Carbohydrate Research, 45 (1975) 151–159

SYNTHESES RELATED TO DENDROKETOSE*

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(Received July 15th, accepted for publication, July 23rd, 1975)

ABSTRACT

A stereospecific synthesis of L-dendroketose [4-*C*-(hydroxymethyl)-L-*glycero*-pentulose] has been attempted starting from 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**1**). A key step in the proposed route is the *O*-debenzoylation of 1,5-di-*O*-benzoyl-4-*C*-(benzoyloxymethyl)-3,4-*O*-isopropylidene-L-*glycero*-pentulose (**6**). However, treatment of **6** with sodium methoxide in methanol at 0° afforded 3,4-*O*-isopropylidenedendroketose as the DL modification. The racemization process was investigated by deuterium-exchange studies.

INTRODUCTION

The synthetic chemistry of branched-chain sugars has developed very rapidly during the last two decades[1]; many of these sugars have been found in antibiotics[1a], and some nucleoside derivatives[2] have exhibited biological activity. In 1949, Utkin[3] reported the preparation of a branched-chain sugar, dendroketose, by treating aqueous 1,3-dihydroxypropanone with sodium hydroxide. The L isomer was reported to be preferentially fermented by a mold, leaving the D isomer, 4-*C*-(hydroxymethyl)-D-*glycero*-pentulose, which could then be isolated. The absolute configuration of the D isomer was established[4] by converting it into D-apionic acid, and hence relating it to D-apiose. Dendroketose, like apiose, can exist in a complex equilibrium between furanoid forms. On conversion of the open-chain structural formulation of dendroketose into its furanoid form, C-4 becomes asymmetric, giving rise to four possible isomers for the D form (see Scheme 1) and four more for the L form. Because of the large number of possible isomers of dendroketose, a purely chemical synthesis of a furanose derivative by a route which would control the stereochemistry at C-4 is of interest. We now describe the results of an investigation of such a synthesis.

The proposed route for the synthesis of a derivative of L-dendroketose, namely, 4-*C*-(hydroxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentulofuranose (**7**), is shown

*Dedicated to the memory of Dr. Hewitt G. Fletcher, Jr.

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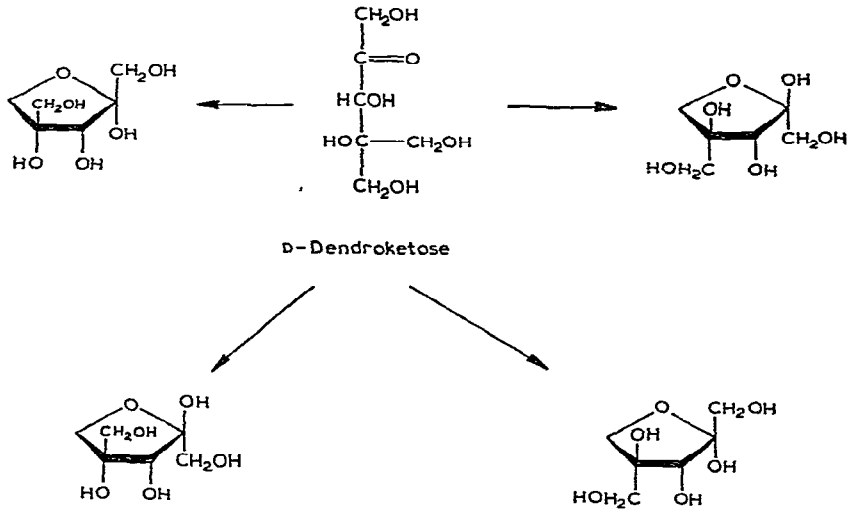
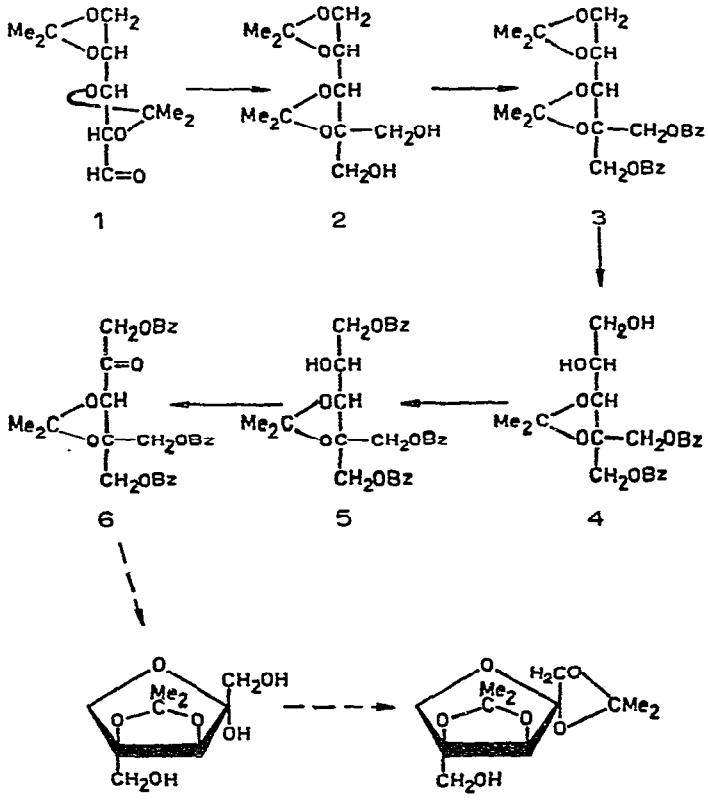


