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A STEREOSPECIFIC SYNTHESIS OF L-DENDROKETOSE DERIVATIVES

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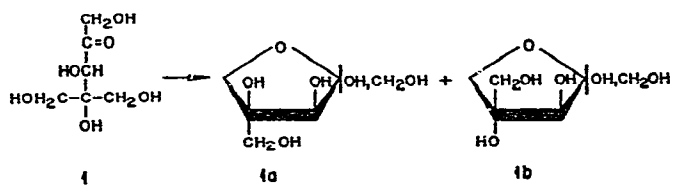
ABSTRACT

The 3,4-*O*- and 1,2:3,4-di-*O*-isopropylidene derivatives (**7** and **8**) of L-dendroketose [4-*C*-(hydroxymethyl)-L-*glycero*-pentulose] (**1**) have been synthesized stereospecifically from 4-*C*-(hydroxymethyl)-1,2:3,4-di-*O*-isopropylidene-L-*erythro*-pentitol (**2**).

INTRODUCTION

The preparation of *O*-isopropylidene derivatives of D-dendroketose was first described by Utkin[1,2]. Alkaline self-condensation of 1,3-dihydroxy-2-propanone, followed by resolution with a *Penicillium* fungus, gave the D isomer, 4-*C*-(hydroxymethyl)-D-*glycero*-pentulose, which was isolated as its 1,2:3,4-di-*O*-isopropylidene derivative[1,2]. An analysis[3] by gas–liquid chromatography (g.l.c.) of the isomers of dendroketose showed four peaks, corresponding to the eight possible cyclic isomers (three chiral centers are present in the ring form, compared with one in the open-chain form). The four isomers originating from L-dendroketose (**1**) are shown in Scheme 1. I.r. and u.v. spectroscopy have shown[3] that dendroketose exists virtually completely



1 1a 1b

Scheme 1

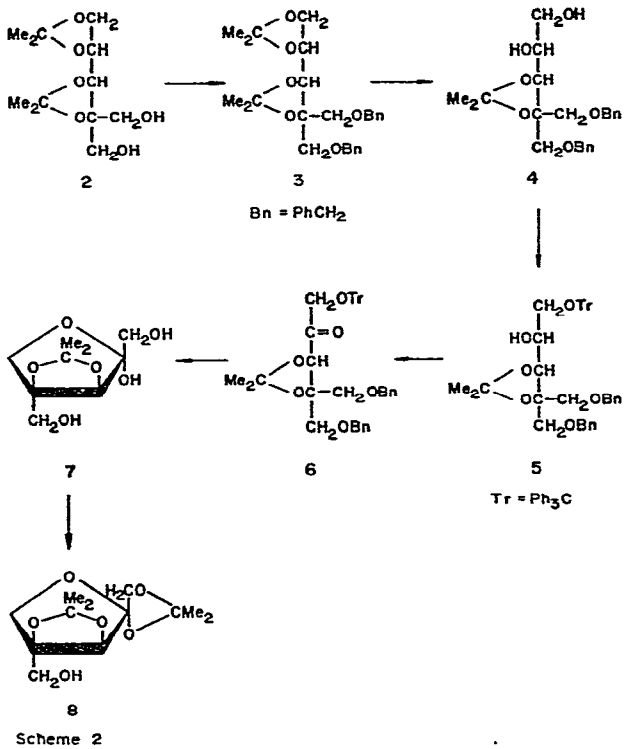
in the cyclic forms. A recent attempt[4] to synthesize derivatives of L-dendroketose from **2**, using benzoyl protecting-groups, led to racemization when an intermediate in the synthesis, 1,5-di-*O*-benzoyl-4-*C*-(benzoyloxymethyl)-3,4-*O*-isopropylidene-L-*glycero*-pentulose, was *O*-debenzoylated with sodium methoxide in methanol at 0°.

In the present synthesis, triphenylmethyl and benzyl groups were used as protecting groups during oxidation of HO-2 in compound **5**; these groups are readily removed by mild, catalytic hydrogenolysis. The 3,4-*O*-isopropylidene group fixes the stereochemistry at C-4 during the reaction sequence, limiting the number of possible products to the two L-*erythro* anomers[4] (**1a**).

