Carbohydrate Research, 64 (1978) 283–288

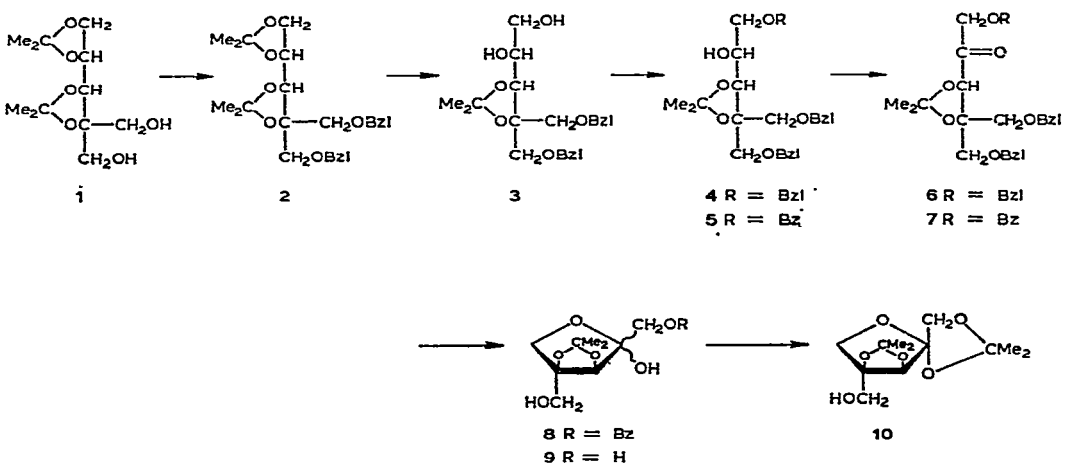
Note

Stereospecific chemical synthesis of L-dendroketose derivatives

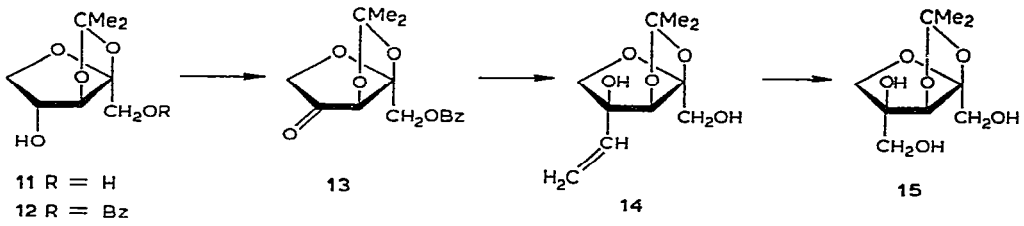
HAROLD C. JARRELL, WALTER A. SZAREK, AND (THE LATE) J. K. N. JONES
Department of Chemistry, Queen's University, Kingston, Ontario K7L 3N6 (Canada)
(Received June 22nd, 1977; accepted for publication, August 8th, 1977)

In an earlier study[1], an attempted, stereospecific synthesis of the branched-chain sugar L-dendroketose [4-*C*-(hydroxymethyl)-L-*glycero*-pentulose], by a route involving the intermediacy of 4-*C*-(hydroxymethyl)-1,2:3,4-di-*O*-isopropylidene-L-*erythro*-pentitol (**1**), resulted in the formation of 1,2:3,4-di-*O*-isopropylidenedendroketose as the DL form. The problem, in that work, that led to the loss of stereospecificity has now been surmounted, and the present article describes* the synthesis of 1,2:3,4-di-*O*-isopropylidene-L-dendroketose (**10**) starting from **1**. In addition, a synthesis of the L-dendroketose derivative 4-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-α-L-*erythro*-pentulofuranose (**15**) from the ketose 1-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-*threo*-pentulose (**11**) has also been achieved.

