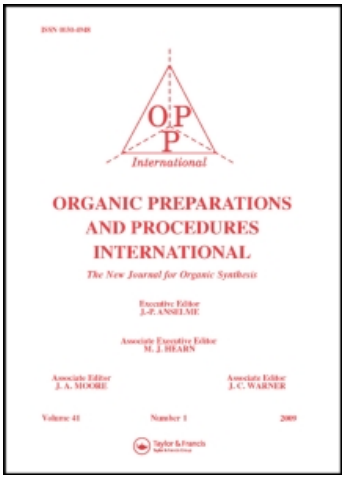

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A FACILE SYNTHESIS OF 5-DEOXY-D-RIBONIC ACID LACTONE AND OF 5-DEOXY-D-RIBOSE

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OPPI BRIEFS

A FACILE SYNTHESIS OF 5-DEOXY-D-RIBONIC ACID LACTONE AND OF 5-DEOXY-D-RIBOSE

Submitted by (07/25/88)

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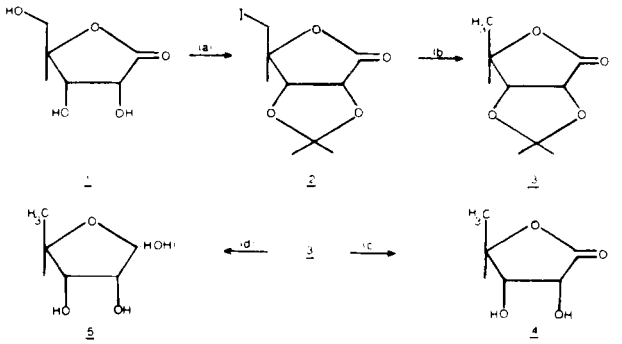
As part of a program to examine complex formation between sugar acids and ferric ion, 5-deoxy-D-ribonic acid lactone (4) was synthesized as shown below from D-ribono-1,4-lactone (1) with the aim of demonstrating that the C_5 hydroxymethyl group is a coordination site on the ligand D-ribonic acid. Compounds 2, 3 and 4 are new. 5-Iodo-2,3-isopropyliden-D-ribono-1,4-lactone (2), was prepared from 5-O-tosyl-2,3-O-isopropylidene-D-ribono-1,4-lactone, obtained from 2,3-O-isopropylidene-D-ribono-1,4-lactone. The last compound generally has been prepared via the Hough method.[1,2] Shah[3] introduced a new modification for its synthesis consisting of stirring a solution of D-ribono lactone in dry acetone in the presence of $CuSO_4$ at room temperature for 72 hrs thus reportedly affording the ketal in 92% yield; we could not reproduce Shah's results, even after taking such precautions as using dry acetone of high purity and freshly prepared anhydrous $CuSO_4$. The equilibration of D-ribono-1,4-lactone with acetone, reached after a long period of boiling as reported by Hough,[1] seems to be necessary before addition of anhydrous $CuSO_4$.

2,3-Isopropylidene-D-ribono-1,4-lactone was always contaminated with unreacted D-ribono-1,4-lactone; the mixture of products was separated by column chromatography on silica gel, using a mixture of increasing polarity of chloroform-acetone in order to obtain a pure ketal derivative. Recrystallization from benzene recommended by Hough, was avoided due to the low solubility of D-ribono-1,4-lactone in this solvent, which always lowered the purity of the recrystallized product, as shown by ^{13}C NMR spectroscopy. The yield of the ketal was not higher than 70%, as reported earlier.[1] The intermediate 3 was quantitatively reduced to 5-deoxy-2,3-O-isopropylidene-D-ribose, which, after deacetalation in acidic medium, afforded 5-deoxy-D-ribose (5).



a) i. Me_2CO, $CuSO_4$, ii. TosCl, Py iii. KI, Me_2CO b) Raney Ni, H_2, 3 atm, 25°
c) Me_2CO(aq), IR(120, H^+) d) i. R_2BH, ii. Me_2CO(aq) IR(120, H^+)

In addition to high yields, the merit of this route is the use of a very inexpensive starting material, D-ribono-1,4-lactone (1) in comparison with the classical preparation of 5-deoxy-D-ribose (5) that begins with expensive D-ribose.[4]

EXPERIMENTAL SECTION

IR spectra were measured with a Beckman Acculab B spectrophotometer. NMR spectra were recorded on a Brucker WP 80 S Y spectrometer in $CDCl_3$ solutions. The ^1H NMR spectra were measured at 80.13 MHz, unless specified otherwise, Me_4Si was used as an internal standard and chemical shifts are expressed in ppm; J values are given in Herz. The ^{13}C NMR spectra were measured at 20.15 MHz and the δ values are in parts per million downfield from Me_4Si δ (Me_4Si) = δ ($CDCl_3$) -76.9. Column chromatography was performed on silica gel 60H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc in hexane or chloroform-acetone as solvents. Paper chromatography was carried out by the descending method on Whatman No. 1 filter paper, using the following solvent systems (v:v): (a) ethyl acetate-acetic acid-water (9:2:2), (b) ethyl acetate-acetic acid-formic acid-water (18:3:1:4), (c) 1-butanol-ethanol-water (40:11:19) and (d) 1-butanol-pyridine-water (6:4:3). Non-reducing compounds were detected on paper chromatograms with an alkaline silver nitrate spray reagent.[1] Deoxy sugars were detected employing $HClO_4$ (70%) as spray reagent.

