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Synthesis and pharmaceutical application of L-ribose

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1. Introduction

Ribose exists in its D-form in nature and is a fundamental component in compounds that control various biological functions. In RNA, ribose forms a framework of chains and provides the base for the three-dimensional structure that transmits genetic information. Ribose is also contained in ATP and NADH, which have critical functions in metabolism. Many kinds of nucleoside analogues containing ribose have been developed as antiviral and anticancer agents by exploiting metabolic pathways. In this decade, the pharmaceutical industry has expanded its application of L-ribose (Fig. 1, **1**), which is the enantiomer of D-ribose. However, L-ribose is not found in nature and it must therefore be synthesized for pharmaceutical use. Simultaneous to an increase in clinical application, the synthetic technology of L-ribose has also progressed, and some companies have started to produce L-ribose on an industrial scale. This review summarizes the recent research of L-ribose in the therapeutic field and the technological progress made in its preparation.

2. Pharmaceutical application of L-ribose derivatives

L-Ribose has long been a focus of academic interest owing to the belief that stereospecificity prevents L-nucleosides from interacting with enzymes in living systems, as well as a limited availability of L-ribose as a starting material. Recently, due to the success of several drugs containing the L-sugar moiety and the greater availability of L-ribose, the clinical application of L-ribose derivatives has increased. In this section, examples of launched drugs or those in development containing L-ribose are described.

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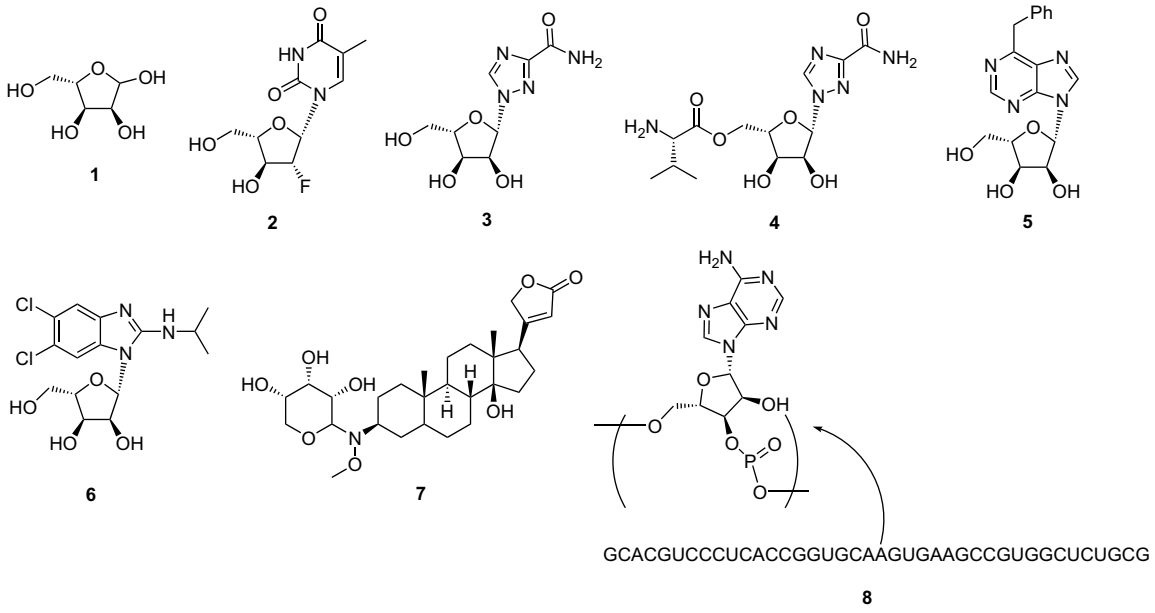


Figure 1. L-Ribose and pharmaceuticals derived from L-ribose.