Compound[2,3] **3**, obtained from the branched-chain alditol[1] **1** *via* the intermediate **2**, was selectively benzoylated at the primary hydroxyl group to give 1-*O*-



*After this work had been completed, a closely related synthesis of **9** and **10** was reported[2]. In addition, **9** and **10** have been prepared[3] from **1** by use of 1,5-di-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentitol (**4**) and the ketose **6**.



benzoyl-5-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentitol **5**) in 70% yield. Oxidation of **5** with chromium trioxide–dipyridine complex[4] afforded 1-*O*-benzoyl-5-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-L-*glycero*-pentulose (**7**) in 87% yield. Hydrogenolysis of **7** over palladium-on-charcoal gave **8**. Compound **8** was *O*-debenzoylated with sodium methoxide in methanol to give **9**, which was treated with acetone in the presence of anhydrous copper(II) sulfate and sulfuric acid to afford **10** having m.p. 87.5–88°, $[\alpha]_D^{26}$ +117° (*c* 1.5, acetone), and a p.m.r. spectrum identical to that of 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose[1]. A comparison of the values of the physical constants of the product with those published by Utkin[5] for 1,2:3,4-di-*O*-isopropylidene-D-dendroketose and with those reported[2,3] for **10** confirmed the identity of the product. Compound **9** has been shown[6] to exist in a cyclic form and not to undergo deuterium incorporation under basic conditions[1]. It is noteworthy that **8** exists in a cyclic form, as shown by its p.m.r. spectrum, and, therefore, does not undergo racemization during *O*-debenzoylation.

In the preparation of 4-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-L-*erythro*-pentulofuranose (**15**), the ketose derivative[7] **11** was selectively benzoylated at the primary hydroxyl group to give 1-*O*-benzoyl-2,3-*O*-isopropylidene-D-*threo*-pentulose (**12**) in 84% yield. Oxidation of **12** with the chromium trioxide–dipyridine complex[4] afforded the unstable diketose **13**, which was characterized as its (*p*-nitrophenyl)-hydrazone. Freshly prepared **13**, on treatment with vinylmagnesium bromide, gave 2,3-*O*-isopropylidene-4-*C*-vinyl-L-*erythro*-pentulofuranose* (**14**). The vinyl derivative **14** was subjected to ozonolysis, followed, without isolation of the ozonide, by reduction with sodium borohydride to give 4-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-L-*erythro*-pentulofuranose (**15**).

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 (temperature 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

*The assignment of the configuration at the branching carbon atom and at the anomeric center in dendroketose derivatives and in **14** was made by ^{13}C-n.m.r. spectroscopy (see Ref. 6).

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*) 1:1 benzene–ethyl acetate; (*D*) 4:1 petroleum ether–ethyl acetate; and (*E*) 2:3 petroleum ether–ethyl acetate. 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 and benzyl ethers 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).

*1-O-Benzoyl-5-O-benzyl-4-C-(benzyloxymethyl)-3,4-O-isopropylidene-*L*-erythro-pentitol* (**5**). — To a solution of 5-*O*-benzyl-4-*C*-(benzyloxymethyl)-3,4-*O*-isopropylidene-L-*erythro*-pentitol[2,3] (**3**, 1.14 g) in dry pyridine (10 ml) at 0°, benzoyl chloride (0.32 ml) in dry pyridine (5 ml) was added dropwise during 30 min, and the mixture was stirred for an additional 1 h. The reaction mixture was concentrated to a syrup, which was dissolved in chloroform; the chloroform solution was washed with cold, saturated aqueous sodium hydrogencarbonate and then with water, dried (magnesium sulfate), and concentrated to dryness several times after addition of toluene. The crude product was purified by column chromatography on silica gel with solvent *A*. Compound **5** was obtained as a colorless, homogeneous syrup (1.0 g, 70%), R_F 0.68 (solvent *A*), $[\alpha]_D^{26}$ +5 ± 0.5° (*c* 2.0, chloroform); ν_{max}^{film} 1730 (OBz), 1370, and 1360 cm^{-1} (CMe_2); p.m.r.: τ 1.9–2.9 (15 H, aromatic), 5.30–6.55 (13 H, 2 benzyl-CH_2, H-2, H-3, 6 methylene H), and 8.6 (6 H, CMe_2).

