

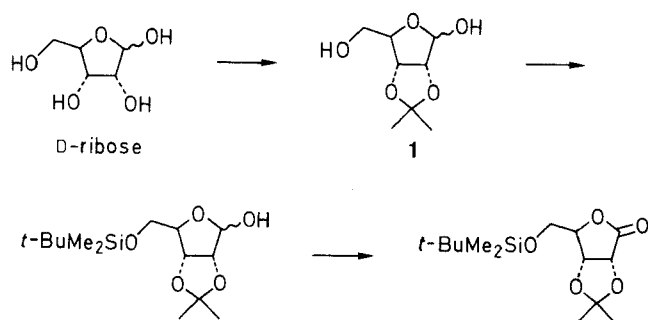
A New Synthesis of D-Ribonolactone from D-Ribose by Pyridinium Chlorochromate Oxidation

Dashan Liu, Carol A. Caperelli*

College of Pharmacy, Division of Pharmacology and Medicinal Chemistry, University of Cincinnati Medical Center, Cincinnati, OH 45267-0004, USA

2,3-*O*-Cyclohexylidene-D-ribonolactone is prepared directly from 2,3-*O*-cyclohexylidene-D-ribose by pyridinium chlorochromate (PCC) oxidation in 55–60% yield.

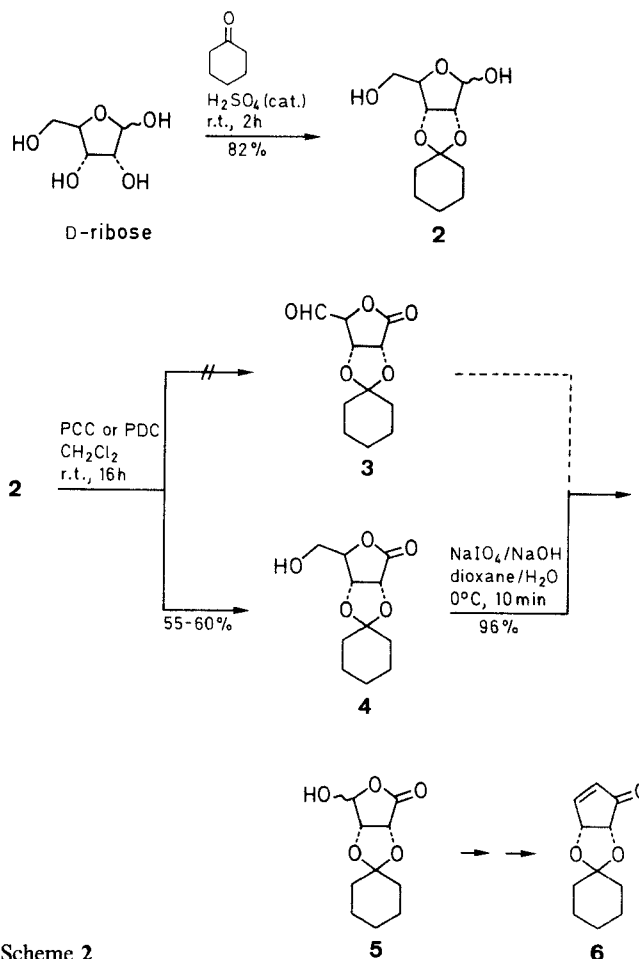
D-Ribonic acid γ -lactone (D-ribonolactone) has been used in recent years as a versatile chiral intermediate in organic synthesis, most notably in the synthesis of carbocyclic nucleosides.^{1–4} However, due to the high cost and unreliable supply of D-ribonolactone from commercial sources, some alternative routes have been sought.^{4,5} During our effort to synthesize chiral carbocyclic ribonucleotides for enzymatic studies of *de novo* purine biosynthesis,^{6,7} we were particularly interested in a recent preparation of 2,3,5-*O*-protected D-ribonolactone from D-ribose⁸ (Scheme 1).