RESULTS AND DISCUSSION

Treatment of 4-*C*-(hydroxymethyl)-1,2:3,4-di-*O*-isopropylidene-L-*erythro*-pentitol (**2**) (synthesized[4] by condensation of formaldehyde[5,6] with 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-D-arabinose) with benzyl chloride in the presence of potassium hydroxide afforded 5-*O*-benzyl-4-*C*-(benzyloxymethyl)-1,2:3,4-di-*O*-isopropylidene-L-*erythro*-pentitol (**3**). Mild, acid-catalyzed hydrolysis of **3** removed the 1,2-*O*-isopropylidene group to give 5-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentitol (**4**). Treatment of **4** with chlorotriphenylmethane in pyridine yielded 5-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-1-*O*-trityl-L-*erythro*-pentitol (**5**). Oxidation of **5** with dimethyl sulfoxide–acetic anhydride afforded 5-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-1-*O*-trityl-L-*glycero*-pentulose (**6**). Catalytic hydrogenolysis of **6** in methanol in the presence of palladium–charcoal resulted in an initial, rapid removal of the trityl group, followed by *O*-debenzylation. The product, 4-*C*-(hydroxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentulofuranose (3,4-*O*-isopropylidene-L-dendroketose) (**7**), had the same R_F value and p.m.r. spectrum as those of 3,4-*O*-isopropylidene-DL-dendroketose, prepared[4] from 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose[1,2]. Compound **7** was optically active, having a specific rotation of +47°. The i.r. spectrum of **7** showed no absorption attributable to a carbonyl group, supporting the observations that dendroketose[3] and 3,4-*O*-isopropylidene-DL-dendroketose[4] exist preponderantly in cyclic forms.

Treatment of **7** with acetone, in the presence of anhydrous copper(II) sulfate and sulfuric acid, yielded crystalline 1,2:3,4-di-*O*-isopropylidene-L-dendroketose (**8**), having m.p. 88–90° and a specific rotation of +118°. Utkin[1] described the preparation of 1,2:3,4-di-*O*-isopropylidene-D-dendroketose, having m.p. 89° and $[\alpha]_D^{16}$ −121°. The p.m.r. spectra, and mobilities in t.l.c., of **8** and 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose (m.p. 81–82°; synthesized[1,3,4] from 1,3-dihydroxy-2-propanone) were identical. The optical activities of **7** and **8** indicate that racemization had not occurred during the sequence of reactions outlined in Scheme 2. The anomeric configurations of 3,4-*O*-isopropylidene- and 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose have been determined[7]. Comparison of the physical data of **7** and **8** with that of the corresponding DL modifications[4] indicates that both **7** and **8** have the same configuration at C-2 as was found for the DL mixtures. The anomeric configurations of the mono- and di-*O*-isopropylidene derivatives of L-dendroketose are shown in structures **7** and **8**.



Scheme 2

EXPERIMENTAL

General. — Melting points were determined with a Kofler hot-stage apparatus, and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer 237 spectrophotometer. Optical rotations were measured with a Bendix-NPL Automatic Polarimeter Type 143D on solutions in chloroform, unless otherwise stated. P.m.r. spectra were recorded with a Varian HA-100 instrument for solutions in $CDCl_3$ with tetramethylsilane as the internal standard, unless otherwise stated. Mass spectra were determined with an A.E.I. MS-9 spectrometer, using the direct-insertion technique and an ionizing voltage of 70 eV. Column chromatography was conducted on Silica Gel 60 (70–230 mesh; Merck). Preparative-layer chromatography (p.l.c.) was performed on plates precoated with a 2-mm layer of Silica Gel 60 F-254 (Merck). T.l.c. was performed on plates precoated with a 250-μm layer of Silica Gel 60 F-254 (Merck) in the following solvent systems (v/v): (*A*) 2:1 ethyl acetate–petroleum ether; (*B*) 2:1 petroleum ether–ethyl acetate; (*C*) 5:1 chloroform–methanol; and (*D*) 10:1 petroleum ether–ethyl acetate. The term "petroleum ether" refers to the fraction of b.p. 100–120°.

