Note

Large-scale preparation of D-allose: observations on the stereoselectivity of the reduction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose hydrate*

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(Received April 25th, 1972, accepted for publication, May 19th, 1972)

The title ketone, obtained [1–5] by oxidation of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**), is known[1–5] to undergo reduction almost stereospecifically by borohydride to give 1,2 5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**), and it has been reported[6] that reduction of the ketone with lithium aluminum hydride gives a 7 3 mixture of the *allo* and *gluco* derivatives, **3** and **1**, respectively The synthetic utility of the title ketone, and the convenient access that it offers to the rare, naturally occurring[7] sugar D-allose, prompted a thorough evaluation of synthetic procedures for converting **1** into **3** by way of the ketone, the cyanohydrin route[8] to D-allose from D-ribose affords only a 30% yield An interest in this laboratory in the synthesis of sugars having specific deuterium (or tritium) labeling, by reduction of carbonyl sugars[9,10] or by enolization procedures[9–11], prompted consideration of the reduction of the ketone with lithium aluminum deuteride to afford, albeit as the minor product, a C-3 labeled derivative of D-glucose that would be useful for biochemical studies[10,12 13]

This report describes the result of a detailed evaluation of synthetic procedures for the ketone and its subsequent reduction to **3** and further conversion into **4** It also gives quantitative data on the product distribution in the reduction of the hydrated ketone (**2**) by sodium borohydride, lithium aluminum hydride, and sodium bis(2-methoxyethoxy)aluminum hydride ("Vitride"). For the oxidation of **1** to **2** it was found that the methyl sulfoxide–acetic anhydride procedure applied to carbohydrates in this laboratory[14,15] and independently by others[4,16] was less effective for large-scale (125 g) work than an improved version of the procedure[5] employing a catalytic amount of ruthenium tetraoxide that is continuously regenerated[17] by the action of an excess of potassium metaperiodate For conversion of **2** into D-allose (**4**), the best procedure found involved reduction of **2** with borohydride and hydrolysis of the

*Supported, in part, by the National Institutes of Health, U S Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland 20014, Grant No GM-11976 (The Ohio State University Research Foundation Project 1820)
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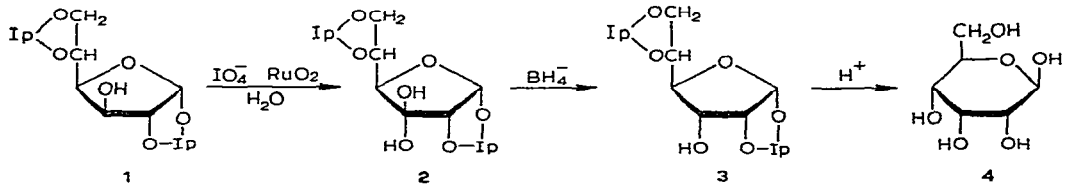
product 3 by use of a cation-exchange resin It was found that all three of the reductants examined gave >98% of the *allo* product 3 from 2, and a preparatively useful route to C-3 labeled derivatives of D-glucose was not achieved



The procedure for oxidation of 1 to 2 is essentially a large-scale adaptation of an earlier procedure[5] that employs a water–chloroform system and a catalytic amount of ruthenium tetraoxide, which is regenerated continuously by the presence of excess periodate The procedure was found quite effective on a 0 5-mole scale, provided that vigorous stirring was maintained by use of a heavy-duty stirring motor and a Morton flask It was necessary to avoid over-oxidation of the ketone (presumably leading to a lactone[18]), as this resulted in a marked decrease in yield

The stereoselectivity of the reduction of 2 by various reductants was examined by use of a g l c system that gave a clear separation of 1 and 3, and verified that the hydrated ketone 2 used was free from any trace of the precursor 1 Reduction with borohydride was found to give an exceedingly small proportion (<<0 5%) of the *gluco* isomer 1, and the use of "Vitride" was also extremely stereoselective, giving 3 as the principal product and only 1 4% of 1 When lithium aluminum hydride was used, the main product, either from the hydrate 2 or the corresponding parent ketone, was again the *allo* isomer 3, and the proportion of *gluco* isomer (1) formed was found to be only 2 7% This result is at variance with the literature report[6] that this reduction affords 1 and 3 in 3 7 proportion, such a distribution might have been observed had the ketone contained some of the unoxidized precursor It is concluded that reduction of 2 with the three reducing agents examined does not afford a method that can be adapted conveniently for preparation of D-glucose-*3-d*, although minute quantities of D-glucose-*3-t* have been obtained by this method[12].

