Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

A SIMPLE, ALTERNATIVE SYNTHESIS OF L-ERYTHROSE

LÉON M. LERNER

Department of Biochemistry, State University of New York, Downstate Medical Center, Brooklyn, New York 11203 (U.S.A.)

(Received April 16th, 1968; in revised form, June 15th, 1968)

ABSTRACT

A new route for the synthesis of 2,3-*O*-isopropylidene-L-erythrofuranose and L-erythrose starting from D-gulono-1,4-lactone is presented. The intermediate, 2,3-*O*-isopropylidene-D-gulono-1,4-lactone, was prepared in a very high yield from 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone. In addition, 1-*O*-benzoyl-2,3-*O*-isopropylidene-β-L-erythrofuranose and 2,3-*O*-isopropylidene-β-L-erythrofuranosyl chloride were prepared.

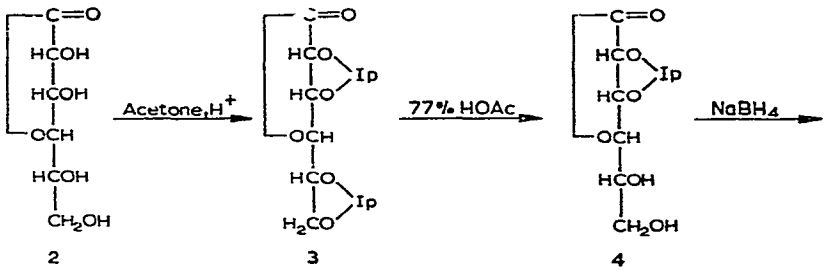
INTRODUCTION

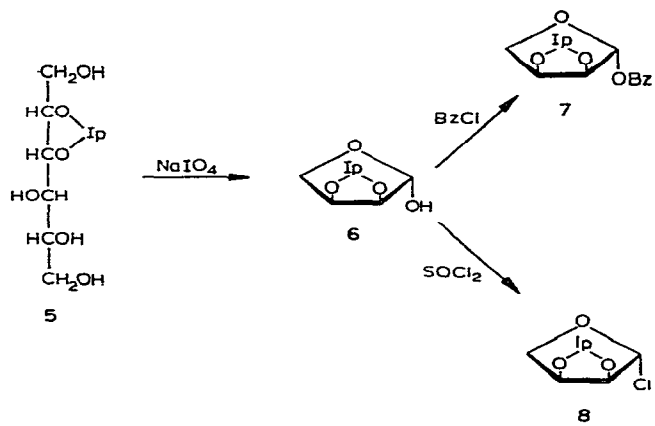
The need for a fairly large quantity of 2,3-*O*-isopropylidene-L-erythrofuranose (**6**) has arisen recently in this laboratory. The usual preparation[1] of **6** starts from 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose (**1**) and proceeds by reduction of C-1 to the alditol followed by oxidative cleavage of C-5 and C-6. This preparation suffers from several disadvantages, the main one being the synthesis of the starting substance **1** which is difficult to obtain in a pure, crystalline form. When 6-deoxy-L-mannose was treated in this laboratory with acetone in the presence of sulfuric acid, a syrupy mixture was obtained which contained at least five components. The best preparation of **1** appeared to start from 6-deoxy-L-mannose which is treated with acetone in the presence of cupric sulfate and a small amount of sulfuric acid[2]. However, purification of **1** by vacuum distillation caused extensive degradation and, in the author's hands, success was best achieved by trituration of the syrup with water followed by decantation of the aqueous solution from the insoluble substance. The aqueous solution could then be utilized directly for the preparation of **6**. The present report describes an excellent new route to **6** starting from commercially available D-gulono-1,4-lactone (**2**).

RESULTS

2,3:5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone (**3**) was prepared in excellent yield by treatment of **2** with acetone and sulfuric acid[3,4]. The important intermediate, 2,3-*O*-isopropylidene-D-gulono-1,4-lactone (**4**), was synthesized by Hulyalkar and Jones[3] in a satisfactory yield by treatment of **3** with warm 83% acetic acid. Application

to **3** of the procedure of Gramera *et al.*[5] gave **4** in very high yield. After reduction of **4** with sodium borohydride, 4,5-*O*-isopropylidene-L-glucitol (**5**) was not isolated, but instead directly treated with sodium periodate. The resulting product **6** was identified by comparison of its properties with those of an original sample[6,7]. Free L-erythrose can be easily obtained by hydrolysis[1]. In addition, 1-*O*-benzoyl-2,3-*O*-isopropylidene-β-L-erythrofuranose (**7**) and 2,3-*O*-isopropylidene-β-L-erythrofuranosyl chloride (**8**), which was desired for nucleoside synthesis, were prepared.