*5-O-Benzyl-4-C-(benzyloxymethyl)-1,2:3,4-di-O-isopropylidene-*L-erythro-*pentitol* (3). — 4-*C*-(Hydroxymethyl)-1,2:3,4-di-*O*-isopropylidene-L-*erythro*-pentitol[4] (2) (55 g) was suspended in benzyl chloride (260 ml), and potassium hydroxide (220 g) was

added. The mixture was stirred for 1 h at 130–140° and cooled, and water (1 litre) was added. The solution was extracted with chloroform, and the extract was washed with water and evaporated under diminished pressure. Removal of the benzyl chloride by co-distillation with water, and finally with ethanol, afforded a syrup (100 g). A sample of the product was further purified (p.l.c., solvent *B*) to give compound **3** as a syrup, R_F 0.73 (solvent *A*), $[\alpha]_D^{20}$ −16.1° (*c* 1.7); ν_{max}^{film} 1377 and 1367 cm^{-1} (CMe_2); no absorption attributable to OH; mass spectrum: *m/e* 442 (M^+), 427 ($M^+ - CH_3$), 351 ($M^+ - C_6H_5CH_2$); p.m.r. data: τ 2.67 (*m*, 10 protons, 2 C_6H_5), 5.41 (*t*, 4 protons, 2 benzyl-CH_2), 5.59–6.44 (*m*, 8 protons, H-2, H-3, 3 CH_2), 8.52, 8.56, 8.60, and 8.68 (3-proton singlets, 2 CMe_2).

Anal. Calc. for $C_{26}H_{34}O_6$: C, 70.6; H, 7.7. Found: C, 70.3; H, 7.7.

*5-O-Benzyl-4-C-(benzyloxymethyl)-3,4-O-isopropylidene-*L-erythro-*pentitol* (**4**). — Compound **3** (48 g) was dissolved in 2:1 (v/v) acetone–ethanol (400 ml), and 0.2M hydrochloric acid (250 ml) was added. The solution was kept for 2.5 h at 60°, made neutral with silver carbonate, the suspension filtered, and the filtrate evaporated to a syrup (42 g). The crude product was applied to a column of silica gel (1.5 kg) and eluted with solvent *B*, yielding pure **4** as a colourless syrup (34 g, 78%), R_F 0.55 (solvent *A*), $[\alpha]_D^{20}$ −3.5° (*c* 2.4); ν_{max}^{film} 3420 (OH), 1380, and 1368 cm^{-1} (CMe_2); mass spectrum: *m/e* 402 (M^+), 387 ($M^+ - CH_3$), 311 ($M^+ - C_6H_5CH_2$); p.m.r. data: τ 2.71 (*s*, 10 protons, 2 C_6H_5), 5.43 (*q*, 4 protons, 2 benzyl-CH_2), 6.00–6.39 (*m*, 8 protons, H-2, H-3, 3 CH_2), 7.64 (broad *s*, 2 protons, D_2O exchangeable, 2 OH), 8.62 and 8.65 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{23}H_{30}O_6$: C, 68.6; H, 7.5. Found: C, 68.8; H, 7.7.

*5-O-Benzyl-4-C-(benzyloxymethyl)-3,4-O-isopropylidene-1-O-trityl-*L-erythro-*pentitol* (**5**). — To a solution of compound **4** (23 g) in dry pyridine (50 ml) was added chlorotriphenylmethane (17.5 g). The solution was stirred for 16 h at room temperature, poured into cold water (200 ml), and extracted with chloroform (3 × 100 ml). The extracts were combined, successively washed with cold 0.5M sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water, and evaporated to a syrup which was chromatographed (solvent *B*) on a column of silica gel (1.6 kg). The product (**5**) was obtained as a thick, colorless oil (32 g, 87%), R_F 0.56 (solvent *B*), $[\alpha]_D^{20}$ −4.2° (*c* 2.3); ν_{max}^{film} 3460 (OH), 1380, and 1368 cm^{-1} (CMe_2); mass spectrum: *m/e* 401 ($M^+ - CPh_3$); p.m.r. data: τ 2.72 (*m*, 25 protons, 5 C_6H_5), 5.42 (*q*, 4 protons, 2 benzyl-CH_2), 5.84 (*d*, 1 proton, H-3), 6.12–6.70 (*m*, 7 protons, H-2, 3 CH_2), 6.35 (*s*, 1 proton, D_2O exchangeable, OH), and 8.65 (*s*, 6 protons, CMe_2).

Anal. Calc. for $C_{42}H_{44}O_6$: C, 78.2; H, 6.9. Found: C, 77.7; H, 6.6.

