Carbohydrate Research, 155 (1986) 212–216
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

A convenient synthesis of L-erythrose*

RAMESH H. SHAH
Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York 11439 (U.S.A.)

(Received August 29th, 1985, accepted for publication, October 8th, 1985)

The improvements in the synthesis of L-erythrose (**5**) have focused on the convenience and ease with which appropriately protected precursors suitable for periodate cleavage can be prepared from readily available starting materials[1–3]. Rappoport and Hassid[1] employed 4,6-*O*-ethylidene-L-glucose for the preparation of **5** by periodate cleavage, followed by acid hydrolysis. Baxter and Perlin[2] prepared **5** from L-rhamnose, a relatively more accessible sugar than L-glucose, by way of its 2,3-*O*-isopropylidene derivative, which was reduced with sodium borohydride and then cleaved with periodate to obtain 2,3-*O*-isopropylidene-L-erythrose (**4**); subsequent hydrolysis of **4** with 50mM sulfuric acid gave **5**. Lerner[3] converted 2,3-*O*-isopropylidene-D-gulono-1,4-lactone, obtained from 2,3:5,6-di-*O*-isopropylidene-D-gulono-1,4-lactone by selective hydrolysis, to **4** by employing the same[2] sequence of reactions. A small-scale preparation of **4** in low yield (29%) from 3,4-*O*-isopropylidene-L-arabinose by treatment with silver carbonate on Celite in refluxing methanol has been described by Morgenlie[4]. However, the method is not attractive because of the lack of convenient access to the starting material as well as the low yield of **4**.

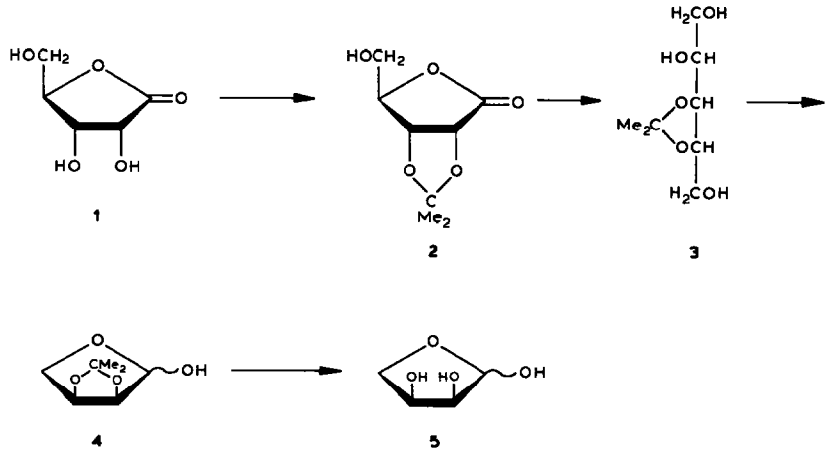
We have investigated alternative, more convenient methods for the synthesis of **5**, and D-ribono-1,4-lactone (**1**) appeared to be an attractive starting material. Although **1** has been widely employed[5,6] in recent years for the synthesis of several natural products, its use for the synthesis of sugars has been limited to date. Sepulchre *et al.*[7] obtained both the 2,3-*O*-cyclohexylidene-D-ribono-1,4-lactone (60% yield) and 3,4-*O*-cyclohexylidene-D-ribono-1,5-lactone (20% yield) by the reaction of **1** with cyclohexanone in benzene at reflux temperature in the presence of a strong cation-exchange resin. The two lactones were separated and converted[7] into 2,3-*O*-cyclohexylidene-L- and -D-erythrose, respectively, using treatments employed previously by other investigators[2,3]; however, no experimental details

*Synthesis of sugars from D-ribonolactone. I.

0008-6215/86/$ 03.50

were given. As part of a program to synthesize 4-, 5-, and 6-carbon aldoses, ketoses, and deoxy analogs from D-ribonolactone (**1**), we describe herein the preparation of L-erythrose (**5**) from **1** *via* the 2,3-*O*-isopropylidene derivative **2** by use of reactions analogous to those employed previously[2,3]. The advantage of **1** over D-gulono-1,4-lactone as starting material for the synthesis of **4** lies in the fact that the former compound directly yields the monoisopropylidene derivative **2**, suitable for borohydride reduction and periodate cleavage, whereas the latter compound requires[3] the selective removal of the 5,6-*O*-isopropylidene group from the 2,3:5,6-di-*O*-isopropylidene derivative.

