A Practical Synthesis of L-Ribose

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L-Ribose was synthesized by a simple four-step method with overall yield of 76.3% from a protected L-arabinose derivative, which is a compatible intermediate for the synthesis of L-deoxyribose. The key step of this strategy is the Swern oxidation and subsequent stereoselective reduction accompanied by inversion of the 2-hydroxy group of protected L-arabinose.

Key words mirror image; L-ribose; L-RNA; L-nucleoside

L-Nucleic acids are attractive molecules as diagnostic and therapeutic agents as well as probes for nucleic acid–ligand interactions,[1,2] due to their unusual interaction with biomolecules.[3—11] For instance, several nucleoside derivatives composed of L-sugars have been shown to have antiviral activity superior to their D-enantiomers.[12—14] In addition, *ent*-aptamers are a potential candidate for therapeutic applications with prolonged stability under physiological conditions.[15—17] L-Ribose is a key intermediate for the synthesis of L-ribonucleosides and L-oligoribonucleotides, For this purpose, some methods for the conversion of L-arabinose,[18—21] D-glucose,[9] L-xylose,[18,22,23] D-galactose[24] and D-ribose[25] into the L-ribose derivatives have been reported. Ikegami and coworkers also reported an excellent method for the syntheses of L-sugars from D-sugar lactones.[26] However, these methods have some drawbacks such as low overall yields, the need for an expensive starting material, many reaction steps and difficulty for large-scale synthesis. Here, we report a simple, short-step synthesis of L-ribose from L-arabinose. This strategy utilizes the key intermediate for the synthesis of L-deoxyribose[7] as a starting material, and therefore is a compatible method for the syntheses of both L-ribonucleosides and L-deoxyribonucleosides.

Results and Discussion

Our synthetic strategy is summarized in Chart 1. We have already reported that methyl 3,4-*O*-isopropylidene-β-L-arabinoside (**2**) can be easily synthesized from L-arabinose in an easy and highly efficient manner.[7] The compound (**2**) was subjected to Swern oxidation followed by reduction with $NaBH_4$ in EtOH at 0 °C. Although the product showed a single spot on TLC, the reduction was not highly stereoselective and gave the ribo derivative (**4**) and arabino derivative (**2**) in a ratio of 4 : 1 as estimated by ^{1}H-NMR spectra. Therefore, we tested some other reducing reagents to improve the stereoselectivety. The results are summarized in Table 1. The best results were obtained with $LiAlH_4$ and $LiAlH(OtBu)_3$, which are even similar to those with the $NaBH_4$ conditions. The use of the bulky reagents L-Selectride, $NaBH(OAc)_3$ and $NaBH(OCH_3)_3$ significantly decreased the selectivity. The selectivity thus may be controlled not sterically but electrostatically. The separation of the ribo derivative (**4**) from the arabino derivative (**2**) could not be achieved at this stage. However, after deprotection of the isopropylidene group with 80% AcOH, methyl β-L-ribopyranoside (**5**) and undesirable **1** could be readily separated by silica gel column chromatography to give pure **5** with 64.7% yield from **2**. With recovered

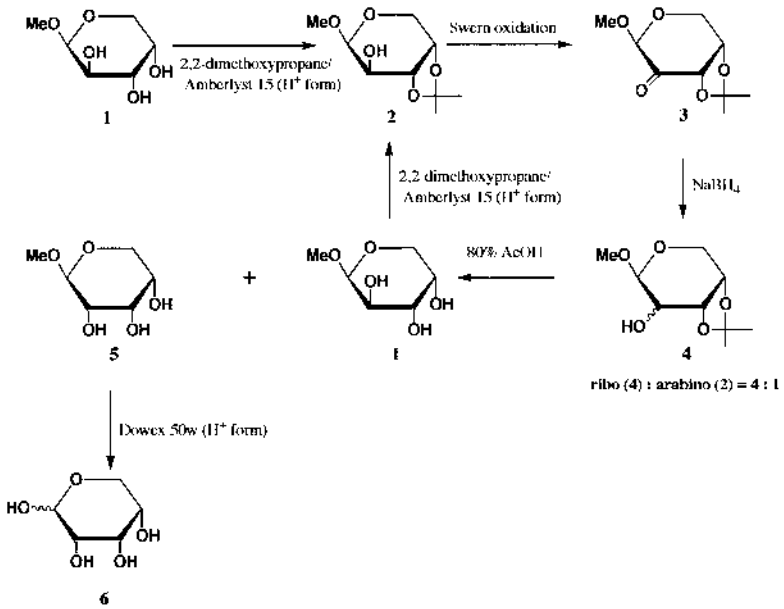

Chart 1

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Table 1. Stereoselectivities for the Reduction of **3**[a)]