Scheme 1



Scheme 2

in Scheme 2. It was felt that, in compound **7**, the stereochemistry at C-4 would be fixed as shown in the structure, since formation of the alternative furanoid ring, involving ring closure by the other hydroxymethyl group at C-4, would require a *trans* fusion of the furanoid ring and the 1,3-dioxolane ring.

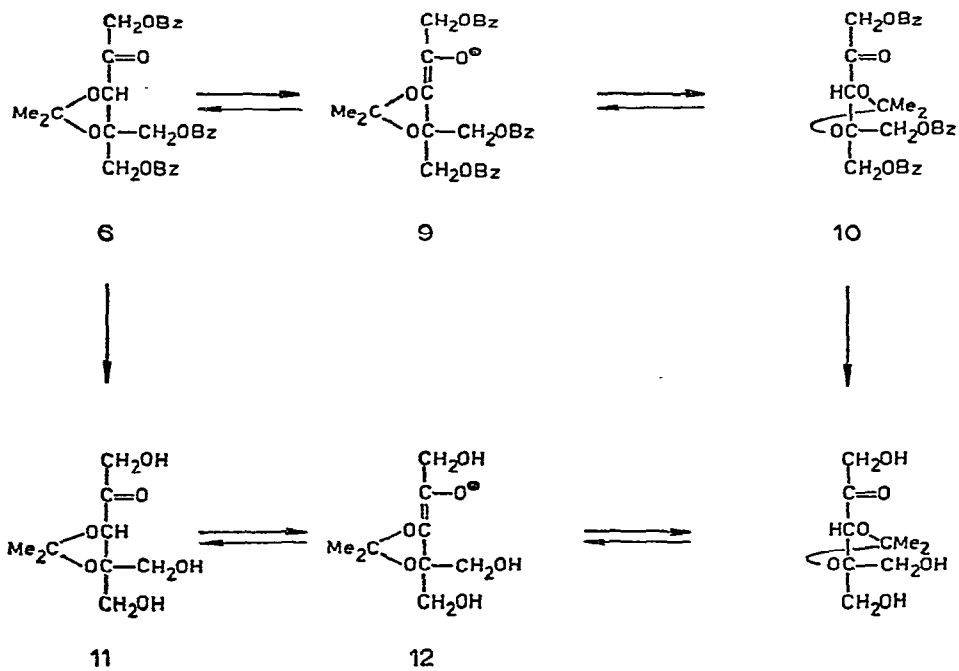
RESULTS AND DISCUSSION

Treatment of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**1**) (prepared from 2,3:4,5-di-*O*-isopropylidene-D-arabinose diethyl dithioacetal by the action of mercuric chloride[5]) with formaldehyde in the presence of sodium hydroxide afforded crystalline 2-*C*-(hydroxymethyl)-2,3:4,5-di-*O*-isopropylidene-D-*erythro*-pentitol (**2**). Compound **2** is presumably formed by a mixed aldol reaction between 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose (**1**) and formaldehyde, followed by reduction of the condensation product by a second molecule of formaldehyde through a crossed-Cannizzaro reaction. A similar use has been made of formaldehyde in the synthesis of L-apiose by Schaffer[6] and of D-apiose by Williams and Jones[7]. Treatment of compound **2** with benzoyl chloride in pyridine gave crystalline 1-*O*-benzoyl-2-*C*-(benzoyloxymethyl)-2,3:4,5-di-*O*-isopropylidene-D-*erythro*-pentitol (**3**). Partial acid-catalyzed hydrolysis of **3** afforded 1-*O*-benzoyl-2-*C*-(benzoyloxymethyl)-2,3-*O*-isopropylidene-D-*erythro*-pentitol (**4**) as a chromatographically homogeneous syrup. Selective benzoylation of the primary hydroxyl group in **4** with 1.1 mol. of benzoyl chloride in pyridine at 0° yielded 1,5-di-*O*-benzoyl-2-*C*-(benzoyloxymethyl)-2,3-*O*-isopropylidene-D-*erythro*-pentitol (**5**). The tribenzoate **5** could be oxidized to the 2-ketone **6** by the modified ruthenium tetraoxide oxidation procedure[8] or by the use of the chromium trioxide–dipyridine complex[9]; the latter method afforded **6** in high yield in less than 5 min. It was not known at this juncture if the integrity of C-3 had been maintained during the oxidation, although the product exhibited a specific rotation of −33°.