D-Ribonolactone (**1**) was converted into **2** in nearly quantitative yield by reaction at room temperature with acetone in the presence of anhydrous copper(II) sulfate; these conditions are a slight modification of the procedure of Hough, Jones, and Mitchell[8] who isolated **2** in 67% yield after recrystallization. This product (**2**) was homogeneous according to t.l.c. and g.l.c., and its m.p., specific rotation, and i.r. data were in accord with the literature values[8]; its 500-MHz ^{1}H-n.m.r. spectrum was similar to that described[9] at 60-MHz.



The reduction of **2** with sodium borohydride to the intermediate (not isolated) 2,3-*O*-isopropylidene-D-ribitol (**3**) was carried out in ~10% aqueous ethanol. Previously, it was reported[8] that the major product from the reduction of **2** with sodium borohydride in water followed by acid hydrolysis was an acid, and that only a small amount of ribitol could be detected. The reaction mixture containing the intermediate **3** was treated with a slight excess of sodium meta-periodate; the overall yield of distilled **4** was 56% from **1**. This product was homogeneous according to t.l.c. and g.l.c., and its boiling point[2,3], specific rotation[2–4], and i.r. data[3] were in agreement with those reported for **4**. The 500-MHz ^{1}H-n.m.r. spectrum for a solution in [^{2}H]chloroform revealed the presence of the β- and α-anomer in a ~10:1 ratio. The ^{1}H-n.m.r. spectrum of β-**4**

was completely resolved from that of α-**4**, as were all of the signals of each anomer. The general appearance of the spectrum was similar to the 60-MHz spectrum of **4** for a solution in deuterium oxide reported by Perlin[10]. It was not possible to compare the chemical shifts and coupling constants since these were not given. These values for the two anomers of **4** determined at 500-MHz were commensurate with their structures.

The isopropylidene group of **4** was hydrolyzed with 37% acetic acid at 100° rather than with 50mM sulfuric acid employed by Baxter and Perlin[2]. The former conditions offer the convenience of the removal of the acid by evaporation under reduced pressure. L-Erythrose (**5**) thus obtained showed chromatographic behavior on t.l.c. identical with that of authentic D-erythrose (purchased commercially). Its specific rotation (+36.8°, equilibrium) in water compared favorably with the value of +39° reported by Baxter and Perlin[2]. Although values ranging[1,2,11–15] from +20 to +39° for the specific rotation of **5** have been reported, it has been suggested by Baxter and Perlin[2], after consideration of various factors, that the specific rotation of L-erythrose (**5**) is +38 (±3°), that of D-erythrose being opposite in sign.

Thus, the method described herein for the synthesis of **5** offers advantages over existing methods with respect to simplicity, ready access to the starting material, and the high yield and purity of the final product.

EXPERIMENTAL

General methods. — Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured at ambient temperature with a Perkin–Elmer Model 241 automatic polarimeter. T.l.c. was performed on Silica gel G with a layer thickness of 0.25 mm in 7:3 toluene–ethyl acetate (solvent *A*) or 3:1:1 ethyl acetate–acetic acid–water (solvent *B*). G.l.c. was performed with a Perkin–Elmer Sigma 3 gas chromatograph, equipped with a flame-ionization detector, on 3% OV-1 (column *A*) and 3% OV-225 (column *B*) (both on Gas-Chrom Q, 100–120 mesh), packed in a 180 × 0.4 cm (i.d.) glass column; helium at a flow rate of 35 mL/min was the carrier gas. Retention times (*T*) are given in min. The *O*-(trimethylsilyl) derivatives for g.l.c. were prepared[16] by treating the compound (2–3 mg) with hexamethyldisilazane (0.25 mL) and chlorotrimethylsilane (0.1 mL) in pyridine (1 mL) for 30 min at room temperature; the reaction mixture was centrifuged and aliquots of the supernatant were injected into the gas chromatograph. The acetates for g.l.c. were prepared by treating the compound (2–3 mg) with 1:1 (v/v) acetic anhydride–pyridine (0.6 mL) for 2 h at room temperature; aliquots of the reaction mixture were injected into the gas chromatograph. I.r. spectra were recorded with a Perkin–Elmer Model 283B spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 500-MHz for solutions in [^{2}H]chloroform with a Bruker WM-500 n.m.r. spectrometer at the Northeast Regional NSF–NMR Facility located at Yale University, New Haven, Connecticut. Coupling constants (Hz) given are first-order values. All evaporations were performed under reduced pressure at 35–40°.

