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Tetrahedron Letters 46 (2005) 5903–5905
Tetrahedron Letters

A highly efficient synthesis of unnatural L-sugars from D-ribose

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Received 11 May 2005; revised 19 June 2005; accepted 22 June 2005
Available online 7 July 2005

Abstract—A preparative and short synthesis of L-ribose and L-apiose was accomplished starting from D-ribose via stereoselective *cis*-dihydroxylation and *C*2-hydroxymethylation, respectively. These L-sugars can serve as versatile intermediates for the synthesis of L-nucleosides.

1. Introduction

Since the discovery of L-β-1,3-oxathiolanyl cytosine (Lamivudine, 3TC)[1] as anti-hepatitis B virus (HBV) drug, L-nucleosides have opened a new era for the development of new antiviral agents. As a result, L-FMAU has been found to be active against HBV and is now undergoing clinical trials.[2] L-2′,3′-Dideoxy-2′,3′-didehydro-5-fluorocytidine (L-Fd4C)[3] exhibited potent anti-HBV activity and is also in clinical trials. L-2′,3′-Dideoxycytidine (L-ddC) showed potent anti-HBV activity and its 5-fluorocytosine derivative exhibited potent antiviral activity against HIV-1 and HBV.[4] Recently, L-thymidine (L-dT) and L-2′-deoxycytidine (L-dC) were found to be active against HBV (Fig. 1).[5,6] The main advantage of these L-nucleosides is to show much less cytotoxicity than their counterparts, D-nucleosides, while maintaining antiviral activity.

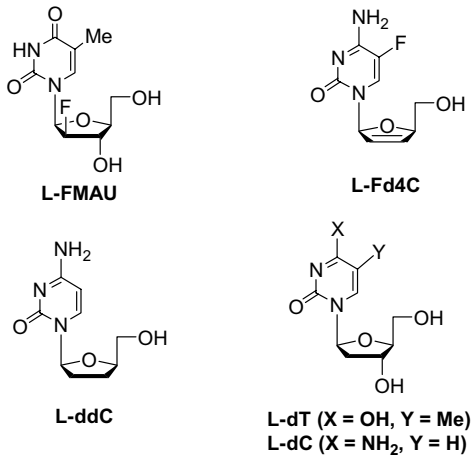

Figure 1. Antiviral active L-nucleosides.

Although all these nucleosides may be synthesized from L-ribose, L-ribose may not be used as a starting material because of high price, indicating that an efficient synthesis of L-ribose is highly desirable. Although several good synthetic routes to L-ribose have been reported from D-carbohydrates such as D-ribose,[7] D-glucose,[8] D-galactose,[9] and D-mannose,[10] we wanted to develop an alternative and practical synthetic methodology to L-ribose, which can be widely utilized for the synthesis of biologically active compounds including L-nucleosides.

On the other hand, L-apiose is also unnatural sugar which has been used for the development of biologically active materials.[11] However, L-apiose is also too expensive to be used for a starting material for the development of biologically active compounds. Thus, it was also of great interest to develop a preparative synthetic method of L-apiose since only a few synthetic methods[12] have been reported so far. Herein, we wish to describe

Keywords: L-Ribose; L-Apiose; *cis*-Dihydroxylation; Hydroxymethylation.
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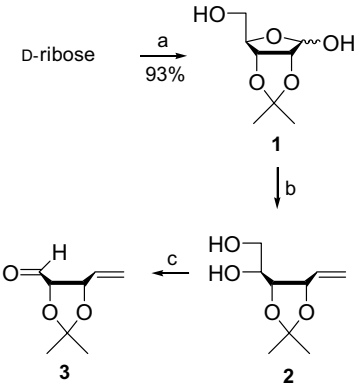
doi:10.1016/j.tetlet.2005.06.117

an efficient and practical synthesis of L-sugars from D-ribose.

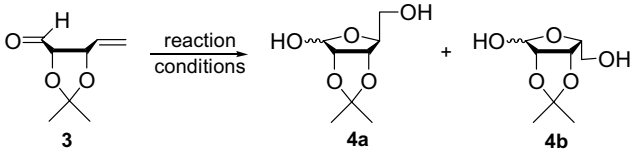
2. Results and discussion

As shown in Scheme 1, the preparative synthesis of L-ribose started from D-ribose. D-Ribose was converted to its 2,3-acetonide **1**[13] by the conventional method. Treatment of **1** with methyltriphenylphosphonium bromide in the presence of potassium *t*-butoxide afforded vinyl diol **2**. Oxidative cleavage of **2** with sodium metaperiodate produced highly volatile vinyl aldehyde **3**,[13] which was a good substrate for *cis*-dihydroxylation.