Run	Reducing agent	Solvent	Temp. (°C)	Time (h)	Yield (%)[a)]	**1** : **5**[b)]
1	$NaBH_4$	EtOH	0→r.t.[c)]	0.5	92.6	1 : 4.0
2	$NaBH_4$	EtOH	−20	1	93.6	1 : 3.3
3	L-Selectride	THF	−78	1	96.3	1 : 0.8
4	L-Selectride	THF	r.t.	1	79.2	1 : 0.8
5	$LiAlH_4$	Et_2O	r.t.	2	73.4	1 : 4.0
6	$NaBH(OMe)_3$	EtOH	r.t.	0.5	98.5	1 : 1.8
7	$NaBH(OMe)_3$	EtOH	−20	0.5	88.6	1 : 2.0
8	$NaBH(OAc)_3$	EtOH	r.t.	1.5	Quant.	1 : 0.8
9	$LiAl[O\text{-}tert\text{-}Bu)_3]_3H$	THF	0	0.5	82.6	1 : 4.0

a) Isolated yields of a mixture of **1** and **5**. *b*) Ratios of **1** and **5** were estimated by ^{1}H-NMR spectra. *c*) r.t., room temperature.

1, the reactions were conducted again to give an additional 11.6% of **5** and the overall yield of **5** from **2** was 76.3%. Deprotection of the anomeric position of **5** was conducted first by treatment with 0.8 M HCl. Neutralization of the reaction mixture with an anion exchange resin (OH^- form) gave L-ribose with relatively lower yields and reproducibility. Therefore, we conducted the reaction using the Dowex 50w cation exchange resin (H^+ form) as an acid catalyst. After filtration of the resin, L-ribose was obtained quantitatively without any laborious purification steps.

In conclusion, we synthesized L-ribose from compound (**2**) in four steps with 76.3% overall yield. This synthetic strategy requires only four reaction steps and only one silica gel chromatographic purification step with moderate overall yield. Compound **2** is a common key intermediate for the syntheses of both L-ribose and L-deoxyribose,[7)] since we have already reported the synthesis of L-deoxynucleosides *via* this compound. This method would be a useful and practical synthetic approach to mirror image nucleic acids.

Experimental

Melting points were measured on a Yanagimoto apparatus and are uncorrected. ^{1}H-NMR spectra were obtained by a Varian gemini-200 or a Varian XL-300 spectrometer. Chemical shifts were measured relative to internal tetramethylsilane for $CDCl_3$ or internal *tert*-butyl alcohol, 1.23 ppm from sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for D_2O. Specific rotations were measured by a JASCO DIP-1000 digital polarimeter. Thin-layer and column chromatography were carried out on Merck coated plates $60F_{254}$ and silica gel 60N. Methyl β-L-arabinopyranoside was synthesized from L-arabinose according to a literature procedure for corresponding D-isomer.[27)]

Methyl 3,4-*O*-Isopropylidene-β-L-arabinopyranoside (2) To the mixture of methyl β-L-arabinopyranoside **1** (16.4 g, 100 mmol) and 2,2-dimethoxypropane (38.6 ml, 300 mmol) in dry dimethylformamide (DMF) (130 ml) was added Amberlyst 15 (1 g, H^+ form) and the whole was stirred at room temperature for 18 h. After filtration of the resin, the solvent was evaporated and the residue was coevaporated with *m*-xylene to give sufficiently pure colorless syrup of **2**. (23.04 g, quant.): ^{1}H-NMR ($CDCl_3$) δ: 1.36, 1.53 (3H each, 2s), 2.43 (1H, br), 3.44 (3H, s), 3.78 (1H, m), 3.93, 3.94 (2H, 2s), 4.15—25 (2H, m), 4.71 (1H, d, J=3.5 Hz). MS (secondary ion (SI)-MS) *m*/*z*: 205 (M^++1). High resolution (HR)-MS *m*/*z*: 205.1093 (Calcd for $C_9H_{17}O_5$: 205.1075).

