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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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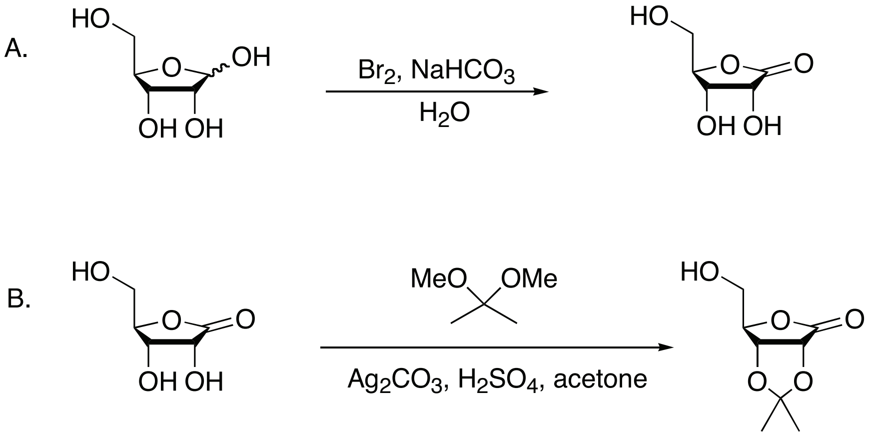
D-RIBONOLACTONE AND 2,3-ISOPROPYLIDENE(D-RIBONOLACTONE)

(D-Ribonic acid, 2,3-*O*-(1-methylethylidene)-, γ-lactone)



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Checked by Anthony Cuzzupe and Peter Wipf.

1. Procedure

Caution! Bromine is volatile and corrosive, and causes severe burns upon contact with skin. Proper protective equipment and an efficient fume hood are required.

A. ***D**-Ribonolactone*. A 1-L three-necked, round-bottomed flask fitted with a mechanical stirrer, a 100-mL pressure-equalizing addition funnel and an internal thermometer is charged with **D**-ribose (100 g, 0.67 mol), sodium bicarbonate (112 g, 1.3 mol, 2 equiv) (Note 1) and water (600 mL). The mixture is stirred at room temperature for 15 min, during which time most of the solids dissolve (Note 2). The flask is then immersed in an ice-water bath. The addition funnel is filled with bromine (112 g, 0.70 mol, 1.04 equiv) (Note 1) and the bromine is added to the vigorously stirred aqueous solution at a rate of about 2 drops/sec such that the reaction temperature does not exceed 5 °C. When the addition is complete (about 1 hr), the funnel is replaced with a stopper and the resulting orange solution is stirred for an additional 50 min. Sodium bisulfite (6.5 g, 62.5 mmol) is added in order to completely discharge the orange color (Note 3). The clear aqueous solution is transferred to a 2-L flask and evaporated on a rotary evaporator (bath temperature 60 ˚C – 70 ˚C, water aspirator pressure) until a wet slurry remains. Absolute EtOH (400 mL) and toluene (100 mL) are added to give a cloudy suspension and the solvent is removed by rotary evaporation (bath temperature 50 ˚C, water aspirator pressure) to provide a damp solid. Absolute EtOH (400 mL) is added and the mixture is heated on a steam bath for 30 min. The hot ethanolic suspension is filtered and the solids are rinsed with hot absolute EtOH (100 mL). The filtrate is cooled to room temperature, and then refrigerated for 16 h. The crystalline product is filtered, rinsed first with cold absolute EtOH (100 mL) then with Et_2O (100 mL), and dried under vacuum (room temperature, 0.25 mmHg) to yield 125 g of crude product (Note 4). The filtrate is concentrated (200 mL) and refrigerated to obtain additional product, which is filtered, washed with cold EtOH (25 mL) and Et_2O (25 mL) and dried under vacuum (room temperature, 0.25 mmHg) to provide 35 g of additional crude product.