The next step in the synthesis involved treatment of **6** with sodium methoxide in methanol at 0°; a syrupy product was obtained, which consisted (t.l.c.) of one major component and two slower-moving, minor components. Treatment of the product with acetone in the presence of anhydrous copper(II) sulfate and sulfuric acid afforded a crystalline di-*O*-isopropylidene derivative which had m.p. 80–81° and $[\alpha]_D$ 0° (acetone). In his initial publication on dendroketose in 1949, Utkin[3] reported the isolation of a di-*O*-isopropylidene derivative of D-dendroketose, having m.p. 89° and $[\alpha]_D^{16}$ −121° (acetone), and of DL-dendroketose, having m.p. 84°. These derivatives were formulated as 1,2:3,4-di-*O*-isopropylidene compounds. Utkin[4] later reported the preparation of an isomeric di-*O*-isopropylidene derivative of D-dendroketose, namely, the 2,3:4,4[1]-di-*O*-isopropylidene compound, m.p. 63.5–64.5°, $[\alpha]_D^{17}$ +60.5° (acetone); the corresponding DL modification was isolated as a syrup. A comparison of the data suggested that the di-*O*-isopropylidene compound obtained in the synthesis starting from **1** was the 1,2:3,4-di-*O*-isopropylidene derivative of DL-dendroketose. The product migrated in t.l.c. at the same rate as a di-*O*-isopropylidene derivative

(m.p. 83–85°) prepared by treatment of a sample of DL-dendroketose (obtained by Utkin's procedure[3] from 1,3-dihydroxypropanone) with acetone and sulfuric acid; moreover, the p.m.r. spectra of the two compounds were identical. In a separate study[10], the configuration at the anomeric center in 1,2:3,4-di-*O*-isopropylidene-dendroketose and in 3,4-*O*-isopropylidenedendroketose was assigned as being as shown in the structural formulas **8** and **7***, respectively, by ^{13}C-n.m.r. spectroscopy.

The production of optically inactive 1,2:3,4-di-*O*-isopropylidenedendroketose in the present work suggested that racemization had occurred at C-3, presumably during the base-catalyzed *O*-debenzoylation of the 2-ketone **6**. A possible racemization process involving enolization is shown in Scheme 3. Compound **6** could give the enolate **9** which, upon protonation at C-3, would afford a racemic mixture of **6** and **10**. If the *O*-debenzoylation reaction proceeded faster than proton abstraction at C-3, then racemization would proceed by way of the enolate **12**. In an effort to establish if an enolization is in fact occurring, and if so, which enolate, **9** or **12**, is the more likely, two deuterium-exchange studies were undertaken.