*5-O-Benzyl-4-C-(benzyloxymethyl)-3,4-O-isopropylidene-1-O-trityl-*L-glycero-*pentulose* (**6**). — To a solution of compound **5** (24 g) in dry dimethyl sulfoxide (80 ml) was added acetic anhydride (20 ml), and the solution was stirred under nitrogen for 16 h at 30°. Iced water (50 ml) was added, and the mixture was freeze-dried. The resulting syrup was washed with water (5 × 20 ml) by decantation, and purified by column chromatography (1.0 kg), initially using solvent *D* as the eluant. The product (**6**) was eluted with solvent *B*, and was obtained as a colorless syrup (18.8 g, 79%),

R_F 0.56 (solvent *B*), $[\alpha]_D^{20}$ −12.0° (*c* 3.1); ν_{max}^{film} 1725 (C=O), 1382, and 1370 cm^{-1} (CMe_2), no absorption attributable to OH; mass spectrum: *m/e* 642 (M^+), 627 ($M^+ - CH_3$), 399 ($M^+ - CPh_3$); p.m.r. data: τ 2.74 (*m*, 25 protons, 5 C_6H_5), 5.50 (3 protons, H-3, CH_2), 5.80–6.68 (*m*, 8 protons, 4 CH_2), 8.58 and 8.66 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{42}H_{42}O_6$: C, 78.5; H, 6.5. Found: C, 78.1; H, 6.4.

*4-C-(Hydroxymethyl)-3,4-O-isopropylidene-*L*-erythro-pentulofuranose (3,4-O-isopropylidene-*L*-dendroketose)* (**7**). — To a solution of compound **6** (9.0 g) in methanol (100 ml) was added palladium-on-charcoal (10%, 1 g), and the mixture was shaken under hydrogen (1 atm.). T.l.c. (solvent *B*) showed an initial, rapid removal of the trityl group, with the formation of a slower-moving compound (R_F 0.36). Hydrogenolysis was continued for a further 30 h, the mixture was filtered, and the filtrate was evaporated to a syrup. A solution of the residue in water (50 ml) was washed with chloroform (4 × 30 ml), and evaporated to afford the product (**7**) as a syrup (2.6 g, 85%), R_F 0.51 (solvent *C*), $[\alpha]_D^{20}$ +47.1° (*c* 2.2, acetone); ν_{max}^{film} 3380 (OH), 1383, and 1370 cm^{-1} (CMe_2); mass spectrum: *m/e* 205 ($M^+ - CH_3$); p.m.r. data (acetone-d_6): τ 5.72 (*s*, 1 proton, H-3), 6.10 (broad *m*, 3 protons, D_2O exchangeable, 3 OH), 5.95–6.35 (*m*, 6 protons, 3 CH_2), 8.58 and 8.64 (3-proton singlets, CMe_2). Compound **7** had the same R_F value and p.m.r. spectrum as those of 3,4-*O*-isopropylidene-DL-dendroketose, prepared[4] from 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose.

Anal. Calc. for $C_9H_{16}O_6$: C, 49.1; H, 7.3. Found: C, 49.2; H, 7.5.

*1,2:3,4-Di-O-isopropylidene-*L*-dendroketose* (**8**). — To a solution of compound **7** (1.5 g) in dry acetone was added anhydrous copper(II) sulfate and sulfuric acid. The mixture was stirred for 1 h at 20°, made neutral with gaseous ammonia, filtered, and the filtrate evaporated to a syrup which crystallized on standing. Recrystallization from petroleum ether gave the product (**8**) as white needles (1.5 g, 89%), m.p. 88–90°, $[\alpha]_D^{20}$ +118° (*c* 1.1, acetone); R_F 0.74 (solvent *C*); $\nu_{max}^{CHCl_3}$ 3210 (OH), 1383, and 1370 cm^{-1} (CMe_2); mass spectrum: *m/e* 245 ($M^+ - CH_3$); p.m.r. data: τ 5.70 (*s*, 1 proton, H-3), 5.71 and 5.94 (2 *d*, 2 protons, H-1,1′), 6.06 and 6.19 (2 *d*, 2 protons, H-5,5′), 6.22 (*s*, 2 protons, CH_2), 7.92 (broad *s*, 1 proton, D_2O exchangeable, OH), 8.54 (*s*, 6 protons, 2 CMe_2), 8.59 and 8.61 (3-proton singlets, CMe_2). Compound **8** had the same R_F value and p.m.r. spectrum as those of 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose (m.p. 81–82°), prepared[1,3,4] from 1,3-dihydroxy-2-propanone. For the D isomer, Utkin[1] found m.p. 89° and $[\alpha]_D^{16}$ −121° (acetone).

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.4; H, 7.8. Found: C, 55.4; H, 7.9.

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