Preparative reduction of 2 with sodium borohydride gave 3 in excellent yield, and the latter was hydrolyzed in water at 45° with Amberlite IR-120 (H^+) resin to afford D-allose, isolated as the crystalline β-pyranose anomer (4) in essentially quantitative yield Examination of the mother liquors after crystallization showed that less than 0 2% of D-glucose had been produced in the reaction

This procedure has been repeated many times by experienced experimentalists and also by beginning undergraduate students, and has been found consistent and reproducible, it gives D-allose in 68–70% overall yield from 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose (1) In our hands, the methyl sulfoxide–acetic anhydride procedure[4,14,16] for oxidizing 1 to the 3-ketone[4,19] is less effective for large-scale work as it is lower-yielding, gives an impure product, and is exceedingly malodorous

EXPERIMENTAL

General methods — Evaporations were performed *in vacuo* at ~40° Melting points were determined with a Thomas–Hoover "Unimelt" apparatus and are uncorrected G l c was performed with a Beckman GC-5 dual-column instrument equipped with flame-ionization detectors, and helium was used as the carrier gas Conditions were either *A*, a 3 mm × 3 3 m column of 10% Carbowax 20M on 60–80 mesh HMDS Chromosorb W, helium flow-rate 80 ml/min, column temperature 200°, injector temperature 250°; or *B*, a 3 mm × 1 8 m column of 3% SE-30 on 80–100 mesh Chromosorb P, helium flow-rate 40 ml/min, column temperature 155°, injector temperature 240° Retention times given are adjusted values, relative to the solvent peak, which was taken as time zero Standard solutions of compounds **1** and **3** were used to calibrate the detector response to allow conversion of peak-area ratios into quantitative ratios, the two compounds gave almost identical responses T l c was performed on 0 25-mm plates of silica Gel G (Merck) activated at 110°, and 10% aqueous sulfuric acid was used for detection

*Preparation of 1,2 5,6-di-*O*-isopropylidene-α-*D*-ribo-hexofuranos-3-ulose hydrate* (**2**) — To a well-stirred solution of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose[19,20] (**1**, 125 g, 0 48 mole) in 550 ml of alcohol-free chloroform (prepared by passing reagent-grade chloroform through a 3 × 50-cm column of neutral alumina, activity I) contained in a 3-l Morton flask (a flask with indented sides), was added water (500 ml), potassium metaperiodate (165 g, 0 72 mole), potassium carbonate (18 g), and 2 g of ruthenium dioxide (50–60% hydrated reagent, Engelhard Industries, Newark, New Jersey, U S A) The mixture was stirred vigorously for 12–15 h at ~25°, by which time t l c (1 1 ether–chloroform or 19 1 benzene–methanol) indicated complete disappearance of the starting material **1** (R_F 0 37 and 0 45, respectively) The resultant ketone hydrate (**2**) was observed as a slower-migrating zone (R_F 0 31 and 0 39, respectively); in some preparations a faster-migrating zone, presumably the parent ketone, was also observed* The oxidation was then terminated by adding 2-propanol (50 ml) and stirring the mixture for 10 min The mixture was then filtered through a pad of Celite, and the filter was washed with two 50-ml portions of chloroform The organic layer was separated, and the aqueous phase was extracted with three 200-ml portions of dichloromethane The combined organic extracts were dried (magnesium sulfate) and evaporated to give the hydrated ketone **2** as a yellowish, crystalline solid suitable for use directly in the next step

Dissolution of the crystalline mass in ~250 ml of warm ether, addition of an equal volume of warm petroleum ether (b p. 30–60°), and allowing the product to

*If t l c showed incomplete reaction, additional potassium metaperiodate and potassium carbonate were added, and the reaction was allowed to proceed until no component corresponding to **1** could be detected (generally 2–3 h) This step was required if removal of alcohol from the chloroform was incomplete It was important to ensure that excess reagent (indicated by a greenish coloration) did not remain in the mixture longer than necessary, as the product **2** is susceptible to further oxidation, leading to substantial decrease in yield

crystallize afforded pure **2** (114 g, 86%), m p 111–112°, $[\alpha]_D^{25}$ +44° (*c* 1, ethanol), lit [3] m p 112–114°, $[\alpha]_D$ +44 5° (ethanol)

Preparation of 1,2 5,6-di-O-isopropylidene-α-D-allofuranose (**3**) — The non-recrystallized product from the preceding preparation was dissolved in 700 ml of 3 7 ethanol–water, and 12 g (1 3 equivs) of sodium borohydride was added portionwise at ~25°, with stirring and cooling to moderate the mildly exothermic reaction After 1 h the solution was evaporated to ~500 ml Water (200 ml) was added and the solution was again evaporated to ~500 ml The solution was extracted with four 200-ml portions of dichloromethane, and the combined extracts were dried (magnesium sulfate) and evaporated to give crystalline **3** (94 g, 75% based on **1**), suitable for use directly in the next step Recrystallization from cyclohexane gave analytically pure **3**, m p 75 5–76°, $[\alpha]_D^{25}$ +37 8° (*c* 1, chloroform), lit [6]. m p 75–76°, $[\alpha]_D$ +38° (chloroform)

