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Synthesis of L-Ribose from D-Ribose by a Stereoconversion through Sequential Lactonization as the Key Transformation

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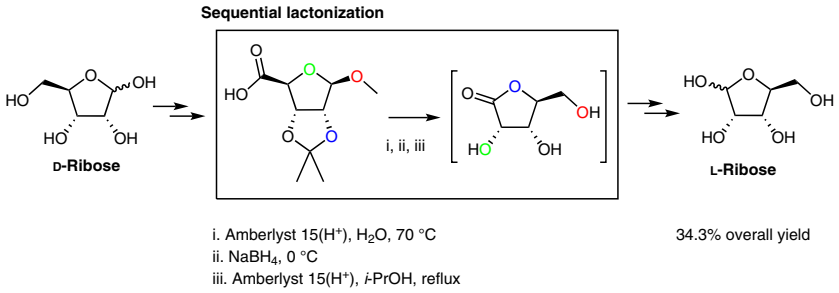

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Abstract L-Ribose, a key precursor of various L-nucleosides can only be synthesized from other sugars or other non-sugar precursors. Herein, the study involves the synthesis of naturally rare L-ribose from readily available D-ribose. Though, many synthetic strategies are developed to meet the increasing demands of L-ribose, seeking innovation, a synthesis employing sequential lactonization as the key transformation was explored. This novel conversion involves protection, oxidation, sequential lactonization, reduction with DIBAL-H, and deprotection.

Key words L-ribose, D-ribose, sugar, lactonization, DIBAL-H, reduction

In contrast to D-ribose, which is found in all almost living cells, L-ribose is naturally non-existent. The accounts of L-ribose dates back to the early 20th century[1] but correlation of naturally occurring D-nucleosides with the synthesized L-nucleosides was not studied until the end of century.[2] Fortunately, such studies led to a new world of developments in the pharmaceutical industry.

Recently, L-ribose has received recognition as the main precursor and basic structural component of several biologically active L-nucleosides, glycoproteins, glycolipids, and oligonucleotides.[3] L-Nucleoside-based drugs have received a great deal of attention around the globe because of their potential to interact with the viral nucleoside synthesis-replication process.[2a] Telbivudine,[4] Clevudine,[5] Levovirin,[6] and Maribavir,[7] as shown in Figure 1, are well-known examples of L-ribose related antiviral agents used for the treatment of hepatitis, AIDS, and other diseases such as immunological disorders. As a result of the emerging importance and high demands of L-ribose, the commercial production as well as laboratory syntheses have been explored worldwide. L-Ribose can be synthesized by chemical transformation from other sugars such as L-arabinose,[8] L-xylose,[9] D-ribose,[10] D-mannono-1,4-lactone,[11] D-glucose,[12] D-galactose,[13] D-fructose[14] or by chemical synthesis as asymmetric chain elongation with non-sugar compounds.[15] Despite all these efforts, L-ribose is still considered an expensive and highly in demand sugar for the synthesis of many biologically significant antiviral active pharmaceuticals. Therefore, we focused our study with an emphasis on the use of inexpensive starting materials and reagents, simple workup procedures, and minimal use of purification techniques. Previously reported methods used expensive reagents, while we have accomplished a practical synthesis of L-ribose using commercially available D-ribose as the starting material. In addition, in the current study, separation steps

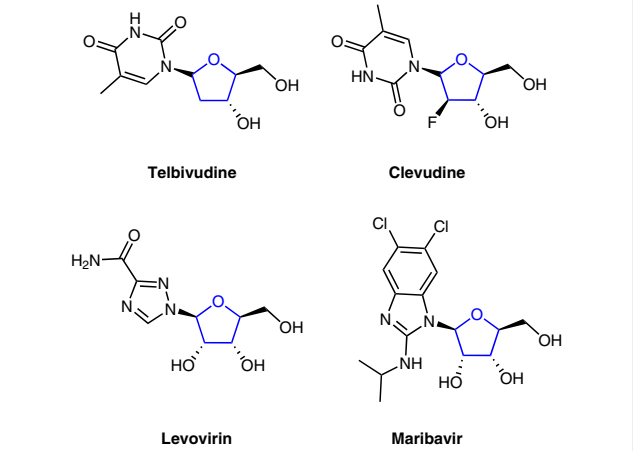
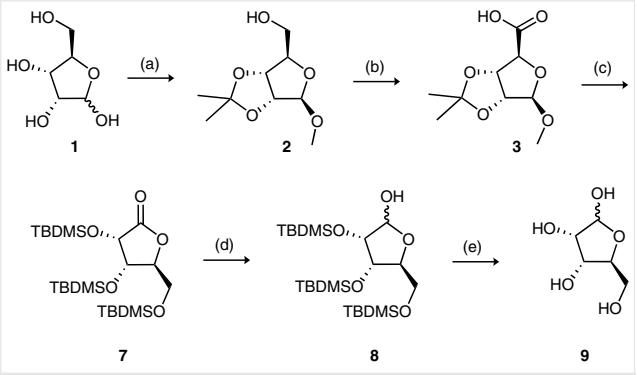