2.1. L-Nucleosides as antiviral agents

Nucleoside-analogue antiviral agents inhibit the nucleoside synthesis–replication process of a virus by exploiting small differences in the nucleoside synthesis process between normal cells and virus cells. From this perspective, many nucleoside derivatives have been designed as antiviral agents. From the 1990s, nucleoside analogues, which bear a sugar moiety of the L-form (L-nucleoside), have received wide attention as antiviral drugs for hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV).[1]

Hepatitis B is one of the major diseases in the world. Of the 2 billion people who have been infected with HBV, more than 350 million have chronic (lifelong) infections, and the hepatitis B market is expected to reach $1 billion in sales value by 2010. Four drugs (lamivudine, entecavir, adefovir dipivoxil, and telbivudine) are currently approved for the treatment of HBV infection. Of these drugs, lamivudine (L-2′,3′-dideoxy-3′-thiacytidine) and telbivudine (1-(2-deoxy-β-L-ribofuranosyl)thymine) have an L-nucleoside structure. Chu prepared clevudine (2′-fluoro-5-methyl-β-L-arabinofuranosyluridine, L-FMAU) **2** from L-ribose and reported its effectiveness as an anti-HBV and anti-EBV drug in 1995.[2] The corresponding D-isomer (D-FMAU) also had anti-HBV activity; however, myelosuppression and neurotoxicity were obstacles to clinical trials. L-FMAU exhibited potent anti-HBV activity with excellent selectivity and few side effects. Clevudine has been developed worldwide as an anti-HBV agent (Bukwang Pharm, Korea; Eisai, China and India; and Pharmasset, North America), and was approved in Korea in 2007 as the first drug prepared from L-ribose. Chu also reported that clevudine has anti-HDV activity.[3]

HCV is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons have chronic HCV infection, and 3–4 million new infections occur each year. The current standard therapy for chronic hepatitis C is ribavirin (1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide)/interferon-α combination therapy; however, ribavirin has a known side effect (hemolytic anemia). Levovirin (1-(β-L-ribofuranosyl)-1,2,4-triazole-3-carboxamide) **3** is an L-enantiomer of ribavirin reported as an immunomodulator by Ramasamy et al. in 1998.[4] In 2000, Tam et al. reported that levovirin possessed anti-HCV activity and had a much better safety profile than ribavirin.[5] Roche had developed levovirin as a replacement for ribavirin in combination with pegylated interferon alfa-2a for the treatment of chronic hepatitis C. However, a limited absorption of levovirin resulted in relatively poor oral bioavailability in human clinical studies, and Roche therefore discontinued development of the drug during phase 2 trials in 2003. To improve oral bioavailability, Huang developed R1518 **4**, a valine ester prodrug of levovirin.[6] R1518 is currently under development in phase 1 studies at Roche.

Hocek et al. prepared a series of purine L-ribonucleosides bearing diverse *C*-substituents (alkyl, aryl, hetaryl, or hydroxymethyl) at the 6 position by Pd-catalyzed cross-coupling reactions of 6-chloro-9-(2,3,5-tri-*O*-acetyl-*b*-L-ribofuranosyl)purine followed by deprotection. Unlike their D-ribonucleoside enantiomers that possess strong cytostatic and anti-HCV activity, the L-ribonucleosides were inactive except for 6-benzylpurine nucleoside **5**, which shows moderate anti-HCV effect in a replicon assay.[7]

Cytomegalovirus (CMV) exists in approximately 50–60% of adults in Western Europe and the United States, and 70–90% of adults in Japan. The virus normally remains latent and does not pose a major health risk. However, CMV infection can result in serious complications in immunologically immature individuals, such as neonates, or in immunocompromised individuals, such as transplant recipients or people with AIDS. There are currently four approved drugs, ganciclovir, foscarnet, cidofovir, and valganciclovir. Treatment-limiting toxicities, such as bone marrow suppression (ganciclovir) and nephrotoxicity (foscarnet and cidofovir), are important disadvantages of these currently approved therapies. Koszalka reported that maribavir **6** (1*H*-β-L-ribofuranoside-2-isopropylamino-5,6-dichlorobenzimidazole) showed significantly higher potency in vitro, with low cytotoxicity and a unique mechanism of action against CMV.[8] Maribavir was originally developed at the University of Michigan and was licensed to GlaxoSmithKline in 1994. ViroPharma acquired worldwide rights, excluding Japan, to the drug candidate from GlaxoSmithKline in August 2003. In 2006, the compound received fast track designation from FDA for the prevention of CMV infection in allogeneic bone marrow and solid organ transplant patients. ViroPharma is currently conducting phase 3 studies of maribavir.

