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Research Article

Convenient Synthesis of 1,4-Dideoxy-1,4-imino-D-ribitol from D-Ribose

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This paper describes a convenient synthesis of 1,4-dideoxy-1,4-imino-D-ribitol (DRB) from D-ribose. L-Lyxonolactone, a key intermediate in this synthesis, was prepared by base-promoted hydrolysis of a 5-chlorinated D-ribonolactone derivative with inversion of configuration at the C-4 position. Cyclization of the generated dimesylated L-lyxitol with benzylamine proceeded with another configurational inversion at C-4 to afford the D-*ribo*-configured pyrrolidine system, which upon deprotection gave DRB.

1. Introduction

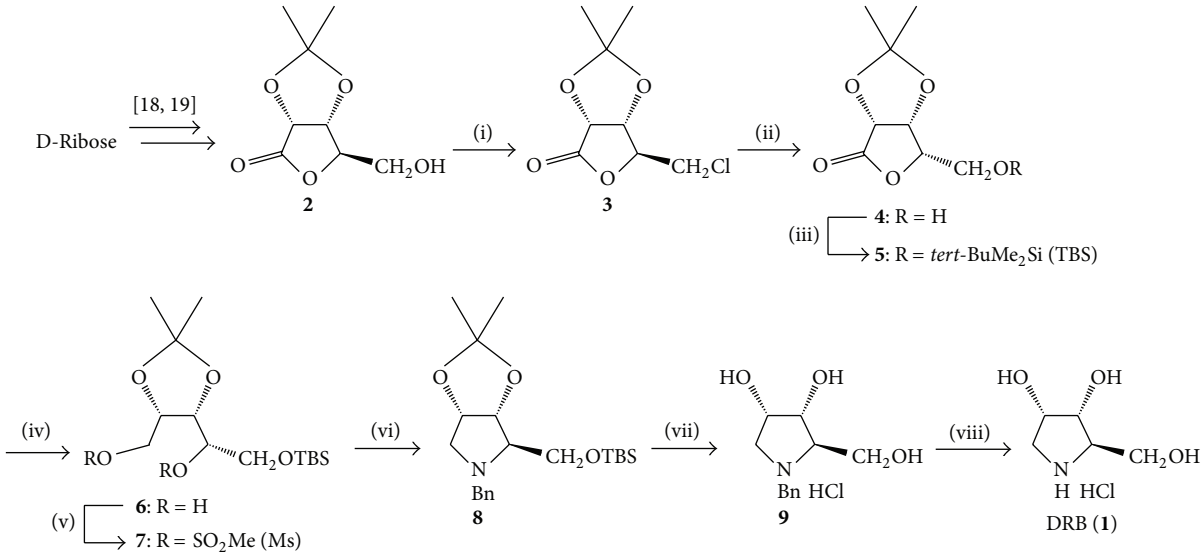
1,4-Dideoxy-1,4-imino-D-ribitol (DRB, **1**) is a polyhydroxylated pyrrolidine alkaloid isolated from the roots of mulberry trees (*Morus alba*) [1] and from the bark and pods of leguminous plants (*Angylocalyx pynaertii*) [2, 3]. Owing to its structural [4-aza]ribofuranose feature, DRB and its derivatives have attracted considerable attention as enzyme inhibitors that mimic glycoside and nucleoside substrates. In fact, DRB was found to be a potent inhibitor of lysosomal β-mannosidase [3] and eukaryotic DNA polymerases [4] and was also employed as a synthetic precursor of some enzyme inhibitors containing the [4-aza]ribosyl group [5–8]. Therefore, there is a need to develop a simple method for the preparation of DRB derivatives.

Two major approaches have been used to construct the DRB framework. One is the stereoselective dihydroxylation of optically active 2-substituted 3-pyrroline derivatives, in which the oxidation is usually carried out using a highly toxic osmium catalyst [9–13]; the other is a sugar-based approach. The D- and L-forms of 1,4-dideoxy-1,4-iminoribitol were prepared from D-gulonolactone (29% overall yield over 9 steps) and D-mannose (28% overall yield over 9 steps), respectively [14–16]. From the viewpoint of atom economy, pentose as a starting material is more favorable. Recently, a related study was reported by Mercer and coworkers [17], in which both enantiomers of 1,4-dideoxy-1,4-iminolyxitol were efficiently synthesized from D- and L-ribonolactone. Since the process involves configurational inversion at the C-4 position, a straightforward precursor to DRB is considered to be L-lyxose, which is an expensive unnatural pentose. Herein, we describe a convenient synthesis of DRB starting from D-ribose via L-lyxonolactone , in which the D-*ribo*-configured pyrrolidine ring is constructed with overall retention of the stereochemistry at C-4 by a double inversion.