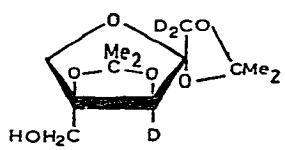


Scheme 3

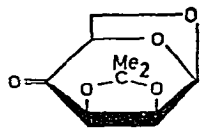
Compound **6** was *O*-debenzoylated under conditions identical to those used before, except that the reaction was performed in methanol-*d* and with sodium

*Only the L isomers are shown in Scheme 2, although the two dendroketose derivatives were obtained as DL modifications.

methoxide prepared by adding clean, metallic sodium to methanol-*d*. The crude material was acetonated to give a product having m.p. 80–81°, $[\alpha]_D$ 0°, and the same mobility in t.l.c. as an authentic sample of 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose[3]. The p.m.r. spectrum of the product was identical to that of the di-*O*-isopropylidene-DL-dendroketose obtained before, except that the signals of H-1 and H-1′ were missing and that of H-3 had greatly diminished in intensity; according to the intensity of the H-3 signal, at least a 70% exchange of protium by deuterium had occurred at C-3. In the ^{13}C-n.m.r. spectrum of the product (see Ref. 10), a signal for C-1 was not observed and the intensity of the C-3 signal was diminished relative to that of the C-3 signal in the spectrum of non-deuterated 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose. Thus, the product contained deuterium at both C-1 and C-3 (see structural formula **8a** for L isomer), a result which indicates that racemization occurs by an enolization process involving C-3 (see Scheme 3).



8a



13

Horton *et al.*[11] have reported that 1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-*lyxo*-hexopyranos-4-ulose (**13**), on treatment with a catalytic amount of sodium deuteroxide in deuterium oxide, undergoes a regiospecific and stereospecific incorporation of deuterium at C-3 to give the 3-*C*-deuterated analogue of the ketone **13**. This result is of interest in the present work, since 1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-*lyxo*-hexopyranos-4-ulose (**13**) and the acyclic form (**11**) of 3,4-*O*-isopropylidene-L-dendroketose each have a keto group, and a hydrogen on an *α*-carbon which is part of a 1,3-dioxolane ring. Horton *et al.*[11] observed that exchange occurred in their system during 8 h at room temperature. In contrast, however, when 3,4-*O*-isopropylidene-DL-dendroketose was treated with a catalytic amount of sodium deuteroxide in deuterium oxide, even after 100 h at room temperature no deuterium was incorporated either at C-3 or at C-1 as evidenced by a lack of any change in the signals for H-3, H-1, and H-1′ in the p.m.r. spectrum, a result which suggests that 3,4-*O*-isopropylidenedendroketose exists mainly in the cyclic form (see structural formula **7** for L isomer). This conclusion implies that the racemization which accompanies the conversion of the tribenzoate **6** into 3,4-*O*-isopropylidene-DL-dendroketose is due to an enolization involving C-3 which occurs *before* *O*-debenzoylation at C-5 and C-4[1]; presumably, had *O*-debenzoylation occurred initially, the *O*-debenzoylated product would have existed in the cyclic form, and hence enolization involving C-3 might not have been observed. This conclusion is supported by the observation[12] that treatment

of 1-*O*-benzoyl-4-*C*-(hydroxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentulose with sodium methoxide in methanol did not give a racemic mixture.

Although the great facility of the racemization observed in the present work renders abortive the proposed stereospecific synthesis of a furanose derivative of one enantiomer of dendroketose, the route outlined in Scheme 2 does offer a viable, alternative (*cf.* Ref. 3) method of preparing a DL modification in high overall yield.

EXPERIMENTAL

General. — Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 automatic polarimeter at 26 ±3°. I.r. spectra were recorded with a Unicam SP 1000 or a Perkin–Elmer 180 spectrophotometer. N.m.r. spectra were recorded at 60 MHz for solutions in chloroform-*d* with tetramethylsilane as the internal standard. T.l.c. was performed with Silica Gel G containing 1–3% of Lumilux Green ZS (Brinkmann) in the following solvent systems (v/v): (*A*) 5:2 petroleum ether–ethyl acetate; (*B*) 3:2 petroleum ether–ethyl acetate; (*C*) 5:1 chloroform–methanol. The term "petroleum ether" refers to the fraction of b.p. 60–80°. The developed plates were air-dried, and compounds located by heating the plates at ~150° after they had been sprayed with 10% aqueous sulfuric acid containing 1% of cerium sulfate and 1.5% of molybdic acid; benzoates were detected by irradiation of the developed plates with short-wavelength u.v. light from a 2537 Å "Mineralight". Column chromatography was performed on silica gel (70–230 mesh).

