroform, were evaporated to give the crystalline product (17.6 g, 97%), m.p. 99–101°. Recrystallization from methanol–ether gave m.p. 100–101°, $[\alpha]_D^{23}$ +30.5°, (chloroform).

Anal. Calc for $C_{22}H_{24}O_{11}S_2$ (528.6): C, 50.0; H, 4.6; S, 12.1. Found: C, 49.7; H, 4.5; S, 12.5.

*2,5-Anhydro-1,6-di-*O*-benzoyl-3,4-dideoxy-*D*-threo-hex-3-enitol* (**6**). — A solution of **5** (17.6 g) in *N,N*-dimethylformamide in (150 mL) containing potassium iodide (13 g) and zinc–copper couple (4 g) was boiled for 10 h under reflux. The cooled mixture was then diluted with chloroform (400 mL), filtered, and the filtrate concentrated to an oil. After the addition and evaporation of xylene (200 mL, to remove residual *N,N*-dimethylformamide), the product was dissolved in chloroform and filtered through a short column of silica gel, eluting with chloroform. Removal of solvent from the combined eluates afforded **6** (8.3 g, 74%) as an oil, $[\alpha]_D^{23}$ (approx.) +172° (*c* 2, methanol).

Anal. Calc. for $C_{20}H_{18}O_5$ (338.3): C, 71.0; H, 5.4; O, 23.6. Found: C, 70.6; H, 5.2; O, 23.4.

*2,5-Anhydro-1,6-di-*O*-benzoyl-*D*-altritol* (**2b**). — Alkene **6** (1 g) was dissolved in a mixture of acetone (2 mL), *tert*-butyl alcohol (1 mL), and water (0.6 mL). 4-Methylmorpholine-4-oxide (0.39 g) and osmium tetraoxide (3 mg) were added, and the solution was stirred for 16 h at room temperature. Celite (0.4 g), sodium hydrogensulfite (0.3 g), and methanol (9 mL) were then added with stirring and the mixture, after filtration, was evaporated to low volume. The concentrate was partitioned between chloroform and dilute aq. hydrochloric acid, the aqueous phase was washed twice more with chloroform, and the combined organic extracts were dried and filtered through silica gel (20 mL). The chloroform and 2% methanol–chloroform eluates were combined and evaporated to a colorless oil that crystallized from ether–heptane to give **2b** (1 g, 91%), m.p. 100–101°, $[\alpha]_D^{23}$ +46.5° (*c* 1.45, methanol).

Anal. Calc. for $C_{20}H_{20}O_7$ (372.4): C, 64.5; H, 5.4. Found: C, 64.6; H, 5.3.

*2,5-Anhydro-*D*-altritol* (**2a**). — Sodium (20 mg) was added to a stirred solution of **2b** (0.8 g) in methanol (10 mL) at room temperature. After 1 h, solvent was evaporated and the residual oil was dissolved in water (10 mL) and passed through a bed of Amberlite IRN-150-resin (7 mL), eluting with water. The concentrated eluate was twice dissolved in ethanol (15 mL) and the solutions re-evaporated to give **2a** as a colorless oil that crystallized on being kept (0.29 g, 82%), m.p. 111–

112°, $[\alpha]_D^{24}$ +45.9° (*c* 2.02, water) [lit.[8] m.p. 112–113°, $[\alpha]_D^{25}$ +44.5° (*c* 1.475, water)].

Anal. Calc. for $C_6H_{12}O_5$ (164.2): C, 43.9; H, 7.4. Found: C, 44.1; H, 7.4.

*2,5-Anhydro-1,6-di-*O*-benzoyl-*D*-iditol* (**3b**). — *Preparation A.* Trifluoroacetic anhydride (2.4 g) was added over 15 min to a stirred mixture of 90% hydrogen peroxide (0.28 g) and dichloromethane (2.4 mL) at 0°. The resulting solution was added during 1 h to a stirred, ice-cooled solution of **6** (0.7 g) in dichloromethane (8 mL) containing disodium hydrogenphosphate (4.1 g). Cooling was discontinued and stirring was maintained for 1 h at room temperature. The mixture was then partitioned between chloroform and water, and the aqueous phase washed twice more with chloroform. The combined organic extracts were dried, concentrated to an oil (~0.75 g), and chromatographed on silica gel (15 mL). Concentration of the chloroform and 1% methanol in chloroform eluates gave **2b** as an oil (~0.2 g) that crystallized from ether–heptane (0.12 g, 15.6%, m.p. 99–101°). Evaporation of the 2–5% methanol–chloroform eluates gave **3b** as an oil (~0.5 g) that crystallized from ether–pentane; 0.45 g (58%), m.p. 102–104° (120–122° after exhaustive drying), $[\alpha]_D^{24}$ +48.2° (*c* 2.97, methanol).