As shown in Scheme 2, several dihydroxylation reactions on vinyl aldehyde **3** were attempted to achieve the desired stereoselectivity for the L-ribo configuration. First, aldehyde **3** was reacted with osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO) to give 2,3-*O*-isopropylidene-L-ribose (**4a**, 56.4% from **1**) and 2,3-*O*-isopropylidene-D-lyxose (**4b**, 9.4% from **1**) in 6:1 ratio after the separation by silica gel column chromatography. Stereoselectivity obtained in this reaction is attributed to forming the osmylate in the opposite direction to the bulky 2,3-isopropylidene group. In order to increase the formation of **4a**, asymmetric dihydroxylations using AD-mix α and AD-mix β were employed.

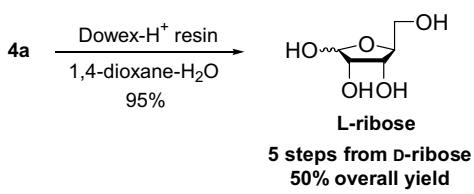


Scheme 1. Synthesis of the key intermediate. Reagents and conditions: (a) acetone, *c*-H_2SO_4, rt, 2.5 h; (b) Ph_3PCH_3Br, K-*t*-OBu, THF, rt, 15 h; (c) $NaIO_4$, H_2O, CH_2Cl_2, rt, 15 min.



reaction conditions	(4a : 4b)[a]
OsO_4, NMO, H_2O	6.67 : 1
AD-mix α	6.25 : 1
AD-mix β	5.05 : 1

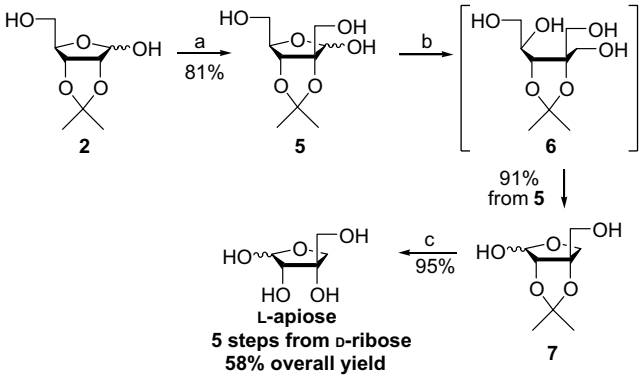
[a]Based on ^1H NMR



Scheme 2. Synthesis of L-ribose.

Another L-sugar, L-apiose was also synthesized from D-ribose, as shown in Scheme 3. Aldol condensation[14] of **2** using 35% formaldehyde and potassium carbonate gave 2-*C*-hydroxymethyl derivative **5** as a single stereoisomer in 81% yield. Reduction of **5** followed by oxidative cleavage with sodium metaperiodate afforded the protected L-apiose **7**. Finally, hydrolysis of **7** with acidic resin produced L-apiose in excellent yield.[12] L-Apiose was efficiently synthesized from D-ribose in five steps and 58% overall yield, using stereoselective hydroxymethylation as a key step.

In summary, we have accomplished the efficient and preparative synthesis of L-carbohydrates such as L-ribose and L-apiose, starting from D-ribose. Our synthetic method is regarded as one of the best procedures from the viewpoints of overall yields, number of steps, and



Scheme 3. Synthesis of L-apiose. Reagents and conditions: (a) 35% formaldehyde, K_2CO_3, CH_3OH, reflux, overnight; (b) (i) $NaBH_4$, CH_3OH, reflux, 1 h; (ii) 0.65 M $NaIO_4$, CH_2Cl_2, H_2O, 60 °C, 1 h; (c) Dowex-H^+resin, 1,4-dioxane–H_2O, 70 °C, 5 h.

mild reaction conditions and will be widely used for the synthesis of biologically active compounds including L-nucleosides.

Acknowledgements

This research was supported by the Grants from Korea Research Foundation (KRF-2003-042-E20111 and KRF-2002-042-E00111).

References and notes

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