Scheme 1

Since our goal was to synthesize the requisite carbocyclic ribonucleotides via (–)-2,3-(cyclohexylidenedioxy)-4-cyclopentenone (6),⁹ it appeared to us that by direct oxidation of 2,3-*O*-protected D-ribose 2 to aldehyde lactone 3, it should be possible to obtain lactol 5 by further oxidation of 3 with basic sodium periodate⁴ (Scheme 2), eliminating the need for protection/deprotection of the primary hydroxy group.

In order to test this approach, we treated 2,3-*O*-cyclohexylidene-D-ribose (2) in dichloromethane at room temperature with 4 equivalents of pyridinium chlorochromate (PCC) to insure complete oxidation of both the lactol and the primary hydroxy group. Surprisingly, after 16 hours the predominant product in the reaction mixture was 2,3-*O*-cyclohexylidene-D-ribonolactone (4). It appeared that although there was a large excess of PCC, the primary hydroxy group was largely unaffected. When the amount of PCC was reduced from 4 to 1.5 equivalents or pyridinium dichromate (PDC) was used instead of PCC, similar results were obtained. In all cases, no significant amount of aldehyde lactone 3 was isolated, whereas the typical yield of purified 4 (column chromatography) ranged from 55–60%. The protected ribonolactone 4 was further converted to the readily crystallizable lactol 5 using a modified literature procedure.² Both 4 and 5 gave spectroscopic data identical



Scheme 2

ical to that reported in the literature.² To the best of our knowledge there is only one previous report in the literature concerning direct oxidation of D-ribose to D-ribonolactone in the presence of an unprotected primary hydroxy group. This was achieved with silver carbonate on Celite in 21% yield.¹⁰ Clearly, our method has some advantages.

Since primary hydroxy groups are usually oxidized to aldehydes easily by PCC under the experimental condition which we employed,¹¹ our results are atypical. To examine the scope and limitations of this reaction, we treated D-ribonolactone 4 with 2 equivalents of PCC in dichloromethane for 16 hours. No change was observed by both GC and TLC analysis. D-Ribose acetonide 1 was similarly treated with 2 or 4 equivalents of PCC in dichloromethane; however, only complicated product mixtures were obtained. These results could indicate that the steric demands of the diol protecting group may play a role in determining the specificity of the oxidation reaction.

PCC oxidation of furanoses has led to some unexpected results as reported recently.⁵ What we describe here should complement those results and can be employed as a convenient method for the preparation of D-ribonolactone.

D-Ribose, PCC and PDC were purchased from Aldrich. TLC grade silica gel for dry column flash chromatography¹² and Kodak silica gel TLC plates were obtained from Fisher Scientific. GC analysis was performed on a Hewlett-Packard 5890 gas chromatography apparatus with an OV17 column. Melting point was determined on a Thomas-Hoover melting point apparatus and was uncorrected. Specific rotation was measured on a Autopol 3 polarimeter using 1-dm cell. IR were measured on a Perkin-Elmer 1600 FTIR spectrometer. ¹H- and ¹³C-NMR spectra were obtained on a Bruker AC-300 spectrometer at 300.13 and 75.45 MHz, respectively. MS was obtained on a Hewlett-Packard 5995 GC/MS spectrometer.

2,3-O-Cyclohexylidene-D-ribose (2):

To a solution of D-ribose (15 g, 0.1 mol) in cyclohexanone (50 mL) is added conc. H₂SO₄ (10 drops). The resulting mixture is stirred at r.t. for 2 h. Solid Na₂CO₃ (0.5 g) is added and solvent is evaporated. The residue is dissolved in CH₂Cl₂ (100 mL) and washed with H₂O (20 mL). The organic layer is dried (MgSO₄), filtered and evaporated. Dry column chromatography (5% MeOH in CHCl₃) gives **2** as a viscous oil; yield: 18.92 g (82%).