2.2. Glycoconjugates comprising L-ribose

Glycoconjugates is the general term used for natural compounds containing a sugar unit, such as a glycoprotein or a glycolipid. These compounds have important roles, for example, in providing a source of energy or as markers for cellular recognition. Among them, a cardiac glycoside (digoxin, digitoxin) extracted from the foxglove plant has long been used in the treatment of various heart conditions. Moreover, recently, digitoxin has been reported to exhibit anticancer properties in vitro. However, in comparison with nucleosides, modification of the attached sugars has not been fully explored owing to the difficulty in chemical transformation of the structure of the complex sugar moiety. Langenhan et al. reported that digitoxin analogues modified by L-ribose **7** (14-hydroxy-3β-[*N*-methoxy-*N*-(L-ribopyranosyl)amino]card-20(22)-enolide) exhibited cytotoxic potency toward human cancer cells and tumor specificity.[9]

2.3. Oligonucleotides comprising L-ribose

The early application of L-ribose in the field of oligonucleotides was used to investigate the structure of ribonucleic acid (RNA). The right-handed helix structure of RNA is derived from the chirality of D-ribose that composes the nucleotide chain. Therefore, a systematic comparison between RNA and its enantiomer derived from L-ribose gives clues to understand the origin of chemical evolution and the biological function of RNA. Visser et al. synthesized both enantiomers of RNA fragment CAAGG from D- and L-ribose, and found a strong association between pentanucleotide RNA strands whose monomers have opposite chirality.[10] Such association can amplify the chirality of RNA. Ashley reported that L-RNA can recognize natural RNA with high affinity and shows resistance to ribonucleases.[11] Eschenmoser investigated the self-templating oligomerization of RNA by using a racemic mixture of RNA strands derived from D- and L-ribose.[12]

Recently, oligonucleotides have been actively applied to various therapeutic areas, and now five categories (antisense, siRNA, ribozyme, aptamer, and decoy nucleic acid) of oligonucleotide drugs are in clinical research. However, oligonucleotides are easily decomposed by nucleases in the living body before reaching the diseased area. In order to overcome decomposition in vivo, oligonucleotide drugs usually employ various drug delivery system or chemical modifications to give properties of resistance against decomposition by nucleases. However, only two drugs, Vitravene (antisense) and Macugen (aptamer), are approved to date. Another way to stabilize oligonucleotides against nucleases is to prepare unnatural L-RNA oligonucleotides using L-ribose as the starting material.

The clinical possibility of L-RNA has been shown by aptamers, which are oligonucleotides derived from an in vitro evolution process called SELEX (systematic evolution of ligands by exponential enrichment). During the SELEX process, aptamers are evolved to bind small molecules or proteins associated with a number of disease states. Using this method, many powerful antagonists of such proteins have been found.[13] In 1996, Klusmann et al. developed the mirror SELEX process to identify L-RNA aptamers, which are now called 'spiegelmers' (German *spiegel*=mirror). Spiegelmers bind to natural amino acids or proteins, and show an extraordinary stability in human serum.[14] This result shows that the inversed chirality of L-ribose gives spiegelmers their high resistance to nucleases, while showing the same high binding affinity and specificity for natural amino acids or proteins, which are characteristics of aptamers. The German company NOXXON Pharma is developing spiegelmers as clinical candidates, including NOX-E36, a 40-mer spiegelmer targeting the chemokine MCP-1 that has potential for treating inflammatory diseases such as lupus nephritis, and NOX-A12 targeting the peptide SDF-1. Recently, Pfizer, Roche and Eli Lilly have entered into a global strategic alliance with NOXXON for the development of spiegelmer drugs.[15]

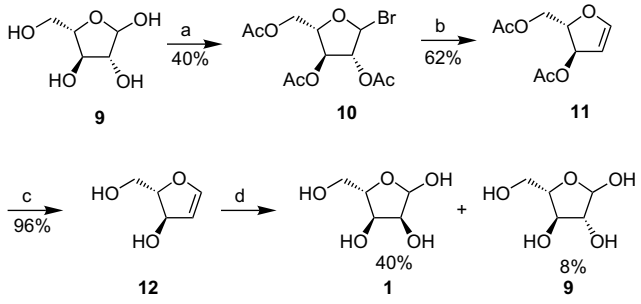
3. Preparation of L-ribose

Reports on the synthetic methods of L-ribose have increased due to the increasing demand for L-ribose in clinical applications.[16] The preparation of L-ribose is categorized into three methodologies: (1) chemical synthesis from sugars, (2) chemical synthesis from non-sugar compounds, and (3) biotransformation from sugars. In this section, the articles and patents regarding the preparation of L-ribose are reviewed.