Anal. Calc. for $C_{20}H_{20}O_7$ (372.4): C, 64.5; H, 5.4. Found: C, 64.7; H, 5.3.

Preparation B. A solution of **7b** (3.2 g, 9.03 mmol) in abs. ethanol (32 mL) was treated with 60% aq. perchloric acid (0.7 mL, 6.4 mmol) and boiled for 1 h under reflux. After evaporation of solvent the residue was partitioned between chloroform and dilute aq. sodium hydrogencarbonate at 0°. The aqueous phase was washed twice with chloroform and dried, combined organic solution were concentrated to an oil that was purified by chromatography on silica gel (60 mL). Evaporation of the combined chloroform and 5% methanol–chloroform eluates afforded **3b** (3.1 g, 92%). Recrystallization of a sample from aq. methanol gave m.p. 121–122° (after exhaustive drying).

*2,5-Anhydro-*D*-iditol* (**3a**). — Sodium (8.7 mg) was added to a stirred solution of **3b** (0.5 g) in methanol (5 mL) at room temperature. After 1 h, solvent was evaporated and the residue was partitioned between dichloromethane and water. The aqueous phase, after two more washings with dichloromethane, was passed through a bed of Amberlite IRN-150 (1.3 mL) and evaporated to dryness. Crystallization from ethanol–ether gave **3a**, 0.2 g (91%), m.p. 115–115.5°, $[\alpha]_D^{24}$ −12.9° (*c* 2.77, water), [lit.[11] (L-**3a**) m.p. 111–113°, $[\alpha]_D^{20}$ +12.6° (*c* 2.53, water)].

Anal. Calc. for $C_6H_{12}O_5$ (164.16): C, 43.9; H, 7.4. Found: C, 43.6; H, 7.4.

*2,5:3,4-Dianhydro-*D*-altritol* (**7a**). — Diethyl azodicarboxylate (15.1 g) was added during 20 min to a stirred solution of **1a** (5.5 g) and triphenylphosphine (21.7 g) in *N,N*-dimethylformamide (125 mL) at 0° (exothermic reaction). Stirring was continued for 30 min at 0° and for a further 2 h at room temperature. The solution was concentrated to an oil, twice dissolved in xylene (150 mL) and re-evaporated (to remove residual *N,N*-dimethylformamide), and purified by chromatography on silica gel (300 mL), eluting with methanol–chloroform mixtures. concentration of the 20 and 30% methanol in chloroform eluates gave crude **8a** (~5 g) which, on re-

chromatographing on silica gel (200 mL), afforded pure product (4.2 g). Crystallization of this oil from ethanol-ether gave **7a**, 3.2 g (65%), m.p. 91.5–93°, $[\alpha]_D^{24}$ −76.3° (*c* 2.73, methanol), [lit.[1a] syrup, $[\alpha]_D$ −67.6° (methanol)].

Anal. Calc. for $C_6H_{10}O_4$ (146.2): C 49.3; H, 6.9. Found: C, 49.5; H, 7.2.

The preparation of **7a** as an oil, incorrectly named as 2,5:3,4-dianhydroallitol, was described after our work was complete (ref. 1a).

*2,5:3,4-Dianhydro-1,6-di-*O*-benzoyl-*D*-altritol* (**7b**). — Benzoyl chloride (5.05 g) was added dropwise to a cooled (0°) solution of **7a** (2.5 g) and triethylamine (3.98 g) in THF (100 mL). After stirring for 1.5 h at 0–5°, the mixture was filtered, concentrated to an oil, and purified by chromatography on silica gel. Evaporation of the combined 50, 30, and 20% heptane–chloroform eluates and trituration of the pure, oily **7b** with pentane afforded 5.7 g (94%), m.p. 73–74°, $[\alpha]_D^{24}$ −70.9° (*c* 1.92, chloroform).

Anal. Calc. for $C_{20}H_{18}O_6$ (354.4): C, 67.8; H, 5.1. Found: C, 67.9; H, 4.9.

ACKNOWLEDGMENTS

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