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EFFICIENT SYNTHESES OF L-RIBOSE AND 2-DEOXY L-RIBOSE FROM D-RIBOSE AND L-ARABINOSE[1]

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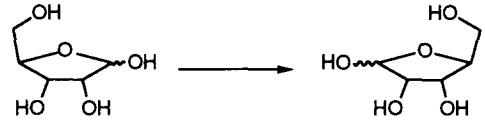
Summary: Interconversion of the ends of D-ribose **2** afforded in 6 steps and 45% overall yield L-ribose **1**, from which 2-deoxy L-ribose **12** was easily prepared. In addition, the inexpensive L-arabinose **13** was also converted into 2-deoxy L-ribose **12** via a reductive radical rearrangement of the arabinopyranosyl bromide **14**.

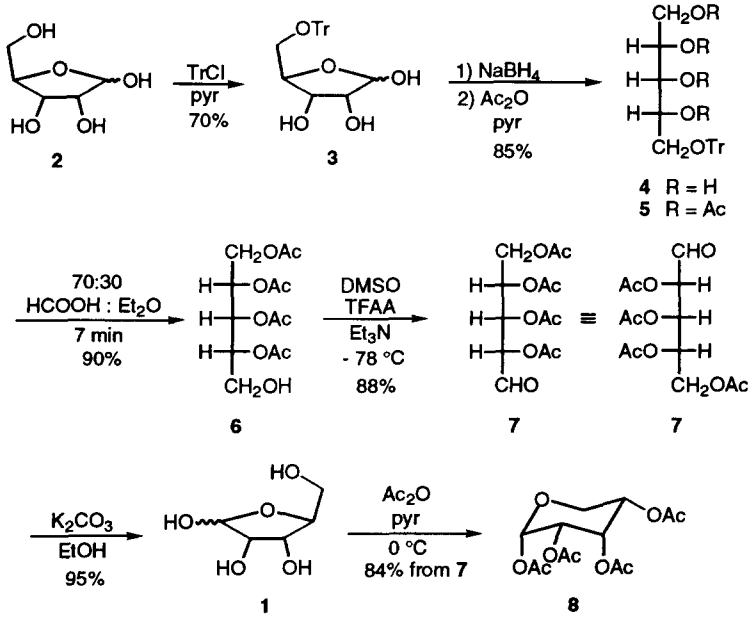
In the last few years, the use of L-carbohydrates and their derived nucleosides in medicinal applications has greatly increased. In particular, several modified nucleosides derived from L-sugars, e.g., L-5-fluoro-2',3'-dideoxycytidine and L-2',3'-dideoxycytidine (L-5FddC and L-ddC), have shown great potential as useful antiviral agents.[3] They possess good antiviral activity but greatly reduced toxicity. In addition, several antisense oligonucleotide therapy approaches utilize L-nucleosides, either normal (L-RNA) or 2'-deoxy (L-DNA) as materials to bind pieces of D-RNA.[4] We report herein an efficient 6-step synthesis of L-ribose **1** from readily available D-ribose **2**.



2 **1**

There are several syntheses of L-ribose **1** known.[5-7] The conversion of L-arabinose into L-ribose has been described[5] while other routes have also been reported.[6,7] The key observation in our synthetic planning was to realize that D-ribose **2** and L-ribose **1** differ only in the groups at C1 and C5, with C2, C3 and C4 being unchanged. Therefore conversion of **2** into **1** would require only the interconversion of the two end groups, namely oxidation of the hydroxymethyl to aldehyde and reduction of the aldehyde to a hydroxymethyl group.[8] This was accomplished in a straightforward manner as shown in Scheme 1. Selective conversion of D-ribose **2** into 5-*O*-trityl D-ribose **3** in 70% yield was already known.[9] Reduction of the aldehyde with sodium borohydride cleanly furnished the tetrol **4**. We attempted several direct oxidations of the trityl ether of **4** in the presence of the alcohols, e.g., hydride abstraction with trityl salts,[10] but these were generally unsuccessful. We therefore prepared the tetraacetate **5** by treatment of crude **4** with acetic anhydride and pyridine to give **5** in 85% yield from **3**. Hydrolysis of the trityl ether could be carried out in 90% yield by treatment of **5** with 7:3 formic acid:diethyl ether for 7 min at 25°C.[11]

