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A Concise, Efficient and Production-Scale Synthesis of a Protected L-Lyxonolactone Derivative: An Important Aldonolactone Core

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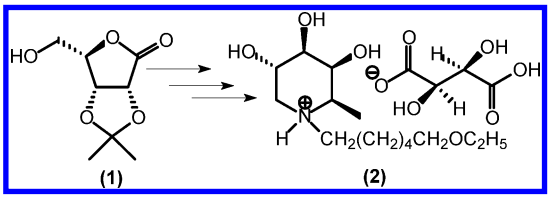
Abstract:

A multikilogram-scale synthesis of L-lyxonolactone-2,3-*O*-isopropylidene is reported. It proceeds efficiently from an optimized, large-scale, aqueous bromine oxidation of D-ribose to D-ribonolactone including a one-pot isopropylidene formation, and subsequent conversion of the D-ribonolactone-2,3-*O*-isopropylidene to L-lyxonolactone-2,3-*O*-isopropylidene via the derived C_5-mesylate and intramolecular relactonization of the product of aqueous potassium hydroxide cleavage of the D-ribonolactone ring. The inversion of configuration at the C_4-chiral center is understood in terms of an intermediating C_4-C_5-epoxide. The overall process is noteworthy for its operational simplicity, stereochemical integrity, and use of inexpensive chemicals.

Background

Aldonolactones find wide application in contemporary organic synthesis because they are inexpensive and serve as valuable chiral synthons for a range of natural products and drugs.[1] They are readily accessible from the corresponding aldose by several methods for anomeric oxidation.[2] Activated aldonolactones have been particularly useful in the synthesis of iminosugars.[3] In this connection we required substantial quantities (200−400 kg) of L-lyxonolactone-2,3-*O*-isopropylidene (**1**), a key intermediate in our synthesis of **UT-231B** (iminosugar, **2**), an analogue of deoxynojirimycin. Iminosugar **2** is currently in clinical trials as an antiviral agent for the treatment of hepatitis C.



(1) (2)

Results and Discussion

Our initial route to **1** involved periodate cleavage of D-gulonolactone-2,3-*O*-isopropylidene (**5**) followed by sodium cyanoborohydride reduction of the thus formed aldehyde (Scheme 1) (**3** → **4** → **5** → **6** → **1**).[4a−c]

Although this route provided access to the first few kilograms of compound **2**, it suffered from a number of limitations:

1. D-Gulonolactone (**3**) is a very expensive and not a readily available material.

2. All the intermediates required chromatographic purification.

3. Attempts to scale-up the periodate cleavage step (**5** → **6**) failed on a 500-g scale.

4. The aldehyde formed in step (**5** → **6**) was unstable and decomposed rapidly.

5. Selective deprotection in step **4** → **5** was difficult to control on a large scale as the second isopropylidene group was sensitive to heat and acid.

6. Handling of periodic acid and sodium cyanoborohydride was problematic on a large scale as the workup for steps **5** → **6** → **1** generated a large amount of toxic byproducts which raised safety concerns.

Because of the need for **1** in the synthesis of **2**, a more reliable synthesis for this critical intermediate was required. This goal was accomplished using the synthetic route shown in Scheme 2; namely, oxidation of D-ribose (**7**) to D-ribonolactone (**8**) followed by isopropylidene formation (**8** → **9**), mesylate formation (**9** → **10**), and base hydrolysis of **10** with intramolecular displacement of the mesylate group (**10** → **1**).

The key transformation **10** → **1** was confirmed on a laboratory scale prior to scale-up using the literature proce-

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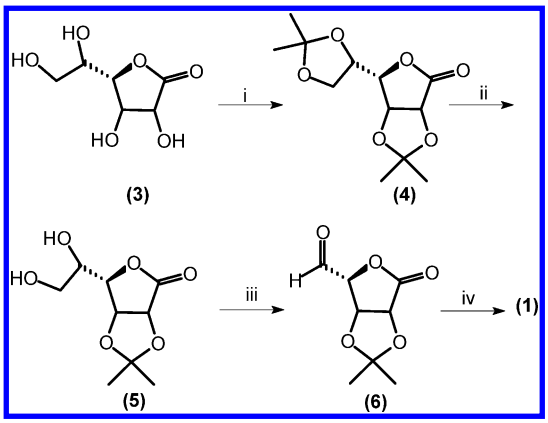
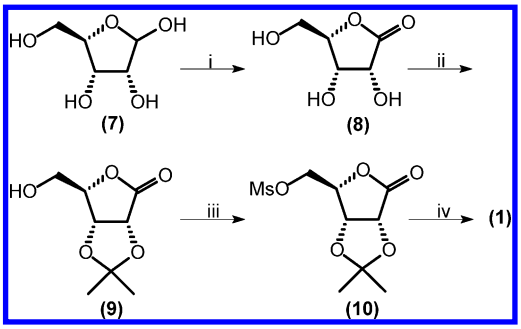
Scheme 1[a]



[a] Conditions: (i) Acetone, H_2SO_4 (*cat.*), 2,2-dimethoxypropane. (ii) 80% Acetic acid in water. (iii) H_5IO_6, THF. (iv) $NaCNBH_3$, acetic acid.

