Carbohydrate Research, 32 (1974) 413–417

Note

A new synthesis of L-ribofuranose derivatives*

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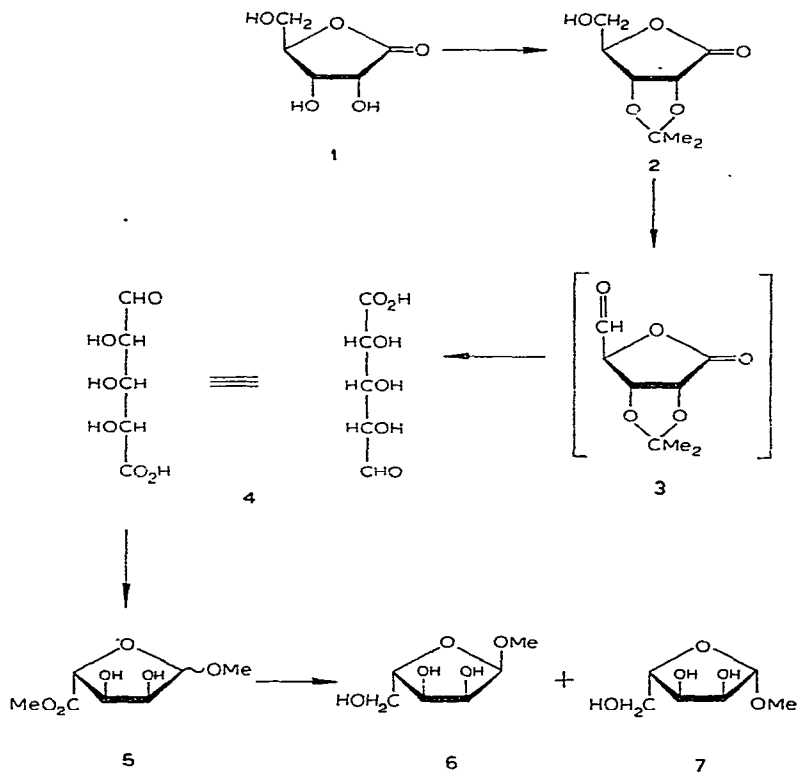
(Received August 31st, 1973; accepted in revised form, October 1st, 1973)

The synthesis of L-ribose and of several nucleoside and nucleotide derivatives of L-ribose has been reported from several laboratories. The most satisfactory methods thus far developed for the synthesis of L-ribose involve the inversion of configuration at C-2 of L-arabinose or at C-3 of L-xylose[1–5]. In this report we describe a new and convenient synthesis of L-ribofuranose derivatives by using D-ribono-1,4-lactone as starting material.

The conversion of D-ribose or D-ribono-1,4-lactone into L-ribose involves the complete inversion of the molecule. The C-5 hydroxymethyl group of D-ribonolactone is oxidized to an aldehyde and becomes C-1 of L-ribose, and C-1 of the lactone is reduced to a hydroxymethyl group to become C-5 of L-ribose. The two key reactions in the synthesis are: (*a*) oxidation of the hydroxymethyl group of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**2**) with methyl sulfoxide–*N*,*N*′-dicyclohexylcarbodiimide and (*b*) reduction of methyl (methyl α,β-L-ribofuranosid)uronate (**5**) with sodium bis(2-methoxyethoxy)aluminum hydride.

Oxidation of **2** was attempted with several reagents, such as methyl sulfoxide–acetic anhydride[6], methyl sulfoxide–phosphorus pentaoxide[7], methyl sulfoxide–*N*,*N*′-dicyclohexylcarbodiimide[8], and also the chromium trioxide–dipyridine complex[9]. Only the methyl sulfoxide–*N*,*N*′-dicyclohexylcarbodiimide reagent was found to be a mild enough oxidant for the conversion of **2** into the 5-aldehyde derivative (**3**) of 2,3-*O*-isopropylidene-D-ribono-1,4-lactone. The other reagents gave consistently unsatisfactory yields; even the chromium trioxide–dipyridine complex, which has been successfully used[9] for the oxidation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, caused extensive over-oxidation. The methyl sulfoxide–*N*,*N*′-dicyclohexylcarbodiimide reagent with pyridinium trifluoroacetate as acid catalyst gave consistently satisfactory yields of **3** (50–70%) when the reaction time was limited to 1.5 h, more prolonged reaction resulted in decreased yields. Removal of the protecting group in 0.1M hydrochloric acid–1,4-dioxane, followed by chromatography on Dowex-1 (X-8) (acetate) gave L-riburonic acid (**4**) as a colorless syrup, which could be

*Supported by U. S. Public Health Research Grants AM-08627 and GM-20307 from the National Institutes of Health.



