Research Article

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

Makoto Oba, Shoi Kawaji, Hironobu Kushima, Takanori Sano, and Kozaburo Nishiyama

Department of Materials Chemistry, Tokai University, 317 Nishino, Numazu, Shizuoka 410-0395, Japan

Correspondence should be addressed to Makoto Oba; moba@tokai-u.jp

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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 pyraetii*) [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

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.

3.2. 5-Chloro-5-deoxy-2,3-O-isopropylidene-D-ribo-1,4-lactone (3) [20, 23]. DMF was added (117 μ L, 110 mg, 1.51 mmol) to a solution of oxalyl chloride (129 μ L, 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. $[\alpha]_{\text{D}}^{23}$ –60.8 (c 1.00, CHCl_3). $^1\text{H-NMR}$ (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)). 1H -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*-BuMe₂SiCl (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, $CHCl_3$)). 1H -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]. 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 1 h. After removal of the solvent, the residue was diluted with $CHCl_3$, washed with saturated aqueous NaHCO₃, 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, $CHCl_3$)). 1H -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 ($CDCl_3$) 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 NaHCO₃, 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, $CHCl_3$)). 1H -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 μ L, 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. $[\alpha]_{\text{D}}^{27} -28.0$ (c 1.01, CHCl_3). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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. $[\alpha]_{\text{D}}^{23} +16.9$ (c 1.00, H_2O). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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 $\text{C}_{12}\text{H}_{18}\text{NO}_3\text{Cl}$: 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). $[\alpha]_{\text{D}}^{25} +57.7$ (c 0.14, H_2O) (lit [14], $[\alpha]_{\text{D}}^{25} +57.6$ (c 0.59, H_2O)). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (D_2O) δ 50.2, 58.6, 62.4, 70.0, 71.8.

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