Scheme 2[a]



[a] Conditions: (i) Br_2, H_2O, K_2CO_3. (ii) Acetone, H_2SO_4 (*cat.*). (iii) Mesyl chloride, Et_3N, CH_2Cl_2. (iv) KOH, H_2O.

dure.[5] The starting point for the synthesis of **1** was the large-scale production of D-ribonolactone-2,3-*O*-isopropylidene (**9**).

There are various methods known in the literature for the synthesis of **9**;[6−10] however, reports by Kaskar et al.[6] and Caperelli et al.[7] showed that none of the methods was suitable for larger quantities of **1**. At this stage we investigated the conventional methods of oxidations in sugar chemistry,[2] and the oxidation of commercially available D-ribose (**7**) with bromine and water worked very well on a 200-kg scale for the synthesis of D-ribonolactone (**8**) as shown in Scheme 2. D-Ribose (**7**) was oxidized to D-ribonolactone (**8**) using bromine/water in the presence of potassium carbonate. In situ protection of the *cis*-diol of D-ribonolactone (**8**) with acetone in the presence of a catalytic amount of sulfuric acid afforded D-ribonolactone-2,3-*O*-isopropylidene (**9**). This step was scaled to 200 kg with a yield of 65%. This process is noteworthy when we consider the key role that D-ribonolactone plays as a "chiral cornerstone" in a wide range of syntheses of acyclic, cyclopentanones, and bicyclics.[11] Using a literature procedure,[5] mesylation of **9** with methanesulfonyl chloride in the presence of triethylamine in dichloromethane

(5) Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857.
(6) Kaskar, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031.
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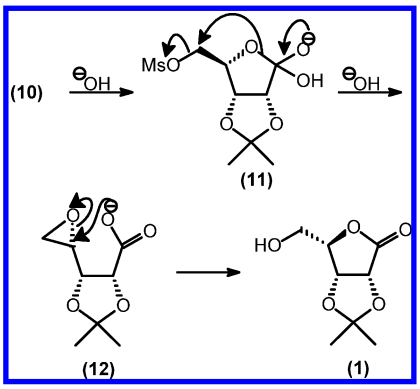
Scheme 3



gave mesylate (**10**). However, scaling up of this step (**9**→**10**) to a 200-kg scale required several process modifications of the literature methods. Specifically, it was determined that the optimal temperature for the reaction was −20 °C for the mixing of the reagents, and an 8-h reaction time at room temperature was required. Without purification, the crude mesylate (**10**) was subjected to aqueous potassium hydroxide treatment. After workup and crystallization of crude **1** from 2-propanol, an analytically acceptable product was obtained in 59% yield.

The mechanism of the inversion of the configuration at the C_4 chiral center in **12** to yield **1** deserves comment. We envision a process in which an intermediary epoxide **12** of the retained configuration at C_4 undergoes subsequent intramolecular ring opening of the epoxide by the carboxylate nucleophile in a favorable 5-endo-*tet* process[12] proceeds with inversion of configuration to yield **1** (Scheme 3).

In conclusion, this is the first study of such a large-scale, practical, and facile synthesis of **1** with an overall yield of 38% starting from D-ribose (**7**). Compared to our earlier synthetic process (Scheme 1) this current process (Scheme 2) is easily scalable, efficient, and cheaper in terms of use of chemicals involved and control of parameters. We have prepared more than 400 kg of compound **9** and 200 kg of compound **1** using this methodology. The procedure used for synthesis of **UT-231B** from **2** will be reported in a future communication.

Experimental Section

All chemicals were commercially available. Melting points were determined on a Fischer Scientific melting point apparatus and are uncorrected. Optical rotations were measured on a DigiPol 781 automatic polarimeter (Rudolph instrument) at a wavelength of 589 nm (sodium D line) in a 1.0-dm cell with a total volume of 1 mL. Specific rotation $[\alpha]_D$ is reported in degrees per decimeter at the specified temperature, and concentration (*c*) was given in grams per 100 mL in the specified solvent. Infrared spectra were recorded on a Thermo Nicolet AVATAR 360 FT-IR, using KBr pellets. The NMR spectra were determined on a JEOL 300 MHz spectrometer, and elemental analyses were performed by Atlantic Microlab, Atlanta, Georgia.

(12) Baldwin, J. E. *J Chem. Soc., Chem. Commun.* **1976**, 734.