The anomeric configuration of the L-erythrose derivatives was established by investigation of the n.m.r. spectra of **6** and **8**. The spectrum of **6** was identical to that published by Perlin[7]. The benzoate **7** was also assigned the β configuration, since no inversion of the anomeric carbon was expected during benzoylation; the high positive specific rotation (+104°) supports this assignment. Compound **8** had a very high positive rotation ($[\alpha]_D$ +168°), and the n.m.r. spectrum showed a sharp singlet for H-1 at τ 3.87, which was farther downfield than that found in **6** due to the electronegative effect of the chlorine atom. This sharp signal for H-1 of **8** was similar to that found previously for H-1 of 2,3:5,6-di-*O*-isopropylidene-D-gulofuranosyl[4] and -D-mannofuranosyl[8] chloride, both of which give sharp singlets near τ 3.90. Compound **8** was, therefore, given a β assignment.

EXPERIMENTAL

Elementary analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. Melting points were determined on a Kofler hot-stage and correspond to corrected values. T.l.c. was performed on silica gel G plates of 0.25-mm thickness, prepared with Desaga equipment. Spots were located with a chromic acid spray followed by careful application of heat from a hot plate. Optical rotations were determined on a Rudolph Model 200 spectropolarimeter, and infrared spectra were recorded on a Perkin–Elmer Model 21 spectrophotometer by preparation of films of the compounds on sodium chloride plates. N.m.r. spectra were determined in $CDCl_3$ by Dr. Harry Agahigian of the Baron Consulting Co., Orange, Connecticut. Evaporations were performed *in vacuo* at a bath temperature of 40–45°.

2,3-O-Isopropylidene-D-gulono-1,4-lactone (**4**). — 2,3:5,6-Di-*O*-isopropylidene-D-gulono-1,4-lactone[4] (**3**, 14 g) was dissolved in a mixture of acetic acid (224 ml) and water (67.2 ml). This mixture was poured into a crystallizing dish and was left to evaporate for 3–4 days. The residual solid (11.6 g) was suspended in a large volume of ethyl acetate and heated under reflux. A small amount of undissolved D-gulono-1,4-lactone was filtered off; m.p. 180–182°, $[\alpha]_D^{24}$ −56.8° (*c* 4.03, water); lit.[9] m.p. 182–185°, $[\alpha]_D^{20}$ −57.1° (*c* 4.0, water).

The filtrate was concentrated and **4** crystallized as large, long needles, 9.8 g (89% yield), m.p. 142–143.5°, $[\alpha]_D^{24}$ −74.5° (*c* 2.75, acetone); lit.[3] m.p. 142°, $[\alpha]_D$ −76.5°. T.l.c. in ethyl acetate showed that the product was homogeneous, R_F 0.17. D-Gulono-1,4-lactone barely migrated in this solvent, whereas **3** had R_F 0.56.

2,3-O-Isopropylidene-β-L-erythrofuranose (**6**). — Compound **4** (9.8 g) was dissolved in water (400 ml), and the solution was added dropwise to a mixture of sodium borohydride (4 g) in water (200 ml), chilled with an ice-bath. After addition of the entire solution, the flask was kept for 4 h at room temperature, and the pH was adjusted to 6.0–6.2 with acetic acid. The flask was cooled again in an ice-bath and sodium periodate (10.8 g) was added in small portions over a 15-min period. The solution was kept in the dark for 3 h at room temperature and concentrated to a volume of 75–100 ml after addition of nonyl alcohol (5–10 drops). The white precipitate was filtered off and washed with ethyl acetate (150 ml). The aqueous layer of the filtrate was extracted twice with 100-ml portions of ethyl acetate. The ethyl acetate portions were combined, washed twice with 50-ml portions of water, and dried ($MgSO_4$). The solution was evaporated to an oil (3.63 g), which was distilled to give 2.44 g of a clear, colorless oil (**6**), b.p. 67–74° (0.45 mm Hg), $[\alpha]_D^{23}$ +83.2° (*c* 4.36, ethyl acetate). A sample of **6** prepared from 6-deoxy-2,3-*O*-isopropylidene-L-mannofuranose, had b.p. 62–67° (0.40 mm Hg) and $[\alpha]_D^{22}$ +82.5° (*c* 4.46, ethyl acetate). Lit.[6] b.p. 50–70° (bath temperature) at 2 mm Hg, $[\alpha]_D$ +72° (*c* 2.4, methanol). Both samples migrated as identical, homogeneous spots on thin-layer plates in 1% methanol–chloroform, R_F 0.14. The i.r. spectra were identical: ν_{max}^{film} 3400 (anomeric OH), 1375 (*gem*-dimethyl), 1160, 1100, 1068, 1045 cm^{-1} (C-O, C-O-C, dioxolane ring).