2. Results and Discussion

The synthetic route to DRB is illustrated in Scheme 1. 2,3-*O*-Isopropylidene-D-ribono-1,4-lactone (**2**) is easily obtained from inexpensive D-ribose using a well-established procedure [18, 19] or is commercially available. At the beginning of the synthesis, we examined the conversion of D-ribonolactone **2** to L-lyxonolactone **4** with inversion of stereochemistry at C-4. A production-scale synthesis of **4** from **2** via a 5-*O*-methanesulfonyl derivative was reported (59% yield at a 200 kg scale) [18]; however, we experienced variable yields at a laboratory scale. In this study, therefore, we adopted an alternative route via the corresponding chloride **3**.

Chlorination of the hydroxyl group at C-5 of **2** was performed using a Vilsmeier reagent prepared in situ from DMF



Scheme 1: Synthesis of DRB (**1**). Reagents and conditions: (i) $(COCl)_2$, DMF, CH_2Cl_2, 97%; (ii) KOH, H_2O, then, 3 M HCl, quant; (iii) TBSCl, imidazole, CH_2Cl_2, 91%; (iv) $NaBH_4$, MeOH, 95%; (v) MsCl, pyridine, 85%; (vi) $PhCH_2NH_2$ ($BnNH_2$), toluene, 86%; (vii) 1 M HCl, quant; and (viii) H_2, 10% Pd/C, H_2O, quant.

and oxalyl chloride to afford 5-chloro-5-deoxy derivative **3** in 97% yield [20]. Treatment of chloride **3** with an aqueous KOH solution followed by acidification gave 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**4**) in quantitative yield. It is believed that configurational inversion at the C-4 position occurred as reported for the mesylate reaction [21]. Namely, a base-promoted ring opening of the chlorinated ribonolactone **3** followed by intramolecular S_N2 reaction gave epoxide **10** (Scheme 2). Subsequent 5-*exo*-tet [22] ring closure between the carboxylate and epoxide proceeded with inversion of configuration at C-4 to furnish the lactone, which was then hydrolyzed to the open-chain derivative **11** under strongly basic conditions. Upon acidification, carboxylate **11** immediately cyclized to lyxonolactone **4**.

After protection of the primary hydroxyl group of **4** as a *tert*-butyldimethylsilyl (TBS) ether in 91% yield, the fully protected lactone **5** was subjected to reductive ring opening by $NaBH_4$ in MeOH to afford partially protected L-lyxitol derivative **6** in 95% yield. Diol **6** was then treated with methanesulfonyl chloride in pyridine to give the corresponding dimesylate **7** in 85% yield. Cyclization of **7** with benzylamine involving inversion at C-4 was performed in refluxing toluene for 3 days to give fully protected DRB **8** in 86% yield. Acidic hydrolysis of both the acetonide and TBS protective groups in 1 M HCl gave *N*-benzyl DRB derivative **9** in quantitative yield. Finally, DRB was quantitatively obtained as its hydrochloride salt by catalytic hydrogenolysis of the *N*-benzyl group. Comparison of the physical and spectral data of DRB with the literature data completely confirmed its identity.