*2-C-(Hydroxymethyl)-2,3:4,5-di-*O*-isopropylidene-*D-erythro-*pentitol* (**2**). — A solution of 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose[5] (**1**, 40 g) in ethanol (800 ml) was treated with formaldehyde (40% solution, 80 ml) and sodium hydroxide (40 g in 600 ml of water) for 24 h at room temperature. T.l.c. (solvent *B*) revealed that all the starting material (R_F 0.39) had been converted into a slower-moving material (R_F 0.19). The reaction mixture was neutralized with 90% formic acid and filtered, and the filtrate was concentrated to a syrup. The residue was dissolved in chloroform, and the solution was washed with water, dried ($MgSO_4$), and concentrated to a syrup which crystallized on standing. The crude material was recrystallized from diethyl ether–petroleum ether to give **2** as white needles (26 g, 55%), m.p. 93–94°, $[\alpha]_D$ −6.4° (*c* 1.9, methanol); lit.[7] for D enantiomer, m.p. 91–92°, $[\alpha]_D$ +14° (*c* 2.0, methanol).

*1-*O*-Benzoyl-2-*C*-(benzoyloxymethyl)-2,3:4,5-di-*O*-isopropylidene-*D-erythro-*pentitol* (**3**). — Compound **2** (5.25 g) was treated with benzoyl chloride (6 ml) in dry pyridine (60 ml) for 1 h at ~10°, with constant stirring. The reaction mixture was filtered, and the filtrate was concentrated to give a syrup, which was dissolved in chloroform (150 ml); the chloroform solution was washed with cold, saturated, aqueous sodium hydrogen carbonate and then with water, dried ($MgSO_4$), and concentrated to dryness several times with benzene and finally with ethanol; the residue crystallized on standing (9.0 g, 94%). Recrystallization from ethanol gave **3**,

m.p. 108–109°, $[\alpha]_D$ −20.5 ±1° (*c* 2.3, chloroform); p.m.r. data: τ 1.73–2.08 (4 protons, aromatic), 2.34–2.83 (6 protons, aromatic), 5.00–6.17 (8 protons, H-2, H-3, six methylene protons), 8.33, 8.58, 8.62, and 8.76 (3-proton singlets, 2 CMe_2); ν_{max} (KBr) 1720–1740 (OBz), 1370, and 1380 cm^{-1} (CMe_2); no absorption attributable to OH.

Anal. Calc. for $C_{26}H_{30}O_8$: C, 66.4; H, 6.4. Found: C, 66.3; H, 6.5.

*1-O-Benzoyl-2-C-(benzoyloxymethyl)-2,3-O-isopropylidene-*D-erythro-*pentitol* (**4**). — Compound **3** (9.0 g) was dissolved in 100 ml of 1:1 (v/v) acetone–ethanol, and 0.2M hydrochloric acid (50 ml) was added, The reaction mixture was kept for 3 h at 50°, neutralized with silver carbonate, and filtered, and the filtrate concentrated to dryness. The syrupy residue was extracted with 1:1 (v/v) ethyl acetate–petroleum ether and the extract concentrated to a syrup, which was extracted with hot petroleum ether to remove unreacted starting material. The residue was dissolved in chloroform, and the solution was dried over magnesium sulfate and concentrated to give **4** as a syrup (7.4 g, 90%), R_F 0.29 (solvent *B*), $[\alpha]_D$ −15 ±0.5° (*c* 2.0, chloroform); ν_{max} (film) 3500 (OH) and 1730 cm^{-1} (OBz); p.m.r. data: τ 1.75–2.16 (4 protons, aromatic), 2.3–2.84 (6 protons, aromatic), 5.00–6.65 (10 protons, H-2, H-3, two OH's, six methylene protons), 8.55 and 8.60 (3-proton singlets, 2 CMe_2).