Anal. Calc. for $C_{30}H_{34}O_7$: C, 71.1; H, 6.8. Found: C, 71.2; H, 7.0.

*1-O-Benzoyl-3,4-O-isopropylidene-*L*-dendroketose* (**8**). — A solution of chromium trioxide–dipyridine complex was prepared by adding chromium trioxide (2.4 g) to a solution of dry pyridine (3.79 ml) in dry dichloromethane (100 ml). A solution of compound **5** (904 mg) in dry dichloromethane (10 ml) was added in one portion, and the mixture was stirred for 40 min at room temperature with exclusion of moisture. The reaction mixture was poured into ice-cold, saturated, aqueous sodium hydrogencarbonate, and the reaction flask rinsed with a small amount of ether; the ether solution was added to the mixture in a separatory funnel, the contents of which were shaken at 0°. The organic solution was separated, washed twice with water, dried (magnesium sulfate), and concentrated to give **7** as an orange syrup (737 mg, 85%), R_F 0.81 (solvent *A*). The i.r. spectrum contained a carbonyl band at 1730 cm^{-1} which was relatively more intense than that in the spectrum of the starting material, but no band attributable to a hydroxyl group.

To a solution of **7** (637 mg) in ethanol (100 ml), 10% palladium-on-charcoal was added, and the mixture hydrogenated at 4 atm for 48 h. The reaction mixture was filtered and the filtrate concentrated to a colorless syrup (424 mg). The crude product was purified by column chromatography on silica gel with solvent *A* to give **8** as a syrup (187 mg), R_F 0.09 (solvent *D*), $[\alpha]_D^{26}$ +55 ± 3° (*c* 1.0, chloroform); ν_{max}^{film}

3500 (OH), 3020, 1725, 1601, and 1570 cm^{-1} (OBz); p.m.r.: τ 1.90–2.75 (5 H, aromatic), 5.30 and 5.35 (2 d, 2 H, H-1,1', $J_{1,1'}$, 12 Hz), 5.65 (s, 1 H, H-3), 6.0 (2 H, H-5,5'), 6.2 (2 H, H-4',4"), 6.95–7.75 (2 H, 2 OH), 8.5 and 8.6 (6 H, CMe_2).

*1,2:3,4-Di-*O*-isopropylidene-β-*L*-dendroketose* (**10**). — To a solution of **8** (157 mg) in 1:1 (v/v) methanol–chloroform (30 ml) at 0°, sodium methoxide (3 ml, 0.2M in methanol) was added, and the mixture stirred at ~5° for 12 h. Dry Ice 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 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 *D*) to contain a single component having the same R_F value, namely 0.65, as that of 3,4-*O*-isopropylidene-DL-dendroketose[1]. The extract was evaporated to a colorless syrup (60 mg), which was treated with dry acetone in the presence of anhydrous copper(II) sulfate and sulfuric acid for 2 h. The solution was neutralized with gaseous ammonia, filtered, and the filtrate concentrated to dryness. A solution of the residue in chloroform was washed with water, dried (magnesium sulfate), and concentrated to an orange oil, which was fractionated on a column of silica gel with solvent *A* to give **10**. Recrystallization from petroleum ether gave **10** as white needles (69 mg), m.p. 87.5–88°, $[\alpha]_D^{26}$ +117 ± 4° (*c* 1.45, acetone). The product had the same mobility (t.l.c., solvent *A*) as that of 1,2:3,4-di-*O*-isopropylidene-DL-dendroketose[1,5], and the p.m.r. spectra of the two products were identical. For the L isomer, m.p. 88.5°, $[\alpha]_D$ +118 ± 1° (*c* 1.0, acetone)[3], and m.p. 88–90°, $[\alpha]_D^{20}$ +118° (*c* 1.1, acetone)[2] have been reported.