*2,3-Isopropylidene(**D**-ribonolactone).* In a 2-L round-bottom flask, the crude ribonolactone (160 g) from above is suspended in dry acetone (700 mL), 2,2-dimethoxypropane (100 mL) and conc. H_2SO_4 (1 mL, 20 mmol) (Note 1). The solution is stirred vigorously at room temperature for 50 min, then silver carbonate (20 g, 73 mmol) is added (Notes 1 and 5). The resulting suspension is stirred at room temperature for 50 min, then the suspension is filtered through a 2 cm Celite pad. The solids are rinsed with acetone (100 mL), and the filtrate is evaporated to dryness. The crude acetonide is dissolved in EtOAc (250 mL) with heating on a steam bath. The resulting suspension is filtered through a 2 cm Celite pad, the solids are rinsed with hot EtOAc (50 mL), and the filtrate is allowed to cool to room temperature. Crystals of 2,3-isopropylidene(**D**-ribonolactone) form spontaneously as the solution cools. The resulting crystalline product is filtered and dried under vacuum (room temperature, 0.25 mmHg) to yield 68.7 g of product. The mother liquor is concentrated to 50 mL to yield 22.5 g of additional product after filtration and drying as above. The solids are combined to afford 91.2 g (73% overall yield from ribose) of white crystalline solid (Note 6, 7).

2. Notes

1. Ribose, bromine and silver carbonate were purchased from Acros Organics. Sodium bicarbonate was obtained from Mallinckrodt Baker, Inc. 2,2-Dimethoxypropane was obtained from Avocado Research Chemicals, Ltd. Deionized water was used as the solvent. All reagents were used as purchased.

2. Some of the sodium bicarbonate remains undissolved, but this does not affect the reaction yield, as the excess will be consumed during the course of the reaction.

3. If any orange color remains at this stage, the product will develop a pale brown color that cannot be removed by activated carbon.

4. The major contaminant is ~40-45% sodium bromide. The submitters recrystallized the crude product twice from hot *n*-BuOH (800 mL) to obtain 80 g of pure material. However, the crude material is of sufficient quality for the subsequent reaction. Pure ribonolactone has the following physical properties: mp 85-87 °C; $[a]_{\mathrm{D}}^{25}$+11.9 (*c* 0.99, H_2O); IR (KBr) cm^{-1}: 3513, 3373, 3159, 1761, 1627, 1397, 1197, 1143; R_f 0.56 (30% v/v MeOH/$CHCl_3$, *p*-anisaldehyde in ethanol stain); ^1H NMR (300 MHz, DMSO-d_6) d 5.73 (d, 1H, D_2O exch, J = 7.7 Hz), 5.35 (d, 1H, D_2O exch, J = 3.8 Hz), 5.15 (t, 1H, D_2O exch, J = 5.4 Hz), 4.40 (dd, 1H, J = 7.7, 5.4 Hz), 4.21 (t, 1H, J = 3.5 Hz), 4.11 (app t, 1H, J = 4.9 Hz), 3.56 (dd, 2H, J = 5.4, 3.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) d 176.5, 85.4, 69.3, 68.6, 60.5.

5. As an alternative to the expensive silver carbonate, the submitters also used 30 g of the weakly basic resin Amberlyst A-21. In this instance, additional acetone (200 mL total) is used to rinse the filtered solids, and care must be taken upon evaporation of the solvent to remove the residual water.

6. The recrystallized **D**-ribonolactone acetonide has the following physical properties: mp 134-137 °C; $[a]_{D}^{24}$-66.7 (*c* 1.03, $CHCl_3$); IR (KBr) cm^{-1}: 3469, 2991, 2952, 2932, 1767, 1467, 1389, 1379, 1224; R_f 0.51 (1:3, hexane:EtOAc; *p*-anisaldehyde in ethanol stain); ^1H NMR (300 MHz, DMSO-d_6) d 5.30 (t, 1H, D_2O exch, J = 5.0 Hz), 4.76 (s, 2H), 4.60 (t, 1H, J = 2.1 Hz), 3.67-3.55 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) d 174.3, 111.6, 82.3, 78.1, 75.0, 60.4, 26.6, 25.1; Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.26; H, 6.46.

7. Extremely pure ribonolactone acetonide melts at >140 ˚C, but material with a melting point >130 ˚C is suitable for most reactions. Very

pure material can be obtained by 1-2 additional recrystallizations from hot EtOAc.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure represents a modification of a previously published procedure for the bromine oxidation of ribose to ribonolactone.[3] The improved procedure allows for the addition of a liquid reagent (bromine) instead of the solid reagent (sodium carbonate) used in the previous preparation, and thus requires neither a powder addition apparatus nor constant attention. Additionally, the present procedure does not require the careful monitoring of pH, the absence of which can lead to the complete failure of the previous preparation.