3.1. Chemical synthesis from sugars

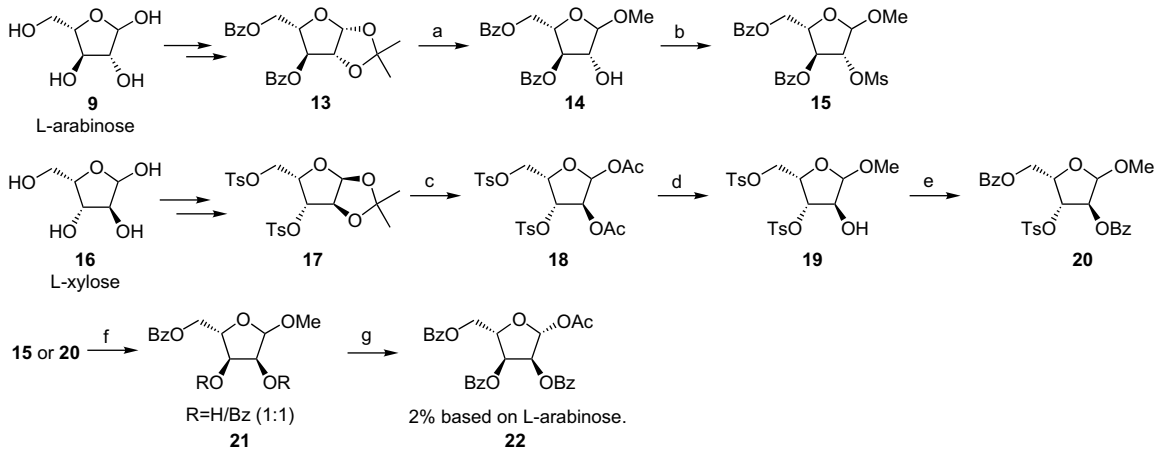
3.1.1. Chemical transformation from L-arabinose or L-xylose

L-Ribose has a partial common structure with various natural sugars and as such, many methodologies using sugars as the starting materials have been reported. The earliest attempts to synthesize L-ribose were by chemical transformations from natural L-aldopentoses, such as L-arabinose or L-xylose. These L-aldopentoses are epimers of L-ribose, and therefore inversion of the 2- or 3-hydroxyl group is employed as a synthetic strategy. L-Arabinose is found in nature as a component of biopolymers, such as hemicellulose and pectin. Austin and Humoller reported the first attempt of a synthetic approach to obtain L-ribose from L-arabinose **9** (Scheme 1).[17] Their strategy involved reductive elimination followed by oxidative addition of a hydroxyl group. Brominated acetyl L-arabinose **10** treated with zinc yielded L-arabinal **11**, followed by deprotection and dihydroxylation of olefin to produce a mixture of L-ribose and L-arabinose. From this mixture, crystalline L-ribose was isolated in 10% yield.



Scheme 1. 'Elimination–addition' approach from L-arabinose (source: Austin and Humoller[17]). Reagents: (a) AcOH, Br_2; (b) 50% AcOH, Zn; (c) NaOH; (d) benzoic peracid, EtOAc.

Acton et al. developed the synthetic route to protected L-ribose from L-arabinose and L-xylose by the 'nucleophilic inversion' approach (Scheme 2).[18] L-Arabinose was converted to 3,5-di-*O*-benzoyl-1,2-*O*-isopropylidene-L-arabinose **13** in 22.5% overall yield and refluxing with methanolic HCl afforded methyl furanoside **14**, which was converted to 2-*O*-mesylate **15**. Nucleophilic inversion of the 2-mesyl group of **15** by sodium benzoate gave monohydroxydibenzoate **21**; however, the reaction of **15** took 72 h to complete. Monohydroxydibenzoate **21** was benzoylated and acetolyzed to provide acetyl tribenzoyl L-ribose **22** (total yield based on L-arabinose: 2%). An improved yield of **19** was obtained when L-xylose **16** was used as the starting material. L-Xylose is another epimer of L-ribose and its availability was recently improved. Di-*O*-tosylate **17** was converted to the methyl α,β-furanoside **19**. Benzoylation of **19** afforded 2-*O*-benzoate **20**, followed by inversion with sodium benzoate to **21** in 6 h. The shorter reaction period, compared with **15**, was a reflection of the reactivity of each