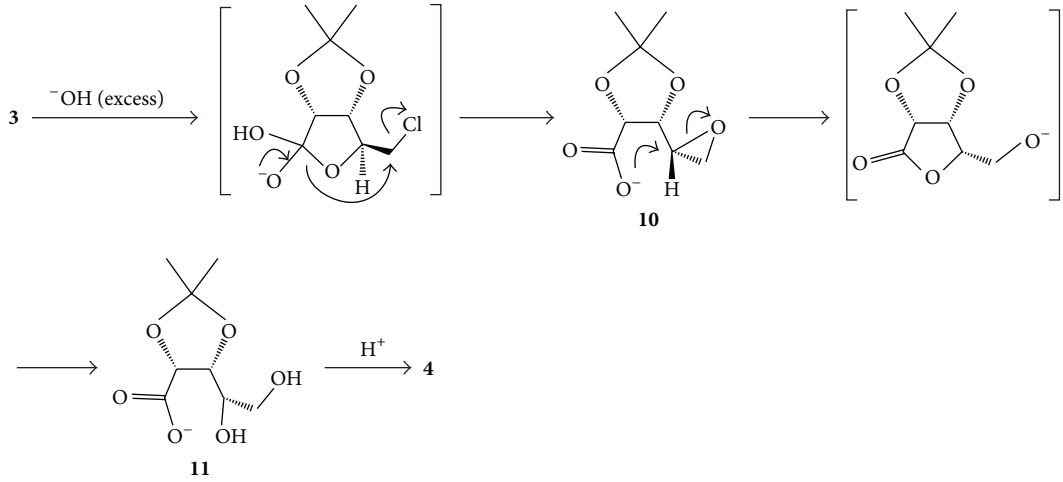
In conclusion, we have achieved a convenient synthesis of DRB in 61% overall yield from D-ribonolactone **2** over eight steps. The D-*ribo*-configured pyrrolidine system was constructed with overall retention of the stereochemistry at C-4 by a double S_N2 inversion.

3. Experimental

3.1. General. Melting points were determined using a Yamato MP-21 melting point apparatus in open capillaries and are uncorrected. ^1H and ^{13}C-nuclear magnetic resonance (NMR) spectra were measured on a Varian Mercury plus 400 spectrometer at 400 and 100 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (δ_H 7.26), HDO (δ_H 4.79), the central peak of deuteriochloroform (δ_C 77.0), or dioxane (δ_C 67.2); J values are expressed in Hz. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. Elemental analyses were performed using a PerkinElmer 2400 Series II analyzer.

All reagents and solvents were of commercial grade and used according to supplier instructions unless otherwise mentioned.

*3.2. 5-Chloro-5-deoxy-2,3-O-isopropylidene-D-ribono-1,4-lactone (**3**) [20, 23].* DMF was added (117 μL, 110 mg, 1.51 mmol) to a solution of oxalyl chloride (129 μL, 194 mg, 1.52 mmol) in CH_2Cl_2 (4 mL) at 0°C, and the mixture was stirred for 12 min. To the resultant cloudy suspension, a solution of compound **2** (188 mg, 0.999 mmol) in CH_2Cl_2 (2 mL) was added dropwise at the same temperature, and the mixture was refluxed for 90 min. The cooled reaction mixture was diluted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on SiO_2. Elution with a mixture of hexane and AcOEt (7/3) gave compound **3** (200 mg, 0.968 mmol, 97%) as a white solid. An analytical sample was obtained by recrystallization from a mixture of EtOH and acetone. Colorless powder, mp 97.5–98.5°C. $[\alpha]_D^{23}$ −60.8 (c 1.00, $CHCl_3$). ^1H-NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.49 (s, 3H), 3.79 (dd, J = 12 and 2 Hz, 1H), 3.85 (dd, J = 12 and 3 Hz, 1H), 4.74 (d, J = 6 Hz, 1H), 4.87 (dd, J = 3



Scheme 2: Plausible reaction pathway for the configurational inversion at C-4 by base-promoted hydrolysis of lactone **3**.

and 2 Hz, 1H), 4.89 (d, J = 6 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 25.4, 26.5, 44.7, 75.2, 78.2, 80.8, 113.7, 173.3.

*3.3. 2,3-O-Isopropylidene-L-lyxono-1,4-lactone (**4**) [18].* Compound **3** (207 mg, 1.00 mmol) was added to a 2.5 M aqueous solution of KOH (1.00 mL, 2.50 mmol), and the resulting mixture was stirred at room temperature overnight. The solution was acidified with 3 M HCl to pH 3 and concentrated. The residue was triturated with acetone (6 mL) and heated to reflux. After removal of the insoluble materials by filtration, the filtrate was dried over $MgSO_4$ and concentrated under reduced pressure to give compound **4** (193 mg) in quantitative yield as a white solid, mp 94-95°C (lit [18], mp 98-99°C). $[\alpha]_D^{25}$ −88.0 (c 0.50, acetone) (lit [18], $[\alpha]_D^{25}$ −89.0 (c 1.00, acetone)). ^{1}H-NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.49 (s, 3H), 2.10 (br s, 1H), 3.97 (dd, J = 12 and 5 Hz, 1H), 4.04 (dd, J = 12 and 7 Hz, 1H), 4.60 (ddd, J = 7, 5, and 4 Hz, 1H), 4.87 (d, J = 6 Hz, 1H), 4.89 (dd, J = 6 and 4 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 25.7, 26.6, 60.8, 76.1, 76.2, 79.1, 114.5, 173.5.