*2,3-*O*-Isopropylidene-β-*D*-threo-pentulofuranose* (**11**). — Two samples of D-arabinitol (7g each) were each dissolved in water (200 ml) in a 500-ml Erlenmeyer flask. To each solution were added D-glucose (0.10 g), potassium dihydrogen phosphate (0.10 g), and yeast powder (1.0 g, ICN Life Sciences Group, Cleveland, Ohio 44128); the solutions were autoclaved for 15 min at 1 atm. Each solution was inoculated with L-sorbitol broth (~5 ml) containing rapidly growing *Acetobacter suboxydans* (A.T.C.C. No. 621H) and kept at room temperature for 14 days. The reaction was stopped by the addition of an equal volume of ethanol, some charcoal, and then boiling the mixture for 30 min. After filtration, the solutions were concentrated to syrups (<50°), which were combined and dissolved in water (25 ml). The aqueous solution was diluted with 95% ethanol (130 ml) and then with absolute alcohol (1 litre). The mixture was thoroughly shaken for 3 h, filtered through charcoal, and Celite, and concentrated to an orange syrup (18 g). The syrup was treated with acetone in the presence of anhydrous copper(II) sulfate and sulfuric acid for 52 h, and then the mixture was neutralized with gaseous ammonia, filtered, and the filtrate concentrated to a syrup; the residue was dissolved in ether. The mixture was filtered and the filtrate concentrated to a dark brown syrup. Distillation afforded **11** as a yellow syrup (b.p. 114–118°/0.08 torr), which, upon dissolution in dry ether and refrigeration, gave **11** as white crystals, m.p. 66–67°; lit.[7] m.p. 67–68°; lit[8]. m.p. 74°.

*1-*O*-Benzoyl-2,3-*O*-isopropylidene-β-*D*-threo-pentulofuranose* (**12**). — To a

solution of **11** (1.0 g) in dry pyridine (10 ml) at 0°, benzoyl chloride (0.62 ml) in pyridine (6 ml) was added dropwise with stirring during 1 h. The product was isolated as just described (see preparation of **5**) to give **12** as a white solid. Crystallization from ether–petroleum ether gave **12** as white needles (1.31 g, 82%), m.p. 76–78°, $[\alpha]_D^{26}$ +17 ± 2° (*c* 1.0, chloroform); ν_{max}^{KBr} 3420 (OH), 1730 (OBz), and 1385–1375 cm^{-1} (CMe_2); p.m.r.: τ 1.75–2.75 (5 H, aromatic), 5.4–6.15 (6 H, H-3, H-4, 4 methylene H); 3.7 (s, 1 H, OH), 8.5 and 8.65 (6 H, CMe_2).

Anal. Calc. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.1. Found: C, 61.0; H, 6.2.

1-O-*Benzoyl-2,3*-O-*isopropylidene*-L-glycero-*2,4-pentodiulofuranose* (**13**) p-*nitrophenylhydrazone*. — A solution of **12** (194 mg) in dry dichloromethane was added to a solution of chromium trioxide–dipyridine complex prepared from chromium trioxide (1.31 g) and pyridine (2.0 ml) in dichloromethane (25 ml). The mixture was stirred for 25 min at room temperature, and then the product was isolated as just described (see preparation of **7**). Compound **13** was isolated as a syrup, which decomposed on being kept at room temperature. To a solution of **13** (292 mg) in methanol (10 ml), *p*-nitrophenylhydrazine (260 mg) was added and the mixture heated under reflux for 1 h. The solution was concentrated, and the residue was subjected to column chromatography on silica gel (solvent *B*); a two-component mixture was isolated (300 mg) as a red syrup having $\nu_{max}^{CHCl_3}$ 3380 (NH), 1730 (OBz), 1600 (aromatic), 1510 and 1340 cm^{-1} (C-NO_2). Separation of the two components, R_F 0.8 and 0.52 (solvent *A*), by column chromatography (solvent *A*) afforded the faster-moving component (20 mg); p.m.r.: τ 1.95 (s, 1 H, N-H), 2.0–3.2 (9 H, aromatic), 4.9 (broad s, 1 H, H-3), 5.24–5.6 (4 H, methylenes), and 8.5 (s, 6 H, CMe_2).