Figure 1 L-Ribose related antiviral agents

such as column chromatography are minimized, and an efficient stereoconversion is achieved without using an expensive chiral auxiliary.

Previously, some reports on L-ribose synthesis have involved Mitsunobu reaction[16] or Swern oxidation,[10c,g] which have drawbacks such as the use of expensive reagents, removal of by-products, and low reaction temperature at oxidation step. In contrast, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-catalyzed oxidation employed in the current study is not only nontoxic but also cheap. It has been used as a mild oxidizing agent with or without a combination of different additives like trichloroacetic acid.[17] The oxidation can also be conducted at room temperature and a combination of TEMPO with NaOCl were employed here for mild oxidizing conditions.[18] Another highlight of this synthesis is that the key transformation combines hydrolysis, reduction, and lactonization together into a 'sequential lactonization' that simplifies the process.

The synthesis of L-ribose commenced with the selective protection of hydroxyl groups of D-ribose, as shown in Scheme 1. The protection of *syn*-diol as well as the anomeric hydroxyl group with sulfuric acid in acetone and MeOH at room temperature afforded the desired product in satisfactory result.[19]



Scheme 1 Synthesis of L-ribose. *Reagents and conditions*: (a) H_2SO_4, acetone, MeOH, r.t., 48 h, 90%; (b) KBr, TEMPO, NaOCl, $NaClO_2$, EtOAc, r.t., 8 h, 99.9%; (c) i) Amberlyst 15 (H^+), H_2O, 70 °C, 5 h, ii) $NaBH_4$, 0 °C, 1 h, iii) Amberlyst 15 (H^+), *i*-PrOH, reflux, 12 h, iv) TBDMSCl, imidazole, DMF, 50 °C, 12 h, 67%; (d) DIBAL-H, CH_2Cl_2, –70 °C, 1.5 h, 77%; (e) CsF, MeOH, r.t., 24 h, 74%.

Protection of alcohols was followed by oxidation of the exposed primary hydroxyl to carboxyl group. Three sets of reaction conditions were found to show promising results, as shown in Table 1. The best productivity was observed using the reaction protocol reported by Zhao et al.[20] for the oxidation catalyzed by TEMPO and subsequent treatment with sodium chlorite and bleach. Despite the quantitative product yield, the reaction conditions were anticipated to be risky on large scale due to the dangers associated with using sodium chlorite and bleach together. Another such attempt to oxidize the alcohol **2** to the corresponding carboxylic acid **3** also involved TEMPO catalysis but was assisted by trichloroisocyanuric acid (TCCA).[21] In contrast to sodium chlorite and bleach, TCCA is nontoxic and a less expensive reagent. Once again, the reaction proceeded well; however, the product appeared to dissolve in water, which made it difficult to remove TCCA from the reaction mixture. Hence, we returned to the first set of reagents, but utilized stepwise addition of NaOCl and $NaClO_2$ to lower the risk factor (Table 1, entry 3).[22]

Table 1 Optimization Studies for Oxidation of Compound **2**

Entry	Reagents and conditions	Yield (%)
1	(i) TEMPO, phosphate buffer (pH 6.7), MeCN (ii) $NaClO_2$, NaOCl, r.t. (iii) NaOH (pH 8), 35 °C, 12 h	quant
2	(i) $NaHCO_3$, NaBr, TEMPO, acetone, r.t. (ii) TCCA, r.t., 4 h	90
3	(i) EtOAc, TEMPO, KBr, H_2O, r.t. (ii) NaOCl (12%), r.t. (iii) $NaClO_2$ (25%), r.t. (iv) concd HCl, r.t., 8 h	quant