*3.4. 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-L-lyxono-1,4-lactone (**5**) [24].* A solution of compound **4** (193 mg), *tert*-$BuMe_2SiCl$ (166 mg, 1.10 mmol), and imidazole (102 mg, 1.50 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 1 h. The reaction mixture was then diluted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on SiO_2. Elution with a mixture of hexane and AcOEt (7/3) gave compound **5** (276 mg, 0.913 mmol, 91%) as a white solid. An analytical sample was obtained by recrystallization from hexane. Colorless powder, mp 87-88°C (data for enantiomer [25]: mp 90–91°C). $[\alpha]_D^{27}$ −52.2 (c 1.00, $CHCl_3$) (data for enantiomer [25]: $[\alpha]_D^{22}$ +54.9 (c 1.03, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 1.38 (s, 3H), 1.45 (s, 3H), 3.93 (dd, J = 11 and 7 Hz, 1H), 3.97 (dd, J = 11 and 6 Hz, 1H), 4.52 (ddd, J = 7 and 6 and 2 Hz, 1H), 4.79–4.82 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ −5.6, −5.4, 18.3, 25.7, 25.8, 26.7, 60.8, 75.7, 76.0, 79.4, 114.0, 173.8.

*3.5. 5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-L-lyxitol (**6**) [24].* $NaBH_4$ (351 mg, 9.28 mmol) was added to a solution of compound **5** (561 mg, 1.85 mmol) in MeOH (19 mL) at 0°C, and the resulting mixture was stirred at room temperature for 1 h. After removal of the solvent, the residue was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to give compound **6** (543 mg, 1.77 mmol, 96%) as a white solid. An analytical sample was obtained by recrystallization from hexane. Colorless powder, mp 64-65°C (data for enantiomer [25]: mp 67–68°C). $[\alpha]_D^{26}$ +9.3 (c 1.02, $CHCl_3$) (data for enantiomer [25]: $[\alpha]_D^{23}$ −9.2 (c 0.08, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.38 (s, 3H), 1.51 (s, 3H), 2.83 (dd, J = 7 and 5 Hz, 1H), 2.90 (d, J = 5 Hz, 1H), 3.63 (dd, J = 10 and 7 Hz, 1H), 3.72 (dd, J = 10 and 6 Hz, 1H), 3.77–3.85 (m, 3H), 4.23–4.25 (m, 2H). ^{13}C-NMR (CDCl3) δ −5.5, −5.4, 18.2, 25.0, 25.8, 27.1, 61.3, 64.5, 69.1, 75.7, 77.3, 108.2.

*3.6. 5-O-tert-butyldimethylsilyl-1,4-di-O-methanesulfonyl-2,3-O-isopropylidene-L-lyxitol (**7**) [24].* Methanesulfonyl chloride (0.411 mL, 608 mg, 5.31 mmol) was added to a solution of compound **6** (543 mg, 1.77 mmol) in pyridine (10 mL) at 0°C, and the resulting mixture was stirred at room temperature overnight. After removal of the solvent, the residue was diluted with AcOEt, successively washed with 1 M HCl and saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to give compound **7** (695 mg, 1.50 mmol, 85%) as a colorless oil. $[\alpha]_D^{26}$ −5.5 (c 1.02, $CHCl_3$) (data for enantiomer [25]: $[\alpha]_D^{24}$ +5.0 (c 0.14, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$) δ 0.097 (s, 3H), 0.103 (s, 3H), 0.90 (s, 9H), 1.38 (s, 3H), 1.51 (s, 3H), 3.08 (s, 3H), 3.11 (s, 3H), 3.83 (dd, J = 11 and 6 Hz, 1H), 3.96 (dd, J = 11 and 5 Hz, 1H), 4.37–4.45 (m, 4H), 4.74 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ−5.6 (2C overlapped), 18.2, 25.4, 25.8, 27.2, 37.6, 38.9, 63.1, 67.9, 74.4, 75.3, 78.9, 109.6.