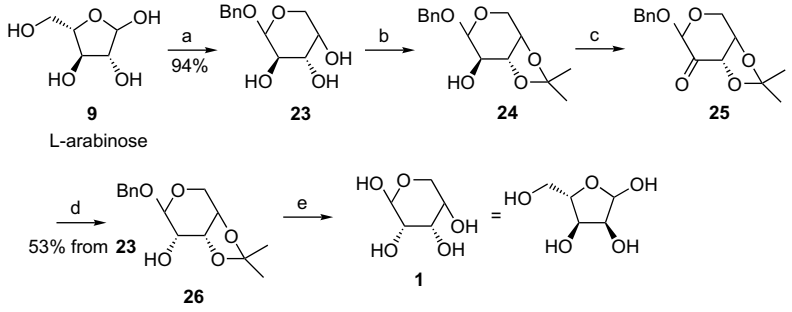


Scheme 2. 'Nucleophilic inversion' approach from L-arabinose or L-xylose (source: Acton et al.[18]). Reagents: (a) MeOH, HCl; (b) MsCl; (c) AcONa; (d) MeOH, HCl; (e) benzoylation; (f) BzONa, DMF; (g) benzoylation.

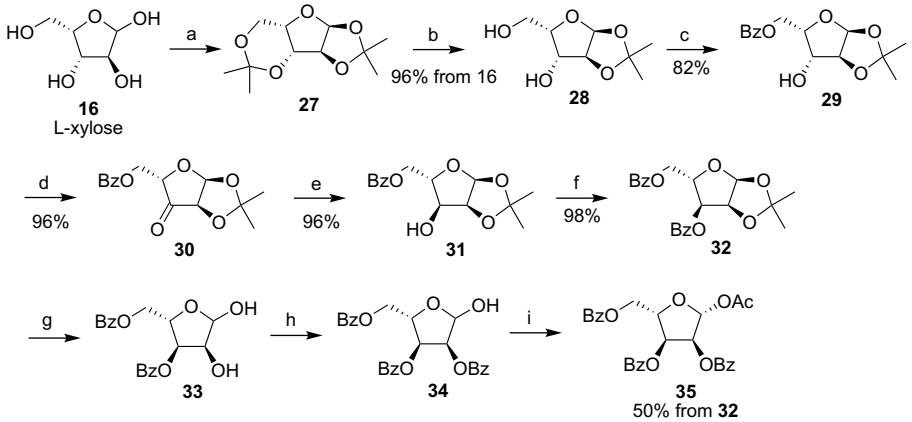
sulfonate. The inversion product was monohydroxydibenzoate **21**, and benzoylation and acetolysis afforded **22** in 12% yield based on L-xylose.

For the preparation of clevudine, Chu et al. prepared L-ribose by an 'oxidation–reduction' approach from L-arabinose (Scheme 3).[19] L-Arabinose **9** was treated with benzyl alcohol and HCl gas to give benzyl-β-L-arabinoside **23** in 94% yield, and 3- and 4-hydroxy groups were protected with dimethoxypropane in the presence of *p*-TsOH to yield benzyl 3,4-isopropylidene-β-L-arabinoside **24**. Compound **24** was subjected to oxidation with pyridinium dichromate (PDC) in refluxing dichloromethane, followed by reduction with sodium borohydride in methanol at 0 °C to give the key intermediate **26** in 53% yield over three steps. Compound **26** was deprotected by 4% trifluoroacetic acid to afford L-ribose. Akagi et al. improved this method using Swern oxidation instead of PDC at the oxidation step.[20]

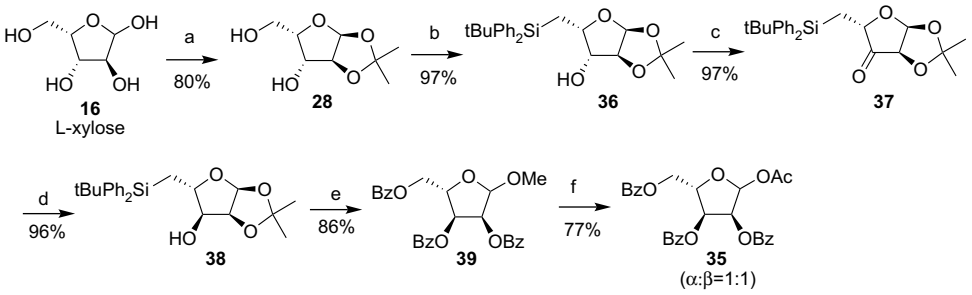
Chu et al. applied the same 'oxidation–reduction' approach to L-xylose (Scheme 4),[21] finding that pyridinium dichromate (PDC) gives the best yield (96%) for the oxidation of the 3-OH of L-xylose derivative **29**. The resulting ketone **30** was stereoselectively



Scheme 3. 'Oxidation–reduction' approach from L-arabinose (source: Chu et al.[19]). Reagents: (a) BnOH, HCl(g); b) DMP, *p*-TsOH; (c) PDC, CH_2Cl_2; (d) $NaBH_4$, MeOH; (e) 4% CH_3CO_2H.



