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One-pot inversion of D-mannono-1,4-lactone for the practical synthesis of L-ribose

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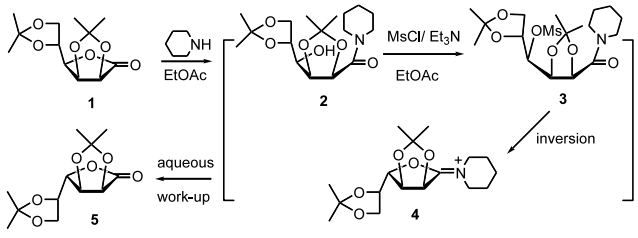
Abstract—L-Ribose was synthesized in a concise manner from D-mannono-1,4-lactone using one-pot inversion conditions. Treatment of D-mannono-1,4-lactone with piperidine, followed by mesylation-induced S_N2-type *O*-alkylation, afforded the desired one-pot inversion in an optimum yield, and the following straightforward transformations provided L-ribose in good yields.

Recently, L-carbohydrates have been increasingly used in medicinal and cosmetic applications.[1] In particular, a number of nucleosides derived from L-sugars have shown very potent antiviral activity and several oligonucleotides using L-nucleosides have shown potential antisense activity.[2] Therefore, it has become necessary to find a practical way to synthesize L-sugars. For example, the synthesis of L-ribose has been an attractive target.[3] As a part of our interest in finding an economical method for the molecule, we tried to develop a practical cyclization way using S_N2-type reaction from natural D-sugars. Herein, we report a concise way of synthesizing L-ribose from D-mannono-1,4-lactone.

In a recent paper, the Ikegami group reported the application of intramolecular *O*-alkylation of a γ-hydoxamate intermediate derived from the same D-mannono-1,4-lactone for the preparation of L-ribose.[3a] Although the cyclization reaction on the basis of Mitsunobu condition was efficient, the use of expensive reagents such as DEAD and the removal of by-products such as phosphine oxide would be a nuisance. Therefore, we hoped to suggest a more practical route, an inversion condition via stepwise opening lactone and mesylation followed by in situ S_N2-type *O*-alkylation in one pot. After the reaction sequence, aqueous work-up was expected to be enough for the hydrolysis. This *O*-alkylation mechanism involving the amide must be similar to that described for the displacement of triflate by dimethylforamide[4] (Scheme 1).



Scheme 1.

First, we tried to find the optimum conditions for converting 2,3,5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone **1** into intermediate **5**. For the first ring-opening aminolysis step, 2 equiv. of piperidine were found to open the γ-lactone smoothly under mild conditions to liberate the hydroxyl group, and intermediate **2** was reacted with methanesulfonyl chloride under triethylamine to afford mesylate **3**, and in situ attack of the carbonyl group furnished the desired inverted stereochemistry, yielding L-gluno-1,4-lactone in 85% yield after aqueous work-up and silica-gel column chromatography.[5] We found that elimination by-products were quite minor and an S_N1-type pathway could be ignored because a negligible amount of starting material was recovered after the quantitative opening of **1**. Intramolecular attack of the piperidine amide seemed to be quite fast and mild. Use of primary amine, such as benzylamine, under various conditions, did not furnish compound **5** at all, though the first aminolysis proceeded.[6]

Keywords: L-ribose; inversion; D-mannono-1,4-lactone.
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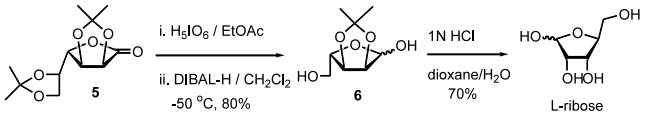
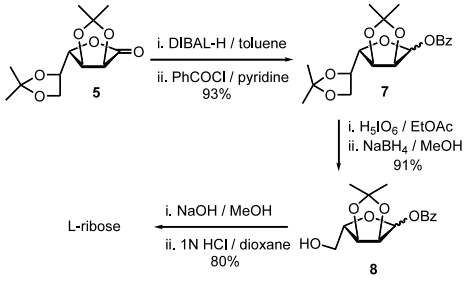


Scheme 2.



Scheme 3.