1-O-Benzoyl-2,3-O-isopropylidene-β-L-erythrofuranose (**7**). — To an ice-cold

solution of **6** (517 mg) in dry pyridine (20 ml) was added benzoyl chloride (1.14 ml). The solution was kept for 45 min at 0°, and then for 17 h at room temperature. The reaction mixture was poured as a thin stream into a stirred mixture of ice and saturated sodium bicarbonate solution. This mixture was stirred for 4 h, and the white crystals were filtered off and washed with water (640 mg), m.p. 108–112°. The product was recrystallized from methanol–water to give feathery, white plates (540 mg), m.p. 108–108.5°, $[\alpha]_D^{23}$ +104° (*c* 4.01, chloroform); homogeneous on t.l.c. in 1% methanol–chloroform, R_F 0.75; ν_{max}^{film} 1730 (benzoate carbonyl), 1385 (doublet, *gem*-dimethyl), 1205, 1175, 1160 (C-O, C-O-C, dioxolane ring), 712 cm^{-1} (monosubstituted phenyl).

Anal. Calc. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.04.

2,3-O-Isopropylidene-β-L-erythrofuranosyl chloride (**8**). — Following Freudenberg *et al.*[10], compound **6** (2 g) was dissolved in dry chloroform (12 ml) and dry pyridine (5 ml). The mixture was cooled in an ice-bath, thionyl chloride (2.1 ml) was added, and the reaction mixture was kept for 5 h at 0°. The mixture was poured on ice, and the chloroform layer was separated. The aqueous layer was extracted twice with chloroform, and the chloroform extracts were combined and washed three times with ice-cold M sodium hydroxide, twice with ice-cold water, and dried ($MgSO_4$). Evaporation of the chloroform resulted in an orange, semisolid residue which sublimed slowly under these conditions. The product (1.01 g) was obtained by sublimation at 0.6 mm Hg 40–60°, as irregular plates which turned into long, rectangular plates just before the m.p. was reached; m.p. 59–60°, $[\alpha]_D^{26}$ +168° (*c* 2.0, chloroform); ν_{max}^{film} 1380 (*gem*-dimethyl), 1230, 1208, 1160 (C-O, C-O-C, dioxolane ring), 705 cm^{-1} (C-Cl); n.m.r. data: (τ) 8.67, 8.53 (singlets, $-CMe_2$), 5.83 ($-CH_2$), 5.08 (H-2, H-3), 3.87 (sharp singlet, H-1). Compound **8** gave an instantaneous alcoholic silver nitrate test. It is quite stable and can be stored in a vial at room environment for several weeks without noticeable deterioration. The analytical sample was prepared by resublimation.

Anal. Calc. for $C_7H_{11}ClO_3$: C, 47.07; H, 6.21; Cl, 19.85. Found: C, 47.17; H, 6.28; Cl, 19.76.

ACKNOWLEDGMENT

This work was supported by Research Grant No. T-442 from the American Cancer Society.

REFERENCES

1 A. S. PERLIN, *Methods Carbohyd. Chem.*, 1 (1962) 67.
2 B. R. BAKER, *Methods Carbohyd. Chem.*, 2 (1963) 441.
3 R. K. HULYALKAR AND J. K. N. JONES, *Can. J. Chem.*, 41 (1963) 1898.
4 L. M. LERNER, B. D. KOHN, AND P. KOHN, *J. Org. Chem.*, 33 (1968) 1780.
5 R. E. GRAMERA, A. PARK, AND R. L. WHISTLER, *J. Org. Chem.*, 28 (1963) 3230.
6 J. N. BAXTER AND A. S. PERLIN, *Can. J. Chem.*, 38 (1960) 2217.
7 A. S. PERLIN, *Can. J. Chem.*, 42 (1964) 1365.
8 J. B. LEE AND T. J. NOLAN, *Tetrahedron*, 23 (1967) 2789.
9 J. U. NEF, *Ann.*, 403 (1914) 269.
10 K. FREUDENBERG, A. WOLF, E. KNOPF, AND S. H. ZAHEER, *Ber.*, 61 (1928) 1743.