*2,3-O-Isopropylidene-*D*-ribono-1,4-lactone* (**2**). — This product was prepared by a modification of the procedure of Hough *et al.*[8]. In the original procedure, a solution of **1** in acetone was boiled under reflux for 92 h; anhydrous $CuSO_4$ was then added and the boiling was continued for an additional 100 h. In the modification, a mixture of **1** (14.8 g), $CuSO_4$ (50 g), and dry acetone (250 mL) was stirred at room temperature; g.l.c. of the trimethylsilyl and acetyl derivatives of an aliquot taken after 48 h indicated the presence of only a trace of **1**. After 72 h, $CuSO_4$ was removed by filtration and washed with dry acetone. The combined filtrates were evaporated to dryness to give a colorless, crystalline residue of **2**; yield, 18.4 g (98%); m.p. 133–138° (lit.[8] m.p. 138–139°); $[\alpha]_D^{24}$ −60.8° (*c* 0.64, 1,2-dichloroethane), −62.4° (*c* 0.50, pyridine), lit.[8] −65.7° (pyridine); R_F 0.32 (solvent *A*); *T* (column *A*, 150°): 4.6 (**2**), 5.5 (Me_3Si derivative of **2**), 5.6 (acetyl derivative of **2**), 11.7* (Me_3Si derivative of **1**), and 11.2* (acetyl derivative of **1**); *T* (column *B*, 225°): 7.0 (**2**), 2.5 (Me_3Si deriative of **2**), 5.0 (acetyl derivative of **2**), 1.9* (Me_3Si derivative of **1**), and 10.2* (acetyl derivative of **1**); $\nu_{max}^{1,2\text{-dichloroethane}}$ 3470 (OH), 1790 (1,4-lactone carbonyl), and 1380 (sh) and 1375 cm^{-1} (*gem*-dimethyl); ^{1}H-n.m.r.: δ 4.84 (d, 1 H, $J_{2,3}$ 5.6 Hz, H-2), 4.79 (d, 1 H, H-3), 4.63 (t, 1 H, $J_{4,5}$ 1.9, $J_{4,5'}$ 2.0 Hz, H-4), 3.99 (d, 1 H, $J_{5,5'}$ 12.3 Hz, H-5), 3.80 (d, 1 H, H-5′), 2.95 (bs, 1 H, D_2O exchangeable, OH-5), 1.47 and 1.39 (2 s, 6 H, CMe_2); lit.[9] (60-MHz ^{1}H-n.m.r. acetone): δ 4.77 (H-2), 4.71 (H-3), 4.60 (H-4), 4.47 (OH-5), 3.84 (H-5), 1.41 and 1.38 (CMe_2); $J_{2,3}$ 5.5, $J_{3,4}$ <0.5, $J_{4,5}$ 2.3, $J_{5,OH}$ 5.0 Hz.

*2,3-O-Isopropylidene-*L*-erythrofuranose* (**4**). — A cold solution of **2** (9.40 g, 50 mmol) in a mixture of water (550 mL) and ethanol (100 mL) was added dropwise to a solution of $NaBH_4$ (4.46 g, 118 mmol) in water (220 mL), with cooling in an ice-bath. The mixture was stirred at room temperature for 15 h, the pH adjusted to 5–6 with 1.7M acetic acid, and the mixture chilled in an ice-bath. $NaIO_4$ (11.76 g, 55 mmol) was added portionwise over 5 min. The mixture was removed from the ice-bath and stirred at room temperature for 3 h. It was concentrated to ~75 mL and filtered to remove a colorless solid, which was washed with ethyl acetate (200 mL). The aqueous filtrate was extracted with ethyl acetate (3 × 50 mL). The combined ethyl acetate extracts and washing were washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to yield crude **4** as a pale yellow oil (6.45 g, 80.6%). The crude product was purified by distillation at 130–135° (bath) and 0.7 KPa; yield, 4.58 g (57.3%); $[\alpha]_D^{23}$ +73.8° (*c* 0.48, methanol), +81.7° (*c* 0.46, ethyl acetate); lit.[2,4] +72° (methanol), +75° (methanol), respectively; lit.[3] +83.2° (ethyl acetate); R_F 0.90 (solvent *B*); *T*: 4.9 (column *A*, 100°), 10.9 (column *B*, 125°); ν_{max}^{film} 3420 (OH), 1725 (w, aldehyde C=O), 1385 (sh) and 1375 (*gem*-dimethyl), and 1160, 1110, 1068, and 1045 cm^{-1} (C–O, C–O–C); ^{1}H-n.m.r. (β-anomer): δ 5.34 (s, 1 H, H-1), 4.78 (dd, 1 H, $J_{2,3}$ 5.9, $J_{3,4}$ 3.5 Hz, H-3), 4.51 (d, 1 H, H-2), 4.06 (bs, 1 H, D_2O exchangeable, OH-1), 4.00 (dd, 1 H, $J_{4,4'}$ 10.3 Hz, H-4), 3.95 (d, 1 H,

*Values given only for the purpose of comparison as **1** was not present in the preparation.