Having obtained compound **5**, we attempted to convert **5** to L-ribose in a new concise manner. Treatment of **5** with H_5IO_6 afforded partial hydrolysis to a diol intermediate and cleavage to aldehyde.[3c] Both functional groups, aldehyde and lactone in the crude product, were readily reduced to alcohol and hemiacetal with 2 equiv. of DIBAL-H to provide **6** in 80% yield. Finally, acidic hydrolysis deprotected the isopropylidene group to afford L-ribose in 70% yield (Scheme 2).

Although the route described above yielded L-ribose in good yields, total 48% from **1**, we wanted to suggest an alternative way. Reduction of **5** with DIBAL-H yielded a mixture which was converted to compound **7** with benzoyl chloride in pyridine in 93% yield, and partial hydrolysis of **7** with H_5IO_6, followed by reduction, afforded compound **8** as a mixture in 91% yield. Finally, hydrolysis with base followed by acid provided L-ribose in 80% yield (Scheme 3).

In conclusion, we have suggested an efficient and practical route to L-ribose by developing one-pot inversion conditions of D-mannono-1,4-lactone. This is the first application of the in situ S_N2-type cyclization for the synthesis of an L-furanose. The process for large-scale production of L-ribose is being developed, and further application of this type of reaction towards the related L-sugars is currently under study.

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5. *Experimental procedure*: 2,3:5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone **1** (160 g, 0.62 mol) was dissolved in anhydrous EtOAc (or CH_2Cl_2, 320 mL) and then piperidine (123 mL, 1.24 mol) was added dropwise at 0°C. The mixture was stirred at room temperature for 4 h. After TLC revealed the completion of reaction, excess piperidine and solvent were removed by distillation under reduced pressure to obtain crude **2**. The reactants were dissolved again by adding EtOAc (or CH_2Cl_2, 1 L). Subsequently, triethylamine (Et_3N, 138 mL) and dimethylaminopyridine (1 g) were added under a nitrogen gas stream, and methanesulfonyl chloride (72 mL) was added dropwise at 0°C. After the addition, the temperature in the reaction vessel was raised to room temperature and the reaction was carried out at room temperature for about 5 h. After TLC revealed the completion of reaction, water was added to quench the reaction. The reaction mixture was extracted with EtOAc (or CH_2Cl_2, 1 L×3) from the aqueous layer. The organic layer was washed with 1% HCl solution, water, and brine. After filtration, the organic layer was dried over anhydrous magnesium sulfate to remove the moisture in the organic layer, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give compound **5** (136 g, yield 85%) as a white solid. Compound **2**: mp 110–111°C; $[\alpha]_D^{20} = -21.5$ ($CHCl_3$, $c = 1.00$); IR (KBr): ν_{max} 3393, 1630; ^1H NMR (500 MHz, $CDCl_3$): δ 4.99 (1H, d, $J = 6.7$ Hz), 4.47 (1H, d, $J = 6.7$ Hz), 4.08 (2H, m), 3.98 (2H, m), 3.67 (1H, m), 3.55 (1H, m), 3.42 (2H, m), 3.27 (1H, d, $J = 8.25$ Hz), 3.08 (bt, 1H). Compound **5**: mp 129–130°C; $[\alpha]_D^{20} = 42.0$ ($CHCl_3$, $c = 1.00$); IR (KBr): ν_{max} 1770; ^1H NMR (500 MHz, $CDCl_3$): δ 4.75 (1H, d, $J = 5.5$ Hz), 4.73 (1H, d, $J = 5.5$ Hz), 4.52 (1H, s), 4.24 (1H, dd, $J = 7.0$, 7.5 Hz), 4.09 (1H, dd, $J = 8.0$, 7.0 Hz), 3.95 (1H, dd, = 8.0, 7.5 Hz), 1.44 (3H, s), 1.35 (3H, s), 1.31 (3H, s), 1.29 (3H, s), 1.31 (3H, s), 1.29 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.08, 113.22, 110.50, 79.56, 78.42, 75.05, 74.97, 64.97, 26.67, 25.49, 25.41, 25.37. Anal. calcd for $C_{12}H_{18}O_6$: C, 55.81 H, 7.07. Found: C, 55.75 H, 7.12.
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