*3.7. N-Benzyl-5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (**8**) [5, 8].*

A mixture of compound **7** (695 mg, 1.50 mol) and benzylamine (891 μL, 874 mg, 8.16 mmol) in toluene (8 mL) was heated to reflux for 3 days. The reaction mixture was then diluted with $CHCl_3$, successively washed with water and saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on SiO_2. Elution with a mixture of hexane and AcOEt (9/1) gave compound **8** (487 mg, 1.29 mmol, 86%) as a colorless oil. $[\alpha]_D^{27}$ −28.0 (*c* 1.01, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.35 (s, 3H), 1.58 (s, 3H), 2.74 (dd, *J* = 10 and 3 Hz, 1H), 3.03 (ddd, *J* = 4, 4, and 2 Hz, 1H), 3.12 (dd, *J* = 10 and 6 Hz, 1H), 3.66 (dd, *J* = 11 and 4 Hz, 1H), 3.74 (d, *J* = 13 Hz, 1H), 3.79 (dd, *J* = 11 and 4 Hz, 1H), 4.04 (d, *J* = 13 Hz, 1H), 4.58 (dd, *J* = 7 and 2 Hz, 1H), 4.67 (ddd, *J* = 7, 6, and 3 Hz, 1H), 7.15–7.38 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ −5.6, −5.5, 18.2, 25.1, 25.9, 27.1, 56.9, 59.2, 63.1, 68.8, 79.4, 83.2, 111.8, 126.8, 128.2, 128.5, 139.2.

*3.8. N-Benzyl-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (**9**)* . A mixture of compound **8** (354 mg, 0.938 mmol) and 1 M HCl (10 mL) was refluxed for 1 h. The cooled solution was washed with $CHCl_3$ and concentrated to give a quantitative yield of compound **9** (250 mg) as a brown solid. An analytical sample was obtained by recrystallization from a mixture of EtOH and acetone. Colorless powder, mp 190-191°C. $[\alpha]_D^{23}$ +16.9 (*c* 1.00, H_2O). ^{1}H-NMR (D_2O) δ 3.43 (dd, *J* = 13 and 3 Hz, 1H), 3.56 (dd, *J* = 13 and 4 Hz, 1H), 3.62 (dd, *J* = 13 and 4 Hz, 1H), 3.68 (ddd, *J* = 8, 4, and 3 Hz, 1H), 3.75 (dd, *J* = 13 and 4 Hz, 1H), 4.21 (dd, *J* = 8 and 4 Hz, 1H), 4.37 (ddd, *J* = 4, 4, and 4 Hz, 1H), 4.48 (d, *J* = 13 Hz, 1H), 4.62 (d, *J* = 13 Hz, 1H), 7.50–7.57 (m, 5H). ^{13}C-NMR (D_2O) δ 57.6, 57.7, 62.0, 69.3, 70.7, 71.5, 130.0, 131.0, 131.5 (2C overlapped). Anal. Calcd for $C_{12}H_{18}NO_3Cl$: C, 55.49; H, 6.99; N, 5.39. Found: C, 55.59; H, 7.22; N, 5.33.

*3.9. 1,4-Dideoxy-1,4-imino-D-ribitol hydrochloride (DRB, **1**) [14].* A mixture of compound **9** (250 mg) and 10% Pd/C (63 mg) in H_2O (20 mL) was stirred at room temperature overnight under an atmospheric pressure of hydrogen. After removal of the catalyst with the use of Hyflo Super-Cel, the mixture was washed with $CHCl_3$ and concentrated to give a quantitative yield of the compound **1** (162 mg) as a brown solid. An analytical sample was obtained by recrystallization from a mixture of EtOH and acetone. Colorless powder, mp 124–126°C (lit [14], mp 128–132°C). $[\alpha]_D^{25}$ +57.7 (*c* 0.14, H_2O) (lit [14], $[\alpha]_D^{25}$ +57.6 (*c* 0.59, H_2O)). ^{1}H-NMR (D_2O) δ 3.37 (dd, *J* = 13 and 2 Hz, 1H), 3.49 (dd, *J* = 13 and 4 Hz, 2H), 3.63 (ddd, *J* = 9, 6, and 3 Hz, 1H), 3.83 (dd, *J* = 13 and 6 Hz, 1H), 3.97 (dd, *J* = 13 and 3 Hz, 1H), 4.21 (dd, *J* = 9 and 4 Hz, 1H), 4.38 (ddd, *J* = 4, 4, and 2 Hz, 1H). ^{13}C-NMR (D_2O) δ 50.2, 58.6, 62.4, 70.0, 71.8.

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