Next, carboxylic acid **3** was transformed into the key skeleton of L-ribose, as shown in Scheme 1, through crucial modifications at C-1 and C-5. Some major changes for the stereoconversion including reduction of the C-1 carbonyl, lactonization, and hydroxyl protection were carried out in a four-step sequence by simple filtration without column chromatography (Scheme 2; path c in Scheme 1). This sequential lactonization began with the deprotection of hydroxyl groups with Amberlyst 15 (H^+) catalyst.[23] Following deprotection, selective reduction of the formyl group to hydroxyl was carried out by adding $NaBH_4$ to the reaction mixture, followed by lactonization assisted by Amberlyst resin. The use of Amberlyst resin has several advantages to traditional sources of H^+ like HCl, such as ease of reaction monitoring, simple separation by filtration, and the absence of counter-ions. After separating the solid residue from the reaction vessel, the reaction contents were treated with *tert*-butyldimethylsilyl chloride (TBDMSCl) using imidazole as base, which led to protection of all three hydroxyl groups. The stereo-inversion during the sequential lactonization was confirmed by X-ray crystallographic analysis. X-ray crystallographic ORTEP plots of compound **3** and **7** are shown in Figure 2[24] (for details, see Supporting Information).

The synthesis of L-ribose was completed by DIBAL-H reduction of lactone **7** to lactol **8**[25] followed by desilylation using a typical fluoride to give L-ribose (Scheme 1).

In summary, we have accomplished an efficient and practical synthesis of L-ribose on gram scale with an overall 34.3% yield using commercially available D-ribose as the starting material. The synthetic strategy employed in the current study made use of inexpensive reagents, mild reac-

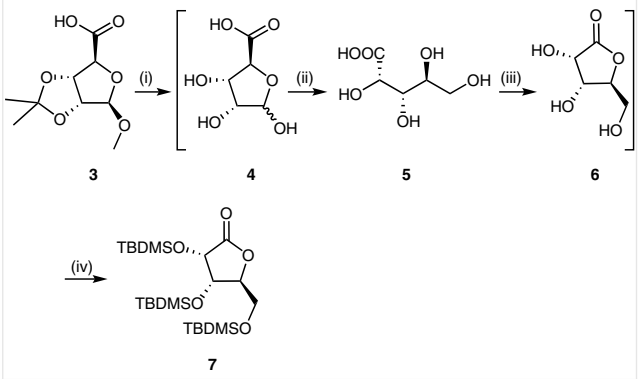
tion conditions, and simple separation techniques. It is especially noteworthy in this synthesis that a stereoconversion is possible by sequential lactonization without the use of an expensive chiral auxiliary.

All solvents were dried and distilled by standard procedures. Commercially available reagents were used without prior purification. Reactions were performed in flame-dried round-bottom flasks under an argon atmosphere and monitored by TLC, visualized by an exposure to UV light and/or by staining to ninhydrin, phosphomolybidic acid ethanolic solution, I_2 crystals, or $KMnO_4$ solution. Crude products were purified by flash column chromatography on silica gel (230–400 mesh). NMR spectra were recorded in $CDCl_3$ on Bruker AV-400 MHz (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer. Chemical shifts are reported relative to TMS as an internal standard. Optical rotations were measured using PerkinElmer-343 instrument.

Methyl 2,3-*O*-Isopropylidene-D-ribofuranoside (2)[26]