Methyl 3,5-*O*-Isopropylidene-β-L-*threo*-pentopyranosid-2-ulose (3) Oxalyl chloride (13.23 ml, 151.6 mmol) dissolved in dry dichloromethane (350 ml) was placed in a 3-neck flask equipped with a thermometer and a dropping funnel under Ar atmosphere. The contents of the flask were cooled to −60 °C and a solution of DMSO (23.4 ml, 331 mmol) in dry dichloromethane (138 ml) was added dropwise over 15 min. Stirring was continued at −60 °C for 10 min, then a solution of **2** (28 g, 137 mmol) in dry dichloromethane (138 ml) was added dropwise into the flask for 15 min. The reaction mixture was stirred for 15 min, and triethylamine (95.9 ml, 689 mmol) was added over 10 min with stirring at −60 °C. The cooling bath was removed and distilled water was added at room temperature. Stirring was continued for 10 min and the organic layer was separated. The aqueous layer was re-extracted several times, and the organic layers were combined, dried with Na_2SO_4 and evaporated to give a pale brown crystalline solid of **3** (33.76 g, quant.). An analytical sample was recrystallized from chloroform–*n*-hexane to afford colorless crystals of **3**, mp 102—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39, 1.46 (3H each, 2s), 3.49 (3H, s), 4.08 (1H, ddd, J=13.5, 0.9, 0.7 Hz), 4.23 (1H, ddd, J=13.5, 2.0, 0.5 Hz), 4.54 (1H, m), 4.68 (1H, d, J=5.7 Hz), 4.70 (1H, s). MS (electron impact (EI)) *m*/*z*: 203 (M^++1). HR-MS *m*/*z*: 203.0917 (Calcd for $C_9H_{15}O_5$: 203.0919).

Methyl β-L-Ribopyranoside (5) To a stirred solution of the above residue of **3** (137 mmol) in EtOH (800 ml), $NaBH_4$ (4.42 g, 117 mmol) was added portionwise at 0 °C. After stirring at room temperature for 30 min, the solvent was evaporated. The residue was extracted with chloroform and washed with distilled water. The organic layer was dried with Na_2SO_4 and concentrated to give yellowish syrup of a mixture of **4** and **2**. This mixture was then treated with 80% AcOH (400 ml) and stirred overnight. The solvent was evaporated, and the residue was coevaporated with toluene three times. The residue was purified with silica gel column chromatography to give a colorless crystalline solid of **5** (14.55 g, 64.7%). Recovered **1** was subjected to the same reactions to give another crop of **5** (2.61 g, 11.6%). ^{1}H-NMR (D_2O) δ: 3.46 (3H, s), 3.60 (1H, dd, J=5.3, 3.2 Hz), 3.69 (1H, dd, J=11.8, 6.9 Hz), 3.82 (1H, dd, J=11.8, 3.4 Hz), 3.87 (1H, m), 4.00 (1H, dd, J=3.2, 3.2 Hz), 4.66 (1H, d, J=5.3 Hz). MS (SI-MS) *m*/*z*: 165 (M^++1). HR-MS *m*/*z*: 165.0770 (Calcd for $C_6H_{13}O_5$: 165.0762); *Anal.* Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.76; H, 7.33.

L-Ribose (6) To a stirred solution of **5** (2.51 g, 15.3 mmol) in distilled water (110 ml) was added 15 ml of Dowex 50w X4 resin (H^+ form) and heated at 90 °C for 17 h. After cooling, the resin was removed by filtration and the solution was concentrated. The residue was coevaporated with EtOH several times to give colorless syrup of **6** (2.59 g, quant.). An analytical sample was recrystallized from EtOH to afford colorless crystals of **6**, mp 86 °C. $[\alpha]_D^{25}$=+20.0° (c=2.0, H_2O); the corresponding D-isomer, $[\alpha]_D^{25}$=−19.7° (c=2.0, H_2O). The ^{1}H-NMR spectrum and SI-MS of **6** completely coincided with those of the corresponding D-isomer. *Anal.* Calcd for $C_5H_{10}O_5$: C, 40.00; H, 6.71. Found: C, 39.93; H, 6.72.

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