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, 1), 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.

2. Results and Discussion

The synthetic route to DRB is illustrated in Scheme 1. 2,3-O-Isopropylidene-D-ribo-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-ribo-1,4-lactone 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...
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 SN2 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 NaBH4 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 SN2 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 13C-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 (δH 7.26), HDO (δH 4.79), the central peak of deuteriochloroform (δC 77.0), or dioxane (δC 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-ribo-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 CH2Cl2 (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 CH2Cl2 (2 mL) was added dropwise at the same temperature, and the mixture was refluxed for 90 min. The cooled reaction mixture was diluted with CHCl3, washed with brine, and dried over MgSO4. After removal of the solvent, the residue was chromatographed on SiO2. 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. [α]D23 60.8 (c 1.00, CHCl3). 1H-NMR (CDCl3) 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
and 2 Hz, 1H), 4.89 (d, J = 6 Hz, 1H). 13C-NMR (CDCl3) 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 MgSO4 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). [α]D25 = -88.0 (c 0.50, acetone) (lit [18], [α]D25 = -89.0 (c 1.00, acetone)). 1H-NMR (CDCl3) 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 (ddd, 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). 13C-NMR (CDCl3) δ 25.7, 26.6, 60.8, 76.1, 76.2, 79.1, 114.5, 173.5.

3.4. 5-O-tert-butylmethylsilyl-2,3-O-isopropylidene-L-lyxono-1,4-lactone (5) [24]. A solution of compound 4 (193 mg), tert-BuMe3SiCl (166 mg, 1.10 mmol), and imidazole (102 mg, 1.50 mmol) in CH2Cl2 (3 mL) was stirred at room temperature for 1h. The reaction mixture was then diluted with CHCl3, washed with brine, and dried over MgSO4. After removal of the solvent, the residue was chromatographed on SiO2. 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 64-65°C (data for enantiomer [25]: mp 67-68°C). [α]D25 = +9.3 (c 1.02, CHCl3) (data for enantiomer [25]: [α]D25 = +9.2 (c 0.08, CHCl3)). 1H-NMR (CDCl3) 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). 13C-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.

3.5. 5-O-tert-butylmethylsilyl-2,3-O-isopropylidene-L-lyxitol (6) [24]. NaBH4 (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 1h. After removal of the solvent, the residue was diluted with CHCl3, washed with saturated aqueous NaHCO3, dried over MgSO4, 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). [α]D25 = +9.3 (c 1.02, CHCl3) (data for enantiomer [25]: [α]D25 = +9.2 (c 0.08, CHCl3)). 1H-NMR (CDCl3) 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). 13C-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-butylmethylsilyl-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 1M HCl and saturated aqueous NaHCO3, dried over MgSO4, and concentrated under reduced pressure to give compound 7 (695 mg, 1.50 mmol, 85%) as a colorless oil. [α]D26 = -5.5 (c 1.02, CHCl3) (data for enantiomer [25]: [α]D25 = +5.0 (c 0.14, CHCl3)). 1H-NMR (CDCl3) 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). 13C-NMR (CDCl3) 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-tet-butylmethylsilyl-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 CHC\textsubscript{3}, successively washed with water and saturated aqueous NaHCO\textsubscript{3}, and dried over MgSO\textsubscript{4}. After removal of the solvent, the residue was chromatographed on SiO\textsubscript{2}. Elution with a mixture of hexane and AcOEt (9/1) gave compound 8 (487 mg, 1.29 mmol, 86%) as a colorless oil. [α]27\textsuperscript{D} \textsuperscript{+} = -28.0 (c 1.01, CHCl\textsubscript{3}). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \delta 0.07 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.35 (s, 3H), 1.58 (s, 3H), 2.74 (dd, \textit{J} = 10 and 3 Hz, 1H), 3.03 (dd, \textit{J} = 4, 4, and 2 Hz, 1H), 3.12 (dd, \textit{J} = 10 and 6 Hz, 1H), 3.66 (dd, \textit{J} = 11 and 4 Hz, 1H), 3.74 (d, \textit{J} = 13 Hz, 1H), 3.79 (dd, \textit{J} = 11 and 4 Hz, 1H), 4.04 (d, \textit{J} = 13 Hz, 1H), 4.58 (dd, \textit{J} = 7 and 2 Hz, 1H), 4.67 (dd, \textit{J} = 7, 6, and 3 Hz, 1H), 7.15–7.38 (m, 5H). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \delta 5.6, –5.5, 18.2, 25.1, 25.9, 27.1, 56.9, 59.2, 63.1, 66.8, 79.4, 83.2, 111.8, 126.8, 128.2, 139.2.

3.74 (d, \textit{J} = 13 Hz, 1H), 3.68 (ddd, \textit{J} = 9, 6, and 3Hz, 1H), 3.83 (dd, \textit{J} = 13 and 3Hz, 1H), 0.09 (s, 3H), 0.92 (s, 9H), 1.35 (s, 3H), 1.58 (s, 3H), 2.74 (dd, \textit{J} = 10 and 3 Hz, 1H), 3.03 (dd, \textit{J} = 4, 4, and 2 Hz, 1H), 3.12 (dd, \textit{J} = 10 and 6 Hz, 1H), 3.66 (dd, \textit{J} = 11 and 4 Hz, 1H), 3.74 (d, \textit{J} = 13 Hz, 1H), 3.79 (dd, \textit{J} = 11 and 4 Hz, 1H), 4.04 (d, \textit{J} = 13 Hz, 1H), 4.58 (dd, \textit{J} = 7 and 2 Hz, 1H), 4.67 (dd, \textit{J} = 7, 6, and 3 Hz, 1H), 7.15–7.38 (m, 5H). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \delta 5.6, –5.5, 18.2, 25.1, 25.9, 27.1, 56.9, 59.2, 63.1, 66.8, 79.4, 83.2, 111.8, 126.8, 128.2, 139.2.

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