To a suspension of D-ribose (**1**; 20.0 g, 133.2 mmol) in acetone (100 mL) and MeOH (100 mL) was carefully added conc. H_2SO_4 (10 mL) at r.t. The resulting solution was stirred for 48 h. After the completion of reaction by TLC monitoring, the solution was neutralized by the addition of solid $NaHCO_3$. The solid was filtered, then the mixture was concentrated, and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated. The crude product was purified by silica gel flash column chromatography to give the product as a pale yellow oil; yield 24.4 g (90%); R_f = 0.2 (hexane/EtOAc = 5:1, v/v); $[\alpha]_D^{25}$ –80.00 (*c* 1.00, $CHCl_3$) {Lit.[26] $[\alpha]_D^{20}$ –75.00 (*c* 1.00, $CHCl_3$)}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.97 (s, 1 H), 4.83 (d, *J* = 5.7 Hz, 1 H), 4.58 (d, *J* = 6.0 Hz, 1 H), 4.42 (t, *J* = 2.7 Hz, 1 H), 3.56–3.72 (m, 2 H), 3.43 (s, 3 H), 3.32 (dd, *J* = 10.0, 3.0 Hz, 1 H), 1.49 (s, 3 H), 1.32 (s, 3 H).



Scheme 2 Sequential lactonization. *Reagents and conditions*: (i) Amberlyst 15 (H^+), H_2O, 70 °C, 5 h; (ii) $NaBH_4$, 0 °C, 1 h; (iii) Amberlyst 15 (H^+), *i*-PrOH, reflux, 12 h; (iv) TBDMSCl, imidazole, DMF, 50 °C, 12 h, 67%.

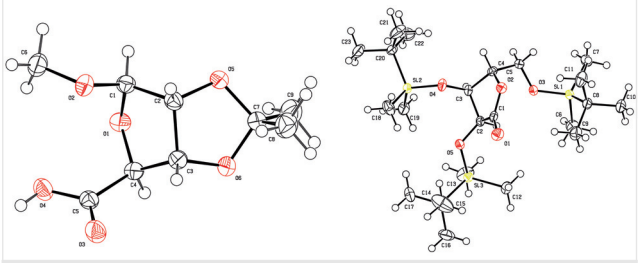


Figure 2 X-ray crystallographic ORTEP plot of compound **3** and **7** with 50% ellipsoidal probability

Methyl 2,3-*O*-Isopropylidene-D-ribofuranosiduronic Acid (3)[27]

KBr (1.70 g, 14.7 mmol) and TEMPO (0.383 g, 2.45 mmol) were added to a solution of **2** (10.0 g, 49.0 mmol) in EtOAc (100 mL), followed by dropwise addition of NaOCl (12%, 39.5 mL, 63.7 mmol) over 30 min at 0 °C. Then, the pH was adjusted to 2 by the addition of 35% HCl, followed by the addition of 25% aq $NaClO_2$ (5.76 g, 63.7 mmol) over 30 min maintaining r.t. Stirring was continued until completion of the reaction after 7 h. After adjusting the pH to 2–3, the product was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and the solvent was removed in vacuo to give the crude product. Recrystallization from hot CH_2Cl_2 with *n*-hexane gave a white solid; yield: 10.68 g (quant.); mp 128.5–129.5 °C (Lit.[27b] mp 129–131 °C); $[\alpha]_D^{20.5}$ –67.29 (*c* 2.47, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.69 (s, 1 H), 5.20 (d, *J* = 6.3 Hz, 1 H) 5.09 (s, 1 H), 4.69 (s, 1 H), 4.59 (d, *J* = 6.0 Hz, 1 H), 3.45 (s, 3 H), 1.50(s, 3 H), 1.34 (s, 3 H).

2,3,5-Tri-*O*-(*tert*-butyldimethylsilyl)-L-ribonic Acid γ-Lactone (7)

To a stirred solution of **3** (5.0 g, 22.9 mmol) in distilled H_2O was added Amberlyst 15 (H^+) (5.0 g). The reaction mixture was maintained at 70 °C for 5 h. After the completion of reaction by TLC monitoring, the mixture was cooled to 0 °C and $NaBH_4$ (3.47 g, 91.7 mmol) was slowly added. When TLC revealed completion of the reaction, the reaction was quenched by the addition of Amberlyst 15 (H^+) to pH 7. The mixture was filtered and the resin was washed with H_2O and MeOH. MeOH in the reaction mixture was evaporated in order to remove boron residues as trimethyl borate, and this procedure was repeated three times. *i*-PrOH (50 mL) and Amberlyst 15 (H^+) (5.0 g) were added to the remaining solution, and the mixture was refluxed for 12 h. The crude mixture was filtered through a short pad of silica gel and concentrated in vacuo. The residue was dissolved in anhydrous DMF (50 mL), and then imidazole (6.24 g, 91.7 mmol) and TBDMSCl (13.81 g, 91.7 mmol) were added, and the reaction mixture was heated to 50 °C for 12 h. After the completion of reaction, the mixture was poured into H_2O and stirred for 30 min. The product was filtered and dissolved in CH_2Cl_2, and the solution was dried ($MgSO_4$) and evaporated to give a crude yellow liquid. The crude product was purified by silica gel flash column chromatography to give compound **7** as a white solid; yield: 7.53 g (67%); mp 113.5–114.5 °C; R_f = 0.5 (hexane/EtOAc = 20:1, v/v): $[\alpha]_D^{20.5}$ –27.17 (*c* 0.99, $CHCl_3$); for D-isomer: $[\alpha]_D^{22}$ +28.2 (*c* 0.99, $CHCl_3$).[28]