crystallized from ethanol as the brucine salt. L-Riburonic acid (**4**) was chromatographically indistinguishable from D-riburonic acid, prepared from benzyl β-D-ribofuranoside by the method of Heyns and Lenz[10]; optical rotatory measurements with **4** showed it to be the L-enantiomer. Treatment of **4** with methanolic hydrogen chloride yielded a mixture of the two methyl (methyl α,β-L-ribofuranosid)uronates (**5**) in 98% yield. The n.m.r. spectrum of **5** clearly shows the presence of both anomers: two singlets can be assigned to the methyl acetal hydrogens, the large singlet at δ 3.40 corresponds to the β-anomer (~90%) whereas the small singlet at δ 3.49 corresponds to the α-anomer (~10%), furthermore the large singlet at δ 4.91 can be assigned to H-1 of the β-anomer ($J_{1,2}$ 0 Hz) and H-1 of the α-anomer gives rise to a doublet ($J_{1,2}$ 5 Hz) at δ 5.04. Similar assignments have been made for methyl α-D-ribofuranoside and methyl β-D-ribofuranoside[11].

Reduction of **5** with sodium bis(2-methoxyethoxy)aluminum hydride[12] gave the two anomeric methyl L-ribofuranosides; these were separable by chromatography on Dowex-2 (X-8) (OH^-)[13]. N.m.r. spectroscopy identified them as methyl α-L-ribofuranoside (**6**) ($J_{1,2}$ 4 Hz) and methyl β-L-ribofuranoside (**7**) ($J_{1,2}$ 0 Hz), respectively[11].

In 1891 Fischer and Piloty[14] reported the conversion of D-glucose into L-gulose. However the reaction sequence used by them for converting the sugar in the

D-series into the one in the L-series is not applicable to a symmetrical aldaric acid such as ribaric acid because the resulting aldose would be a racemic mixture.

EXPERIMENTAL

General methods. — Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points were measured on a hot stage equipped with a microscope, and are not corrected. N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer; tetramethylsilane was used as reference standard and lock signal. Chemical shifts are reported on the δ scale. Optical rotatory measurements were made in 1-dm tubes with a Zeiss–Winkel polarimeter. G.l.c. of the trimethylsilyl derivatives was performed on a column (5 ft × 0.125 in.) of poly(ethylene glycol)sebacate on Chromosorb Q maintained at 150 or 180°, with helium at 25 ml.min^{-1} as the carrier gas. Descending chromatography on Whatman No. 1 paper was conducted with the following solvent systems: solvent *A*, 18:4:4 ethyl acetate–acetic acid–water; *B*, 5:3:1 ethyl acetate–propyl alcohol–water; and *C*, 7:0.7:2.3 butyl alcohol–acetic acid–water. Sugars on chromatograms were located by spraying with a 4% solution of *p*-anisidine hydrochloride in butyl alcohol, or with 0.5% sodium periodate and 0.5% benzidine solutions. Carbohydrates in solution were determined by the phenol–sulfuric acid reaction[15] or by the ferricyanide reduction method[16]. D-Riburonic acid was prepared from benzyl β-D-ribofuranoside by the procedure of Heyns and Lenz[10]; m.p. of the brucine salt, 195–197°. 2,3-*O*-Isopropylidene-D-ribono-1,4-lactone (**2**) was prepared as described by Hough *et al.*[17]; m.p. 137–139°.

L-*Riburonic acid* (**4**). — To a solution of 3 g (16 mmoles) of **2** in 60 ml of dry methyl sulfoxide was added 10 g (48 mmoles) of *N,N'*-dicyclohexylcarbodiimide, 0.66 ml (8 mmoles) of pyridine, and 0.62 ml (8 mmoles) of trifluoroacetic acid. The reaction mixture was stirred for 90 min at room temperature. It was then diluted with 200 ml of ethyl acetate and a solution of oxalic acid (4.37 g) in methanol (10 ml) was added. The suspension was stirred for 15 min, treated with 100 ml of saturated aqueous sodium chloride, and filtered to remove *N,N'*-dicyclohexylurea. The filtrate separated into two phases and the aqueous phase was extracted once with 100 ml of ethyl acetate. The combined organic phases were washed once with 100 ml of saturated aqueous sodium chloride and once with 100 ml of saturated aqueous sodium chloride, adjusted to pH 7 with sodium hydrogen carbonate. The ethyl acetate phase was dried with anhydrous sodium sulfate, concentrated to approximately 10 ml, and filtered to remove some residual *N,N'*-dicyclohexylurea. The filtrate was then evaporated to dryness, the residue was dissolved in 20 ml of 1,4-dioxane and 0.1M hydrochloric acid (30 ml) was added slowly with heating. The solution was boiled for 3 h under reflux, cooled, and the mixture filtered to remove some residual *N,N'*-dicyclohexylurea. The filtrate was adjusted to pH 8 with M sodium hydroxide, and applied to a column (2 × 25 cm) of Dowex-1 (X-8) (acetate) (200–400 mesh). The column was washed with 200 ml of water and then eluted with 0.5M acetic acid.