2,3-O-Isopropylidene-D-ribono-1,4-lactone.- IR(neat): 3470 (OH), 1790 (1,4-lactone car-bonyl) and 1380 (sh) and 1375 cm^{-1} (gem-dimethyl); ^1H NMR: δ 4.81 (d, 1H, H-2), 4.79 (d, 1H, H-3), 4.63 (t, 1H, H-4), 3.89 (m, 1H, H-5, H-5), 2.60 (bs, 1H, D_2), exchangeable OH-5), 1.47 and 1.39 (2s, 6H, CMe_2); ^{13}C NMR: δ 175.2 (s, C-1), 112.9 (s, $C(CH_3)_2$), 82.3 (d, C-4), 78.1 (d, C-2), 75.5 (d, C-3), 61.6 (t, C-6), 26.5 and 25.2 (2q, $(CH_3)_2$); MS m/e (relative intensity): 173 (M^+-CHO, 39), 129 (5), 85 (20), 68 (10), 59 (37), 55 (12), 43 (100), 30 (50), 15 (25).

5-O-Tosyl-2,3-O-isopropylidene-D-ribono-1,4-lactone.- IR(neat): 1790 (1,4-lactone carbonyl);^1H NMR: δ 7.77-7.38 (dd, 4H, Ar-H), 4.75 (d, 1H, H-2), 4.79 (d, 1H, H-3), 4.68 (t, 1H, H-4), 4.28 (dd, 2H, H-5, H-5), 2.46 (s, 3H, CH_3-Ar), 1.45 and 1.39 (2s, 6H, CMe_2); ^{13}C NMR: δ 173.8 (s, C-1), 145.7 and 131.5 (s, C quaternary Ar), 130 and 127.7 (d, C-methine-Ar), 113.5 (s, C-$(CH_3)_2$), 78.9

(d, C-4), 77.2 (d, C-2), 74.7 (d, C-3), 68.3 (t, C-5), 26.4(q, CH_3-Ar), 25.2 and 21.4 (2q, $(CH_3)_2$-C); MS m/e (relative intensity): 327 (M^+-CH_3, 100), 172 (10), 155 (67), 127 (40), 113 (5), 91 (30), 85 (50), 68 (53), 43 (68), 8 (25).

5-Iodo-2,3-isopropylidene-D-ribono-1,4-lactone (2).- A mixture of 5-O-tosyl-2,3-0-isopropylidene-D-ribono-1,4-lactone (8.0 g, 23.4 mmol), acetone (80 ml) and potassium iodide (15.5 g) was boiled under reflux for 20 hrs. The solution was freed of potassium p-toluenesulfonate by filtration, and concentration of the filtrate gave a residue which was dissolved in water (30 ml) and extracted with ethyl acetate (6 x 30 ml). The organic phase was washed with aqueous sodium thiosulfate and water, dried (Na_2SO_4) and concentrated to give a crude product. Recrystallization from a mixture of ethyl acetate/ethyl ether gave 4.7 g (68%) of 2, mp. 90-92°, $[\alpha]_D^{25}$ = -33.19° (c 0.7, $CHCl_3$); IR(neat): 1785 cm^{-1} (1,4-lactone-carbonyl); ^1H NMR: δ 5.0 (d, 1H, H-2), 4.60 (t, 2H, H-3, H-4), 3.40 (d, 2H H-5, H-5'), 1.47 and 1.40 (2s, 6H,CMe_2): ^{13}C NMR δ 172.8 (s, C-1), 113.6 (s, $\underline{C}(CH_3)_2$), 80.7 (d, C-4), 79.8 (d, C-2), 74.9 (d, C-3), 26.3 and 25.1 (2q, $(CH_3)_2C$) and 5.4 (t, C-5); MS m/e (relative intensity): 298 (M^+, 5), 127 (5), 69 (15), 43 (100), 28 (22), 15 (15). Found for $(M-15)^+$: 282.9488 ($C_8H_{11}O_4I$-15 requires 282.9469).