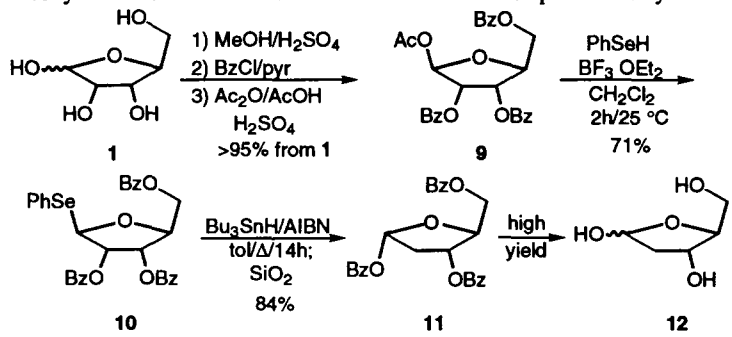
The alcohol **6** was isolated without any problems due to acetyl transfer. Several methods for oxidation of the hydroxymethyl group to aldehyde were studied but the Swern oxidation turned out to give the highest yields. Addition of the alcohol **6** to a mixture of DMSO and trifluoroacetic anhydride in dichloromethane followed by addition of Et_3N at -78°C furnished, after column chromatography, in 88% yield the aldehyde **7**, namely L-ribose 2, 3, 4, 5-tetraacetate. Thus this protected L-ribose derivative is available from D-ribose **2** in only five steps and 47% overall yield. L-Ribose **1** itself was prepared in 95% yield by basic hydrolysis of **7** using potassium carbonate in ethanol. In order to prove the structure of the L-ribose **1**, we carried out its peracetylation[12] to give the L-ribopyranose tetraacetate **8** in 84% overall yield from the aldehyde **7**. The optical rotation of **8** (+55.2 °) matched that of D-ribopyranose tetraacetate[12] but had the opposite sign, thus proving the structure and chirality of our synthetic material.[13] We have therefore shown that L-ribose **1** is available from D-ribose **2** in 6 steps in 45% overall yield.



Scheme 1

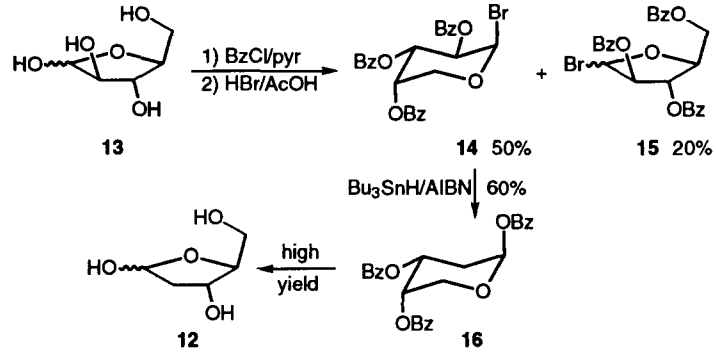
2-Deoxy-L-ribose **12** can also be prepared by an extension of this route (Scheme 2). Formation of methyl L-riboside followed by perbenzoylation and anomeric acetylation afforded the tetraester **9** in essentially quantitative yield over the three operations.[14] Treatment with phenylselenol and acid gave the β-seleno-phenyl ribopyranoside **10** in 71% yield after column chromatography. The method of Giese[15] was used to make the desired 2-deoxy carbohydrate, namely refluxing a solution of **10** with tributylstannane and AIBN furnished in 84% yield the tribenzoyl 2-deoxy-L-ribopyranoside **11** (mp 111-3 °C; for D-isomer lit. mp 110-112 °C[16], 111 °C[17], 102 °C[15]; $[\alpha]_D^{25}$ = -76 °; for D-isomer lit $[\alpha]_D^{25}$ = +75.3 °[16], +78.0 °[17], +77.3 °[15]). Basic hydrolysis of **11** is known to produce **12** in

high yield. Thus 2-deoxy L-ribose **12** is available from L-ribose in five steps and nearly 60% overall yield.



Scheme 2

Finally we have also developed a second, more efficient route to 2-deoxy L-ribose beginning with readily available L-arabinose, **13** (Scheme 3). Formation of the perbenzoate[18] and conversion to the anomeric bromide afforded the two isomers, the pyranosyl bromide **14**[19] in 50% yield and the furanosyl bromide **15**[20] in 20% yield after column chromatography. Reductive rearrangement of the pyranosyl bromide **14** under the conditions of Giese[15] gave the expected product **16** in 60% yield ($[\alpha]_D^{25}$ = +213 °, for D-isomer lit. $[\alpha]_D^{25}$ = -195 °[16]) which could be then hydrolyzed to 2-deoxy L-ribose **12** in good yield. Thus the inexpensive L-arabinose **13** can be converted into 2-deoxy L-ribose **12** in four steps and nearly 30% overall yield.



Scheme 3

We are currently examining the chemistry of the various intermediates in this synthetic sequence in order to determine if other molecules of importance to medicine can be prepared by this route.

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