D-Ribonolactone-2,3-*O*-isopropylidene (9). D-Ribose (75 kg, 500 mol, 1.0 equiv) was dissolved in water (207 L) at ambient temperature and cooled to 10−15 °C. To this cold, clear solution was added solid potassium carbonate (82.5 kg, 597 mol, 1.2 equiv) while maintaining the internal temperature between 10 and 15 °C. The reaction solution was cooled to 0−5 °C, and bromine (87.4 kg, 547 mol, 1.1 equiv) was added slowly with stirring over a period of 3−4 h. (***Caution***: The temperature was kept below 5 °C during the addition of bromine as this step was highly exothermic, and care must be taken while handling bromine. Protective clothing was used at all times, including full face respirator equipped with an NIOSH-approved organic vapor-acid gas canister, laboratory coat, and protective gloves.) After the addition of bromine was complete, the reaction mixture was stirred overnight while allowing the temperature to rise to ambient. The solution was treated slowly with 88% formic acid (25 L) at room temperature to adjust the pH to 2−3. The acidic solution was concentrated in vacuo at 50 °C to yield a brown solid. This brown solid was dissolved by adding acetone (1500 L, 1185 kg, 20 403 mol, 41 equiv). To this clear solution was added 4 Å molecular sieves (37.5 kg) and concentrated sulfuric acid (7.5 L). The reaction mixture was heated at reflux temperature for 4 h under nitrogen. Then the mixture was cooled to 25−30 °C and maintained at this temperature for 8 h. The reaction mixture was adjusted to a pH of 5.5−6.0 by adding sodium hydroxide flakes (30 kg). The reaction mixture was filtered, and the filtrate was concentrated in vacuo below 40 °C to afford a crude, solid mass. This crude solid was dissolved by stirring in ethyl acetate (250 L) at 40 °C. The solution was filtered, and the filtrate was concentrated in vacuo to 50% of the original volume. This solution was cooled to −5 °C to obtain solid D-ribonolactone-2,3-*O*-isopropylidene (**9**) that was collected by filtration and dried under vacuum at 35 °C. The yield of **9** was 51.7 kg (55%; on a 200-kg scale the yield improved to 65%); mp 136−138 °C (lit[13] mp 138−139 °C). IR (KBr): 3455, 1762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.95 (brs, 1H, OH), 3.75−3.80 (dd, 1H, C-5′H), 3.95−3.99 (dd, 1H, C-5H), 4.60−4.62 (m, 1H, C-4H), 4.74−4.78 (d, 1H, C-3H), 4.80−4.83 (m, 1H, C-2H).

L-Lyxonolactone-2,3-*O*-isopropylidene (1). To D-ribonolactone-2,3-*O*-isopropylidene (**9**) (50 kg, 266 mol, 1.0 equiv) was added dichloromethane (750 L) and triethylamine (29.8 kg, 41.0 L, 294 mol, 1.1 equiv) under nitrogen. This mixture was stirred at ambient temperature until it became clear, and then it was cooled to −20 °C. To this solution was slowly added methanesulfonyl chloride (33.3 kg, 22.5 L, 291 mol, 1.1 equiv), and the solution was stirred for 1 h at −20 °C. The solution was allowed to attain ambient temperature, and it was maintained at this temperature for 8 h. The reaction was quenched with water (400 L), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 200 L). The organic layers were combined, washed with water (2 × 200 L), and concentrated in vacuo below 30 °C to obtain the semisolid mesylate (**10**). To this crude mesylate was added a solution of potassium hydroxide (36.5 kg, 651 mol, 2.44 equiv) in 245 L of water maintaining the temperature below 30 °C. This solution was stirred for 4 h at the same temperature and then adjusted to pH 2.5 to 3.0 by adding 3 M hydrochloric acid (33.5 L). The acidic solution was concentrated in vacuo maintaining the temperature below 45 °C to afford a solid mass. The solid mass was triturated with acetone (300 L) and heated to reflux. The acetone was decanted, dried over sodium sulfate (35 kg), and filtered. The clear filtrate was concentrated in vacuo below 35 °C to yield the crude product. The product was crystallized from 2-propanol (100 L) to afford white, crystalline L-lyxonolactone-2,3-*O*-isopropylidene (**1**), 17.1 kg (43.1%, on a 200-kg scale the yield improved to 59%); mp 98−99 °C (lit[5] mp 92−93 °C), $[\alpha]_D^{25}$ −89° (c = 1.0, acetone), [lit[5] $[\alpha]_D^{20}$ −85.6° (c = 1.0, acetone)]. IR (KBr): 3423, 1778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.72 (brs, 1H, OH), 3.75−3.77 (d, 1H, C-5′H), 3.91−4.01 (m, 2H, C-5H and C-5′H), 4.60−4.64 (m, 1H, C-4H), 4.83−4.89 (m, 2H, C-3H and C-2H). Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.38. Found: C, 50.96; H, 6.44.

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