Anal. Calc. for $C_{23}H_{26}O_8$: C, 64.2; H, 6.1. Found: C, 64.3; H, 6.6.

*1,5-Di-O-benzoyl-2-C-(benzoyloxymethyl)-2,3-O-isopropylidene-*D-erythro-*pentitol* (**5**). — To a solution of **4** (7.37 g) in dry pyridine (50 ml) at 0°, benzoyl chloride (1.7 ml) was added dropwise during 30 min, and the mixture was stirred for an additional 30 min at 0°. The reaction mixture was processed in the usual manner. The crude product was purified by column chromatography on silica gel with solvent *A*. The tribenzoate **5** was obtained as a colorless, homogeneous syrup (6.47 g, 71%), R_F 0.45 (solvent *A*), $[\alpha]_D$ −5 ±0.5° (*c* 1.0, chloroform); ν_{max} (film) 3500 (OH) and 1730 cm^{-1} (OBz); p.m.r. data: τ 1.75–2.16 (6 protons, aromatic), 2.33–2.83 (9 protons, aromatic), 5.18–5.82 (9 protons, H-2, H-3, OH, six methylene protons), 8.52 and 8.58 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{30}H_{30}O_9$: C, 67.4; H, 5.6. Found: C, 67.7; H, 5.8.

*1,5-Di-O-benzoyl-4-C-(benzoyloxymethyl)-3,4-O-isopropylidene-*L-glycero-*pentulose* (**6**). — (*a*) A solution of chromium trioxide–dipyridine complex was prepared by adding chromium trioxide (3.77 g) to a solution of dry pyridine (6.05 ml) in dry dichloromethane (90 ml); the mixture was vigorously stirred for 20 min to give a dark-red solution. A solution of compound **5** (1.65 g) in dry dichloromethane (10 ml) was added in one portion, and the mixture stirred for 25 min at room temperature with exclusion of moisture. T.l.c. showed that all of the starting material had been consumed and that a single component, R_F 0.45 [3:1 (v/v) petroleum ether–ethyl acetate], had been produced, which gave a positive reaction with *p*-anisidine hydrochloride[13]. The reaction mixture was poured into ice-cold, saturated, aqueous sodium hydrogen carbonate, and the reaction flask rinsed with a small amount of diethyl ether; the ether solution was added to the mixture in a separatory funnel, the contents of which were then shaken at 0°. The organic solution was separated, washed twice with water,

dried ($MgSO_4$), and concentrated to a yellow syrup. Toluene was evaporated several times from the residue to remove traces of pyridine and give **6** (1.6 g, 100%), $[\alpha]_D$ −33 ±1° (*c* 2.0, chloroform); no absorption attributable to OH in the i.r. spectrum; p.m.r. data: τ 1.75–2.2 (6 protons, aromatic), 2.3–2.75 (9 protons, aromatic), 4.7 (2-proton singlet, C-1 methylene protons), 5.1–5.5 (5 protons, H-3, four methylene protons), 8.4 and 8.55 (6 protons, CMe_2).

(*b*) To a solution of compound **5** (1 g) in carbon tetrachloride (100 ml), potassium carbonate (62 mg) and ruthenium dioxide (20 mg) were added; potassium periodate (0.659 g) in water (10 ml) was then added, dropwise, with rapid stirring. After 24 h, all of the starting material had reacted to give a faster-moving component (t.l.c.). The excess of ruthenium tetraoxide was destroyed by the addition of 2-propanol, and the mixture was filtered through Celite .The organic phase was washed with water, decolorized, dried ($MgSO_4$), and concentrated to afford the 2-ketone **6** as a chromatographically homogeneous syrup (662 mg).