Industrial preparations of ribonolactone involve the epimerization of arabinonic acid salts under very caustic and harsh conditions, followed by fractional crystallization of the resulting ribonic acid salts from the arabinonic/ribonic acid salt mixture, and the cyclization of the resulting salts.[4-6] An alternative rhenium-catalyzed oxidation procedure requires the preparation of an expensive catalyst and the removal of substantial amounts of benzalacetone (used as a terminal oxidant) and its reduction products.[7]

D-Ribonolactone is no longer commercially available in large quantities, and is very expensive. The acetonide is also very expensive. Although the above preparation of **D**-ribonolactone and **D**-ribonolactone acetonide is not high-yielding, the starting materials are inexpensive and the preparation is quite convenient. **D**-Ribonolactone and its derivatives have been used for the syntheses of many nucleoside analogs[8,9] and natural products.[10,11]

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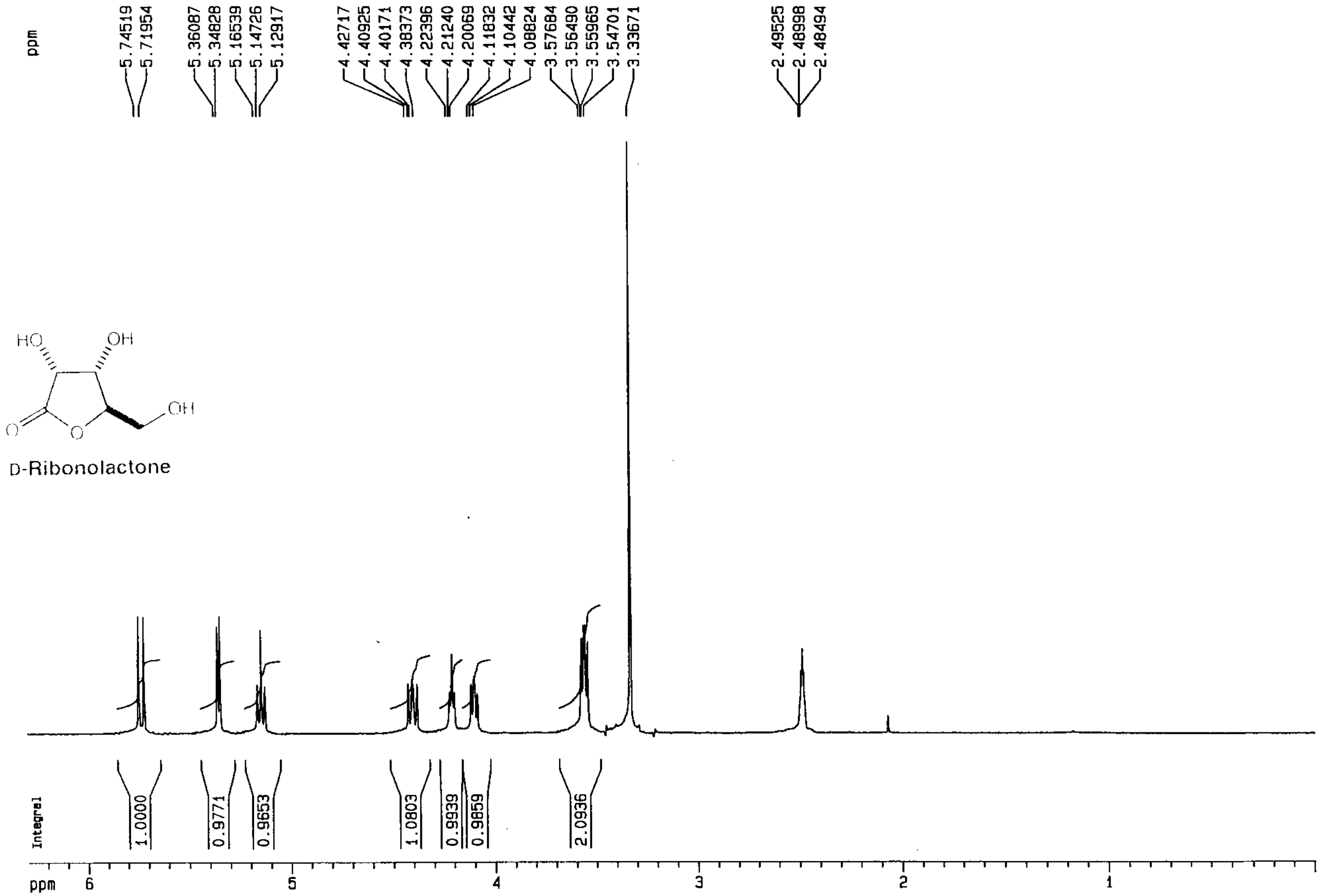
Appendix
Chemical Abstract Nomenclature (Registry Number)