L-Riburonic acid was eluted in fractions (12 ml) 160–280, which were pooled and evaporated to dryness to give 1.83 g (69%) of **4** as a colorless, viscous syrup, $[\alpha]_D^{26}$ −21.9° (*c* 4.8, water); (lit.[10]: D-riburonic acid $[\alpha]_D^{20}$ +24.8°). The syrup was dissolved in 2 ml of ethanol and treated with a concentrated alcoholic solution of brucine. The precipitated salt was collected by filtration, washed with ethanol and crystallized from 60% ethanol; m.p. 201–203°. When mixed with the brucine salt of D-riburonic acid, the m.p. was lowered to 196–205°. R_F (solvent *A*) 0.18, (solvent *C*) 0.21.

Methyl (methyl α,β-L-ribofuranosid)uronate (**5**). — A solution of 1.83 g (11.1 mmoles) of syrupy **4** in 25 ml of anhydrous methanol containing 0.5% hydrogen chloride was boiled for 10 min under reflux. The cooled solution was neutralized with silver carbonate and the mixture filtered. The filtrate was evaporated to a colorless syrup; yield 2.1 g (98%). G.l.c. of the *O*-trimethylsilyl derivatives showed that the products contained only traces of impurities. An analytical sample of **5** was prepared by chromatographing a chloroform solution on Florosil. A mixture of the α- and β-anomers of **5**, eluted by chloroform, was evaporated to dryness and crystallized from chloroform–petroleum ether at −20°; m.p. 57–59°; R_F (solvent *A*) 0.75.

Anal. Calc. for $C_7H_{12}O_6$: C, 43.75; H, 6.25. Found: C, 44.05; H, 6.44.

G.l.c. of the *O*-trimethylsilyl derivatives showed that the crystalline sample consisted of both anomers, retention times 8.8 min (β-anomer) and 11.2 min (α-anomer) at 150°. N.m.r. data (chloroform-*d*): δ 5.04 (doublet, $J_{1,2}$ 5 Hz, H-1, α-anomer), 4.91 (singlet, H-1, β-anomer), 4.52 (doublet, $J_{2,3}$ 4 Hz, H-2 or 3), 4.46 (singlet, H-4), 4.04 (doublet, $J_{2,3}$ 4 Hz, H-2 or 3), 3.78 (singlet, $-CO_2CH_3$), 3.49 (singlet, $-OCH_3$, α-anomer), and 3.40 (singlet, $-OCH_3$, β-anomer).

Methyl α-L-ribofuranoside (**6**) *and methyl β-L-ribofuranoside* (**7**). — To a solution containing 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene (7 ml) and dry tetrahydrofuran (150 ml) was added a solution of crude **5** (2.1 g, 10.9 mmoles) in dry tetrahydrofuran (50 ml). The reaction mixture was boiled for 4 h under reflux. Excess reductant was decomposed with ethyl acetate (20 ml) and 3.6M sulfuric acid (6.25 ml). Methanol (50 ml) was then added and the reaction mixture boiled for 10 min under reflux with vigorous stirring. The inorganic salts were removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in approximately 5 ml of water and applied to a column (2.5 × 45 cm) of Dowex-2 (X-8) (OH^-) (200–400 mesh). Elution with water gave two well-resolved compounds, detected with the phenol–sulfuric acid reagent, which were eluted in fractions (12 ml) 22–32 and 52–95, respectively. The fractions containing each compound were separately pooled and evaporated to dryness. The compounds in the two peaks were identified as **6** and **7**, respectively, by n.m.r. spectroscopy and by paper chromatography. Thus far, compounds **6** and **7** have failed to crystallize.

Compound **6**, 270 mg (16%), had R_F (solvent *B*) 0.46; retention time 5.2 min by g.l.c. at 150°; $[\alpha]_D^{27}$ −104° (*c* 2.0, water) (lit.[18,19] D-enantiomer R_F (solvent *B*) 0.55; $[\alpha]_D$ +146°); n.m.r. data (deuterium oxide): δ 5.43 (doublet, $J_{1,2}$ 4 Hz, H-1), 4.64–4.36 (multiplet, H-2,3,4), 4.22 (doublet of doublets, $J_{4,5}$ 3.6 Hz, $J_{5,5'}$ 12.7 Hz, H-5), 4.06 (doublet of doublets, $J_{4,5'}$ 4.6 Hz, H-5'), and 3.89 (singlet, $-OCH_3$).

Compound 7, 940 mg (57%), had R_F (solvent *B*) 0.53; retention time 5.2 min by g.l.c. at 150°; $[\alpha]_D^{27}$ +46° (*c* 1.9, water) (lit.[18] D-enantiomer R_F (solvent *B*) 0.61; $[\alpha]_D$ −50°); n.m.r. data (deuterium oxide): δ 5.36 (singlet, H-1), 4.70–4.37 (multiplet, H-2,3,4), 4.27 (doublet of doublets, $J_{4,5}$ 3.4 Hz, $J_{5,5'}$ 12.4 Hz, H-5), 4.05 (doublet of doublets, $J_{4,5'}$ 6.0 Hz, H-5'), and 3.87 (singlet $-OCH_3$).

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