Anal. Calcd for $C_8H_{11}IO_4$: C, 32.21; H, 3.59. Found: C, 32.25; H, 3.74

5-Deoxy-2,3-isopropylidene-D-ribono-1,4-lactone (3).- Calcium carbonate (3.36 g, 3.36 mmol) and Raney Nickel (excess) were added to a solution of 5-iodolactone 2 (1.0 g, 3.36 mmol) in ethanol (16 ml), and the mixture was stirred for 5 hrs followed by filtration and evaporation. A solution of the residue in a small amount of water was extracted with ethyl acetate (5 x 15 ml), dried (Na_2SO_4) and concentrated, yielding 3 as a transparent syrup (0.56 g, 96%); $[\alpha]^2{}_D{}^5$ = -60° (c 3.0, $CHCl_3$) lit[5]; -61° (c 3.7, $CHCl_3$). IR(neat): 1790 cm^{-1} (lactone peak); ^1H NMR: δ 4.5 (dt, 3H, H-2, H-3, H-4), 1.47 and 1.40 (2s, 6H, $(CH_3)_2C$), 1.36 and 1.50 (d, 3H, H-5); ^{13}C NMR: δ 173.6 (s, C-1), 113.5 (s, $\underline{C}(CH_3)_2$), 80.15 (d, C-4), 78.8 (d, C-2), 74.5 (d, C-3), 26.4 and 25.3 (q, $(CH_3)_2C$), 19.2 (q, C-5).

5-Deoxy-D-ribono-1,4-lactone (4).- A mixture of a solution of 5-deoxy-2,3-O-isopropylidene-D-ribono-1,4-lactone (1 g, 5.8 mmol) in 40% aqueous acetone (20.0 ml) together with Amberlite resin IR-120(H^+) (1.5 ml) was heated at 50°. The reaction was monitored using TLC until the disappearance of starting material was observed. After cooling, the solution was decanted from the resin, concentrated to an amorphous solid, and submitted to flash chromatography, employing a mixture of methanol/acetone as eluting agent. Pure compound 4 (0.63 g, 80%) was obtained, $[\alpha]_D^{25}$ = +26.7° (c, 10.5, CH_3OH): IR(neat): 1785 cm^{-1} (lactonecarbonyl peak); ^1H NMR: δ 4.55 (dd, 2H, H-2, H-4), 4.20 (d, 1H, H-3), 1.35-1.44 (d, 3H, H-5); ^{13}C NMR: δ 176.0 (s, C-1), 81.0 (d, C-4), 70.2 (d, C-2), 66.3 (d, C-3), 14.8 (q, C-5); MS m/e (relative intensity): 133 (M^++1, 15), 73 (15), 70 (10), 60 (30), 45 (20), 42 (42), 31 (47), 29 (100), 27 (43); found for M^+: 132.1150 ($C_5H_8O_4$ requires 132.1156).

5-Deoxy-D-ribose (5).- Compound 3 was reduced with disiamylborane, applying the Kohn method[6] for obtaining aldoses from acylated aldonolactones. Compound 3 (117.3 mg) in 5.0 ml tetrahydrofuran was slowly added to 10 ml of tetrahydrofuran containing 0.017 mole of

disiamylborane in a nitrogen atmosphere. After standing overnight at room temperature, 10 ml of water was slowly added and mixture was refluxed for 0.5 hr. The solution was cooled to 0° and 20 ml of 30% hydrogen peroxide was slowly added dropwise while the pH was maintained between 7 and 8 with 3N sodium hydroxide.

The mixture was concentrated to a small volume and extracted several times with chloroform. The combined chloroform extracts were washed and dried over calcium chloride. The chloroform was evaporated and the syrup obtained was chromatographed on silica gel, obtaining pure 5-deoxy-2,3-O-isopropylidene-D-ribonofuranose, 95 mg, 0.545 mmol, 80%; $[\alpha]_D^{25}$ = -26.94° (c 0.73, $CHCl_3$); IR(neat): no lactone peak at 1736- 1790 cm^{-1}; ^1H NMR: δ 5.42 and 5.28 (s and d, mixture of anomers, C-1H), 4.50 (m, 3H, H-2, H-3, H-4), 2.8 (bs, 1H, OH), 1.47 and 1.39 (2s, 6H, $(CH_3)_2C$) 1.56 and 1.31 (d, 3H, H-5); ^{13}C NMR: δ 112.0 (s, $\underline{C}(CH_3)_2$), 102.9 (d, C-1), 86.22 (d, C-4), 85.3 (d, C-2), 82.8 (d, C-3), 26.2 and 24.7 (q, $(CH_3)_2C$), 21.36 (q, C-5); MS (m/e): 157 (M^+-17, 8), 149 (5), 139 (5), 123 (8), 110 (50), 97 (45), 83 (43), 71 (100), 55 (60), 43 (98), found M^+: 174.0901 ($C_8H_{14}O_4$, requires: 174.0888).

5-Deoxy-2,3-O-isopropylidene-D-ribonofuranose (75 mg, 0.43 mmol) was desacetalyzed in the same manner as described for 4; this gave pure 5-deoxy-D-ribose, 57 mg, 0.43 mmol, 100%; $[\alpha]_D^{25}$ = +10° (c 4, H_2O), lit[4] = +11.2° (c 4, H_2O). Paper chromatography showed only one spot ^{R}Rhamnose: 1.16 (solvent: d); MS (m/e): M^+: 134.0561 ($C_5H_{10}O_4$ requires 134.0576.

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