1,2:3,4-Di-O-*isopropylidene*-DL-*dendroketose*. — To a solution of the 2-ketone **6** (4.0 g) in 50 ml of 1:1 (v/v) methanol–chloroform at 0°, sodium methoxide (8 ml, 0.2M in methanol) was added, and the mixture was stirred at ~5° overnight. Solid carbon dioxide was added to neutralize the mixture, which was then concentrated to dryness. The residue was partitioned between chloroform and water; the aqueous solution was extracted twice with chloroform and then concentrated to a syrup. The residue was extracted with hot, 1:1 (v/v) acetone–ethyl acetate; the extract was shown by t.l.c. (solvent *C*) to contain one major (R_F 0.56) and two slower-moving, minor components (R_F 0.47 and 0.08). The extract was evaporated, and the crude product was treated with dry acetone in the presence of anhydrous copper(II) sulfate and sulfuric acid for 1 h. The solution was neutralized with gaseous ammonia, filtered, and concentrated to dryness. A solution of the residue in chloroform was washed with water, dried ($MgSO_4$), and concentrated to a syrup, which crystallized from petroleum ether. The product had m.p. 81–81.5°, $[\alpha]_D$ 0° (*c* 1.28, acetone), and the same mobility (t.l.c., solvent *A*) as a sample (m.p. 83–85°) of 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose prepared by treatment with acetone and sulfuric acid of a sample of DL-dendroketose obtained by Utkin's procedure[3] from 1,3-dihydroxypropanone. The p.m.r. spectra of the two products were identical.

1,2:3,4-Di-O-*isopropylidene*-DL-*dendroketose*-1,1,3-d_3. — To a solution of the 2-ketone **6** (2.8 g) in 50 ml of 1:1 (v/v) chloroform–methanol-*d* at 0°, sodium methoxide (8 ml, 0.2M in methanol-*d*) was added, and the mixture was kept at ~5° overnight. A syrupy product (800 mg) was isolated as in the preceding experiment, and this was acetonated to afford a crystalline material (500 mg). Recrystallization from petroleum ether gave white needles, m.p. 80–81°, $[\alpha]_D$ 0° (*c* 1.0, acetone); p.m.r. data: τ 5.75 (0.3-proton singlet, H-3)*, 6.0–6.35 (4 protons, four methylene protons), 8.05 (1 proton, OH), and 8.6 (12 protons, 2 CMe_2); ν_{max} (KBr) 3380 (OH), 1365, and 1380 cm^{-1} (CMe_2).

*The appearance of a diminished H-3 signal is indicative of only partial deuteration at C-3.

*3,4-O-Isopropylidene-*DL*-dendroketose.* — To a solution of 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose (5.0 g) in 100 ml of 1:1 (v/v) acetone–ethanol, 0.2M aqueous hydrochloric acid (50 ml) was added, and the reaction mixture was heated at reflux temperature until the formation of non-migrating [t.l.c., 2:1 (v/v) petroleum ether–ethyl acetate] material was first observed. The reaction mixture was neutralized with silver carbonate, filtered, and concentrated to a brown syrup, which was extracted with hot petroleum ether. The residue was dissolved in chloroform, and the solution was dried ($MgSO_4$); t.l.c. showed the presence of starting material (R_F 0.72), a minor component (R_F 0.33), and a major component (R_F 0.12), in addition to non-migrating material. The component having R_F 0.12 was obtained as a homogeneous, colorless syrup (1.71 g) by column chromatography on silica gel with 3:1 (v/v) petroleum ether–ethyl acetate. The compound reduced Fehling's solution, and was identified as 3,4-*O*-isopropylidene-DL-dendroketose; p.m.r. data (deuterium oxide with tetramethylsilane as the external standard): τ 5.5 (1-proton singlet, H-3), 5.6–6.3 (6 protons, six methylene protons), and 8.15–8.45 (6 protons, CMe_2); for ^{13}C-n.m.r. data, see Ref. 10.

*Treatment of 3,4-O-isopropylidene-*DL*-dendroketose with sodium deuteroxide in deuterium oxide.* — To a solution of 3,4-*O*-isopropylidene-DL-dendroketose (100 mg) in deuterium oxide (1.5 ml), 0.2 ml of a M solution of sodium deuteroxide in deuterium oxide was added. The mixture was kept at room temperature, and monitored by p.m.r. spectroscopy; even after 100 h, no change was observed in the spectrum.

ACKNOWLEDGMENTS

The authors are grateful to the National Research Council of Canada for financial support in the form of research grants and a scholarship (to H.C.J.). One of us (A.D.) also thanks the Universidade Federal do Paraná, Brasil, for a leave of absence to pursue studies at Queen's University.

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