H'-4), 1.41 and 1.26 (2 s, 6 H, CMe_2); (α-anomer): δ 4.94 (bs, 1 H, D_2O exchange converted the signal into a doublet, $J_{1,2}$ 3.6 Hz, H-1), 4.70 (dd, 1 H, $J_{2,3}$ 6.2, $J_{3,4}$ 3.8 Hz, H-3), 4.44 (dd, 1 H, H-2), 4.06 (bs, D_2O exchangeable, OH-1), 3.92 (d, 1 H, $J_{4,4'}$ 11.0 Hz, H'-4), 3.49 (dd, 1 H, H-4), 1.49 and 1.32 (2 s, 6 H, CMe_2).

L-*Erythrose*. — A solution of **4** (1.0 g) in a mixture of water (10 mL) and acetic acid (6 mL) was heated at 100° for 2.5 h, and then evaporated to dryness. Water (2 × 10 mL) was added to and evaporated from the residual syrup to remove traces of acetic acid. L-Erythrose (**5**) was obtained as a pale yellow syrup; yield, 0.80 g (106%); $[\alpha]_D^{24}$ +2.3 (10 min) → +36.8° (equilibrium, 4 days) (*c* 0.53, water); lit.[2,11,15] +39, +32.7, and +30.5° (all in water), respectively; R_F 0.50 (major, monomer*), 0.20 (minor, dimer or trimer) (solvent *B*) (authentic D-erythrose purchased from Sigma Chemical Co., St. Louis, MO showed the same two spots). T.l.c., after keeping the solutions of **5** and D-erythrose at room temperature for several days, revealed the presence of only the faster-moving spot, only traces of the slower-moving spot being evident.

ACKNOWLEDGMENTS

The author gratefully acknowledges the financial support of this work by the Pharmaceutical Services Institute of St. John's University. The author thanks Mr. Winston Mullings for recording the i.r. spectra and Mr. Peter Demou for recording the ^{1}H-n.m.r. spectra. Support of the NSF Northeast Regional NMR Facility at Yale University, which was funded by Grant Number CHE-7916210 from the Chemistry Division of NSF, is gratefully acknowledged.

REFERENCES

1 D. A. Rappoport and W. Z. Hassid, *J. Am. Chem. Soc.*, 73 (1951) 5524–5525.
2 J. N. Baxter and A. S. Perlin, *Can. J. Chem.*, 38 (1960) 2217–2225.
3 L. M. Lerner, *Carbohydr. Res.*, 9 (1969) 1–4.
4 S. Morgenlie, *Acta Chem. Scand.*, 26 (1972) 2518–2522.
5 K. S. Bhat, S. Y. Chen, and M. M. Joullie, *Heterocycles*, 23 (1985) 691–729.
6 C. S. Wilcox and L. M. Thomasco, *J. Org. Chem.*, 50 (1985) 546–547.
7 A.-M. Sepulchre, A. Gateau, and S. D. Gero, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 269 (1969) 1312–1314.
8 L. Hough, J. K. N. Jones, and D. L. Mitchell, *Can. J. Chem.*, 36 (1958) 1720–1728.
9 R. J. Abraham, L. D. Hall, L. Hough, K. A. McLauchlan, and H. J. Miller, *J. Chem. Soc.*, (1963) 748–749.
10 A. S. Perlin, *Can. J. Chem.*, 42 (1964) 1365–1372.
11 A. Wohl, *Ber. Dtsch. Chem. Ges.*, 32 (1899) 3666–3672.
12 O. Ruff, *Ber. Dtsch. Chem. Ges.*, 34 (1901) 1362–1372.
13 R. A. Weerman, *Recl. Trav. Chim. Pays-Bas*, 37 (1917) 16–51; *Chem. Abstr.*, 12 (1918) 1463–1465.
14 V. Deulofeu, *J. Chem. Soc.*, (1932) 2973–2975.
15 G. E. Felton and W. Freudenberg, *J. Am. Chem. Soc.*, 57 (1935) 1637–1640.
16 C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Am. Chem. Soc.*, 85 (1963) 2497–2507.
17 A. S. Serianni, E. L. Clark, and R. Barker, *Carbohydr. Res.*, 72 (1979) 79–91.

*Monomeric forms include the α- and β-furanose, the *aldehyde*, and the aldehyde hydrate; the presence of the last-named in solutions of **5** in water has been reported[17].