D-Ribose; (50-69-1)
Sodium bicarbonate: Carbonic acid monosodium salt; (144-55-8)
Bromine; (7726-95-6)
Sodium bisulfite: Sulfurous acid, monosodium salt; (7631-90-5)
D-Ribonolactone: D-Ribonic acid, γ-lactone; (5336-08-3)
2,2-Dimethoxypropane: Propane, 2,2-dimethoxy-; (77-76-9)
Silver carbonate: Carbonic acid, disilver(1+) salt; (534-16-7)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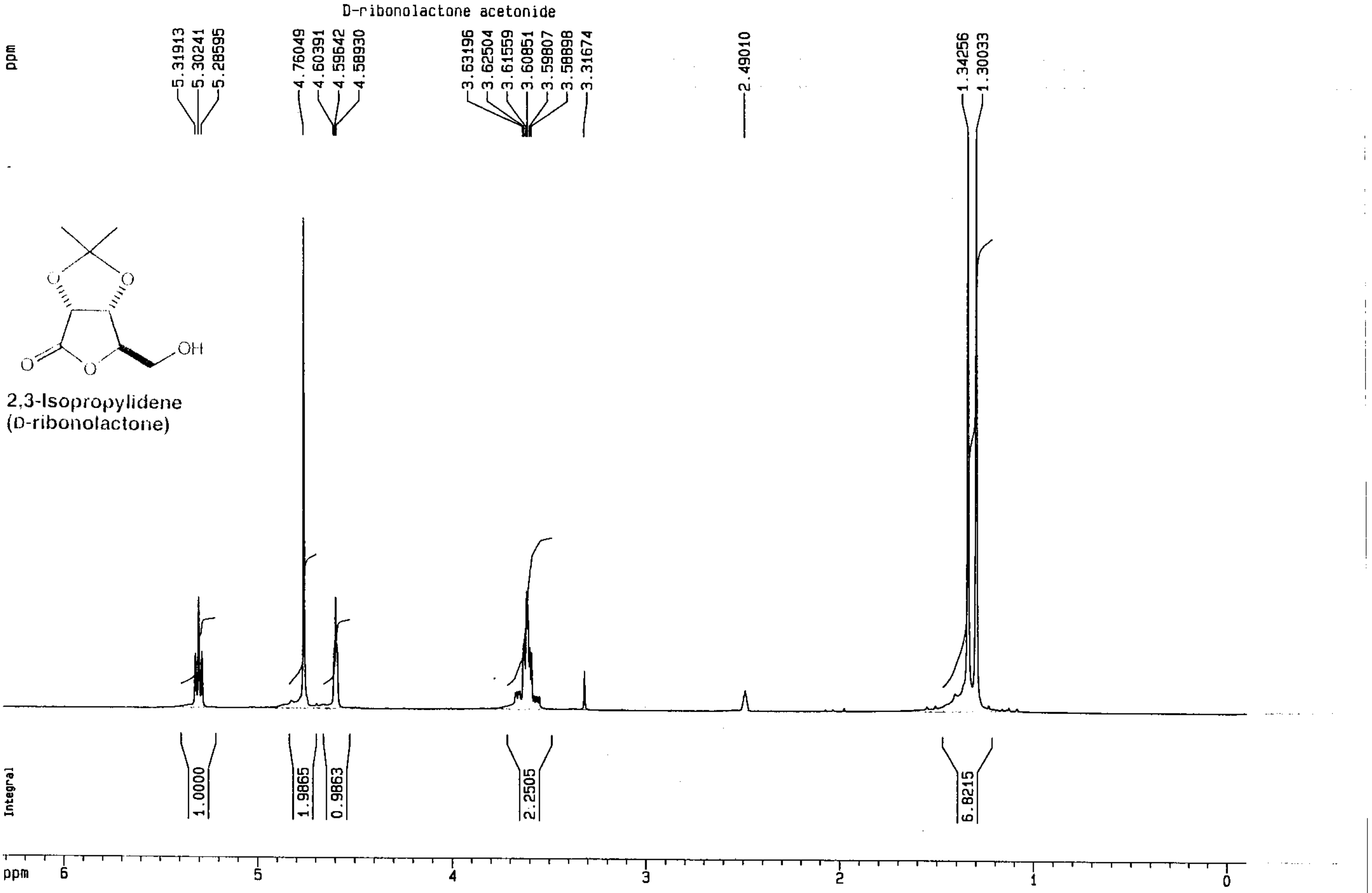

2,3-Isopropylidene
(D-ribonolactone)