Preparation of β-D-allose (**4**) — To a stirred suspension of **3** (90 g, 0 35 mole) in water (700 ml) kept at 45 ±5° was added 150 g of Amberlite IR-120 (H^+) ion-exchange resin (moist resin, 50 mesh, analytical grade) The mixture was stirred for 3 h, and then filtered through a pad of Celite, and the resin was washed with two 50-ml portions of water The filtrate was either lyophilized or evaporated, to give crystalline **4** (62 g, 99 5%) The product was recrystallized by dissolving it in the minimum volume of water at 60° and adding 2 vol of ethanol Slow cooling and seeding gave white crystals of chromatographically and analytically pure *β*-D-allose (**4**) (yield 59 g) From the mother liquors there was obtained, after slow crystallization at −20°, a further 2 55 g of **4** (total yield 61 55 g, 98 8%), m p 141–142° (lit [21] m p 141–142°) (a dimorph having m p 128° was also encountered on occasion), $[\alpha]_D^{25}$ −2 5° (2 min) ⟶ +14 5° (equil , *c* 1, water, complex mutarotation observed) (lit [22] $[\alpha]_D$ +14 4° in water), $R_{glucose}$ 1 28 (chromatography on Whatman No 1 paper; 8 2 1 ethyl acetate–pyridine–water as developing solvent)

The residual syrup (0 45 g) obtained by evaporation of the final mother liquor was trimethylsilylated with *N*-(trimethylsilyl)imidazole in dry pyridine ("Tri-Sil Z", Pierce Chemical Co , Rockford, Illinois, U S A) G l c analysis in system *B* showed three major components, one corresponding to per(trimethylsilyl)ated *β*-D-allose (retention time 10 2 min) in ~75% proportion, and the other two corresponding to per(trimethylsilyl)ated *α* (and *β*)-D-glucose (retention times 12.1 and 18.9 min, respectively in ~25% proportion) The amount of D-glucose detected corresponds to 0.15% of **1** and 99 85% of **3** being formed in the borohydride reduction of **2**

Analytical studies on the reduction of the hydrated ketone **2** — *A With lithium aluminum hydride* To a solution of 210 mg (0 76 mmole) of **2** (shown to be free of **1** by g l c in system *A*) in anhydrous ether (20 ml) was added lithium aluminum hydride (30 mg), and the mixture was heated for 4 h under reflux in an atmosphere of nitrogen The solution was cooled and the excess reagent was decomposed by adding 10% aqueous ammonium chloride (0 5 ml) The mixture was filtered, the salts were washed with three 5-ml portions of ether, and the filtrate was dried (magnesium sulfate) and evaporated to a syrup that crystallized to a solid mass upon addition of ether (183 mg,

93%) A solution of this total, crude product in tetrahydrofuran was analyzed by g l c (system *A*), and three components were observed, the major one (97 3% of the reduced products, T 43 6 min) corresponds to the *allo* derivative **3**, a minor component (2 7 ±0 5% of the reduced products, average of 3 experiments, T 49 1 min) corresponds to the *gluco* derivative **1**, and a rapidly eluted product (~10% of the total products, T 1 9 min) corresponds to the peak obtained when the unreacted ketone hydrate **2** was processed similarly Crystallization of the crude product from cyclohexane afforded 170 mg (86%) of pure **3**

Similar results were obtained when the nonhydrated ketone was used as starting material.

B With sodium bis(2-methoxyethoxy)aluminum hydride The foregoing procedure (*A*) was repeated with 102 mg (0 37 mmole) of **2**, but with 0 5 ml of a 70% solution (1 79 mmole) of sodium bis(2-methoxyethoxy)aluminum hydride ("Vitride", Eastman Organic Chemicals, Rochester, N.Y , U S A) in benzene as the reductant The crude product was freed from 2-methoxyethanol by keeping it *in vacuo* at 5 torr. G l c analysis (system *A*) of the product (95 mg, 96%) indicated **3** as the near-exclusive product, and the proportion of a component corresponding to the *gluco* derivative **1** amounted to only 1 4±0 5% (average of 3 experiments) Crystallization of the product gave pure **3** in high yield

C With sodium borohydride Reduction of **2** (100 mg) by a scaled-down version of the preparative experiment already given, and g l c analysis of the product (system *A*) showed quantitative reduction of **2** and the near-exclusive formation of the *allo* derivative **3** Only a trace (≪0 5%) of the *gluco* product **1** was detected

ACKNOWLEDGMENTS

The authors thank Messrs. V Bolender, G Derr, R Nickol, and J Wright who, as part of their undergraduate laboratory course, checked the preparative procedures, and also Mr W. P. Freeman for repeating the entire preparative sequence several times.

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