¹H-NMR (CDCl₃/TMS): δ = 1.3–2.0 (m, 10 H), 3.75–3.79 (m, 4 H), 4.42 (s, 1 H), 4.59 (d, 1 H, J = 6.0 Hz), 4.85 (d, 1 H, J = 6.0 Hz), 5.43 (br s, 1 H).

2,3-O-Cyclohexylidene-D-ribonolactone (4):

Method A: 2,3-O-Cyclohexylidene-D-ribose (**2**, 11.39 g, 49 mmol) is dissolved in CH₂Cl₂ (150 mL). To this solution is added PCC (21.35 g, 98 mmol) with vigorous stirring. The resulting mixture is stirred at r.t. for 16 h. Et₂O is added and the resulting suspension is filtered through a pad of Florisil. The solvent is evaporated, leaving a pale yellow oil, which is purified by dry column chromatography (EtOAc/hexanes, 2:1) to give **4** as a viscous oil; yield: 6.7 g (59%, > 95% purity by GC).

IR (neat): ν = 3480, 1786, 1449, 1368 cm⁻¹.

¹H-NMR (CDCl₃/TMS): δ = 1.2–1.8 (m, 10 H), 3.79 (dd, 1 H, J = 12.0, 2.1 Hz), 3.96 (dd, 1 H, J = 12.0, 2.1 Hz), 4.65 (s, 1 H), 4.76 (d, 1 H, J = 5.5 Hz), 4.84 (d, 1 H, J = 5.5 Hz).

¹³C-NMR (CDCl₃/TMS): δ = 23.60, 23.71, 24.66, 34.77, 36.22, 61.57, 75.21, 77.77, 83.09, 113.65, 175.32.

MS (70 eV): m/z = 229 (M + 1), 228 (M), 200, 199, 186, 185, 172.

Method B: 2,3-O-Cyclohexylidene-D-ribose (**2**, 7.78 g, 33.8 mmol) is dissolved in CH₂Cl₂ (140 mL). To this solution is added PDC (48.35 g, 128 mmol). The resulting mixture is stirred at r.t. for 16 h.

Product **4** is isolated and purified in the same manner as in method A; yield: 4.6 g (59%).

2,3-O-Cyclohexylidene-L-erythruronolactone (5):

2,3-O-Cyclohexylidene-D-ribonolactone (**4**, 11.36 g, 50 mmol) is dissolved in dioxane (60 mL). NaOH (1.96 g, 50 mmol) in H₂O (60 mL) is added. To this solution is added NaIO₄ (10.6 g, 50 mmol) in H₂O (60 mL) at 0°C with stirring. The resulting white suspension is stirred at 0°C for 10 min. A solution of BaCl₂·2H₂O (4.03 g, 16 mmol) in H₂O (20 mL) is added. The white precipitate is filtered off. The filtrate is evaporated and the resulting viscous oil is dissolved in H₂O (50 mL). The solution is acidified to pH = 3 with 10% HCl at 0°C and extracted with EtOAc (100 mL). The aqueous phase is acidified again to pH 3 followed by extraction with EtOAc (50 mL). The organic phases are combined and dried (MgSO₄). Evaporation of solvent gives a solid product. Recrystallization of the solid from CH₂Cl₂ and hexanes gives **5**; yield: 10.36 g (96%); mp 106–108°C (Lit.² mp 107–108°C); $[\alpha]_D^{25}$ –43.3° (c = 1.60, CHCl₃) (Lit.² $[\alpha]_D^{25}$ –39.8° (c = 1.65, CHCl₃)).

¹H-NMR (CDCl₃/TMS): δ = 1.2–1.8 (m, 10 H), 4.61 (d, 1 H, J = 5.5 Hz), 4.8 (br s, 1 H), 4.91 (d, 1 H, J = 5.5 Hz), 5.81 (s, 1 H).

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