Anal. Calc. for $C_{21}H_{21}N_3O_7$: C, 59.0; H, 5.0; N, 9.8. Found: C, 59.0; H, 5.6; N, 9.4.

2,3-O-*Isopropylidene-4*-C-*vinyl*-L-erythro-*pentulofuranose* (**14**). — Vinyl bromide (3.9 ml) in tetrahydrofuran (10 ml) was added with stirring to a cooled (<45°) three-necked flask containing magnesium turnings (1.37 g), a crystal of iodine, and tetrahydrofuran (10 ml). After all of the magnesium had been consumed, the mixture was heated to reflux for 15 min, and then cooled to −15°. A tetrahydrofuran solution of freshly prepared **13** (908 mg in 10 ml) was added dropwise, and then the reaction mixture was stirred at room temperature overnight. Cold 10% aqueous ammonium chloride was added slowly. The organic layer was separated, and the aqueous phase was saturated with sodium chloride and continuously extracted with chloroform. The organic solutions were combined, dried (magnesium sulfate), and concentrated to a syrup (1.54 g), which was fractionated on a column of silica gel (solvent *E*) to give **14** as a homogeneous syrup (295 mg, 44%), R_F 0.38 (solvent *B*), $[\alpha]_D^{26}$ −35.5 ± 1° (*c* 1.1, chloroform); ν_{max}^{film} 3500 (OH), 3026 (CH), and 1645 cm^{-1} (C=C); p.m.r.: τ 4.02, 4.47 and 4.72 (3 H, $J_{AB(trans)}$ 17.5 Hz, $J_{AK(cis)}$ 10.7 Hz, $J_{BK(gem)}$ 0.9 Hz), 6.30 and 6.34 (2 d, 2 H, H-1,1′, $J_{1,1'}$ 12.5 Hz), 5.80 (s, 1 H, H-3), 7.00 (2 H, 2 OH), 8.40 and 8.60 (6 H, CMe_2).

Anal. Calc. for $C_{10}H_{16}O_5$: C, 55.4; H, 7.5. Found: C, 55.7; H, 7.7.

4-C-(*Hydroxymethyl*)-*2,3*-O-*isopropylidene*-L-erythro-*pentulofuranose* (**15**). —

An ozone–oxygen mixture was bubbled through a cooled (−15°) solution of **14** (380 mg) in chloroform (30 ml). After 45 min, the reaction mixture was warmed to room temperature, treated dropwise with sodium borohydride (400 mg) in 50% aqueous ethanol (24 ml), and the resultant mixture was heated under reflux for 30 min. The excess of sodium borohydride was destroyed with glacial acetic acid (pH ~7). The chloroform solution was separated and the aqueous phase concentrated to dryness; the residue was extracted several times with dichloromethane. The chloroform and dichloromethane solutions were combined, dried (magnesium sulfate), and concentrated to a syrup which was purified by chromatography on silica gel (solvent *C*) to afford **15**, as a colorless, homogeneous syrup (158 mg), R_F 0.44 (solvent *C*), $[\alpha]_D^{26}$ −19.4 ± 1° (*c* 1.0, chloroform); ν_{max}^{film} 3450 (OH) and 1380 cm^{-1} (CMe_2); p.m.r.: τ 5.6 (s, 1 H, H-3), 6.0–6.7 (9 H, 3 OH and 6 methylene H), 8.4 and 8.6 (6 H, CMe_2).

Anal. Calc. for $C_9H_{16}O_6$: C, 49.0; H, 7.3. Found: C, 49.2; H, 7.4.

ACKNOWLEDGMENTS

The authors are grateful to the National Research Council of Canada for financial support in the form of a scholarship (to H.C.J.) and grants (to W.A.S. and J.K.N.J.).

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