IR (neat): 2929, 2885, 2857, 1791, 1472 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.58 (d, *J* = 5.0 Hz, 1 H), 4.25–4.30 (m, 2 H), 3.87 (dd, *J* = 12.0, 3.0 Hz, 1 H), 3.78 (dd, *J* = 12.0, 3.0 Hz, 1 H), 0.95 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.10 (s, 3 H), 0.11 (s, 3 H), 0.14 (s, 3 H), 0.19 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.20, 85.63, 71.96, 70.54, 62.39, 25.84, 25.82, 25.68, 18.44, 18.30, 18.17, –4.57, –4.63, –4.84, –5.05, –5.53, –5.66.

HRMS (ESI/TOF-Q): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{50}O_5Si_3$ + H: 491.3044; found: 491.3048.

2,3,5-Tri-*O*-(*tert*-butyldimethylsilyl)-L-ribose (8)

The γ-lactone **7** (5.0 g, 10.18 mmol) was dissolved in CH_2Cl_2 and cooled till –70 °C. A solution of DIBAL-H in CH_2Cl_2 (1.0 M, 10.18 mL, 10.18 mmol) was slowly added via a syringe over 30 min. The mixture was stirred for 1 h. After completion of the reaction by TLC monitoring, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered, evaporated, and the residue was purified by column chromatography to give the product **8** as a white solid; yield: 3.85 g (77%); mp 39.5–40.5 °C; R_f = 0.4 (hexane/EtOAc = 20:1, v/v); $[\alpha]_D^{20.1}$ –31.62 (*c* 1.00, $CHCl_3$).

IR (neat): 3503, 2858, 2739, 1472, 1390 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.04 (dd, *J* = 7.6, 4.0 Hz, 1 H), 4.24 (d, *J* = 11.2 Hz, 1 H), 4.14–4.12 (m, 1 H), 4.09–4.05 (m, 2 H), 3.67 (dd, *J* = 11.2, 2.8 Hz, 1 H), 3.55 (dd, *J* = 11.2, 4.8 Hz, 1 H), 0.93 (s, 9 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H), 0.58 (s, 3 H), 0.54 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 97.95, 85.67, 74.39, 72.67, 63.73, 26.13, 26.11, 25.97, 18.59, 18.50, 18.24, –4.45, –4.51, –4.58, –4.78, –5.17, –5.31.

HRMS (ESI/TOF-Q): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{52}O_5Si_3$ + H: 493.3201; found: 493.3199.

L-Ribose (9)[29]

To a solution of compound **8** (2.70 g, 5.48 mmol) in MeOH (20 mL) was added anhydrous CsF (3.33 g, 21.9 mmol). The reaction mixture was stirred at r.t. for 24 h. After completion of the reaction by TLC monitoring, the solvent was evaporated, and the residue was purified by preloaded silica gel chromatography. The product was dried under full vacuum overnight to give L-ribose (**9**) as a white gummy solid; yield: 0.61 g (74%); R_f = 0.2 ($CHCl_3$/MeOH = 5:1, v/v); $[\alpha]_D^{20}$ +20.00 (*c* 0.1, H_2O) {Lit.[29] $[\alpha]_D^{25}$ +18.3 (*c* 1.8, H_2O)}.

The ^1H NMR spectrum of L-ribose is superimposable with that of the corresponding D-isomer (starting material).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588857.

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