Scheme 4. 'Oxidation–reduction' approach from L-xylose (source: Chu et al.[21]). Reagents:(a) $CuSO_4$, H_2SO_4, acetone; (b) 0.2% HCl/H_2O; (c) BzCl, pyridine, CH_2Cl_2, 0 °C, 1 h; (d) PDC, Ac_2O, CH_2Cl_2, reflux; (e) $NaBH_4$, EtOH, AcOEt; (f) BzCl, pyridine; (g) 1% HCl, CH_3OH; (h) BzCl, pyridine; (i) Ac_2O, AcOH, H_2SO_4.



Scheme 5. 'Oxidation–reduction' approach from L-xylose (source: Moyroud and Strazewski[22]). Reagents: (a) acetone, H_2SO_4; (b) *t*-$BuPh_2SiCl$, imidazole, DMF; (c) CrO_3, pyridine, CH_2Cl_2; (d) $LiAlH_4$, CH_2Cl_2; (e) MeOH, H_2SO_4, BzCl, pyridine; (f) Ac_2O, AcOH, H_2SO_4.

reduced by sodium borohydride to the desired L-ribose derivative **31** due to the stereoelectronic effect of the 1,2-*O*-isopropylidene group. The resulting protected L-ribose **35** was used as an intermediate for the synthesis of clevudine (Scheme 4).

Moyroud and Strazewski reported a similar route from L-xylose (Scheme 5).[22] The reduction step was performed with lithium aluminum hydride at −78 °C and led to the L-ribosyl derivative **38** in 96% yield. This derivative was deprotected and O-methylated at C-1 in one pot followed by O-benzoylation to obtain **35**, which could be used for glycosidation.

3.1.2. *Metal-catalyzed epimerization of L-arabinose*

The metal-catalyzed epimerization of aldoses was widely examined by Bilik, and is now known as the Bilik reaction. The advantage of this method is that inversion of the hydroxyl group proceeds without a protection step. There have been extensive studies on the metal-catalyzed epimerization of L-arabinose in aqueous media, and many groups have reported various methods for the preparation of L-ribose (Table 1). The original system reported by Bilik was the homogeneous reaction of L-arabinose with molybdic acid. L-Arabinose was heated in aqueous media containing molybdic acid to give a 2:1 mixture of L-arabinose and L-ribose. Most of the L-arabinose was separated by crystallization from MeOH and the resulting mixture was treated with a cation-exchange resin in barium form to give L-ribose in 26% yield.[23]

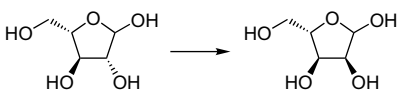
Two decades after his pioneering work, Bilik's reaction was noted again as a practical method for preparing L-ribose. For the scale up of the epimerization process, a fixed catalyst is required to avoid the separation step of the molybdenum ion. Arena et al. developed the fixed molybdate catalyst using an anion-exchange resin bearing a benzyltrimethylammonium group and used it for the continuous conversion of L-arabinose to L-ribose.[24] They treated Amberlite IRA-400 (strongly basic gel-type resin with quaternary ammonium functionality) with aqueous Na_2MoO_4 and the resulting molybdenum-containing resin was used for the continuous reaction. In 1992, Kubala and Burdatsova also used the molybdenum fixed anion-exchange resin and raised the yield by recycling recovered L-arabinose. He prepared 5.4 kg of L-ribose from 10 kg of L-arabinose; this was the first report on the preparation of L-ribose in kilogram scale.[25]

The strong acidity of molybdic acid often causes side reactions; therefore, various improvements of the catalyst system were reported by many groups in order to raise the selectivity of L-ribose. Abe et al. found that epimerization proceeds more rapidly when catalyzed by dioxobis(2,4-pentanedionato-*O*,*O*′)-molybdenum in DMF.[26] L-Arabinose gave an epimeric mixture containing L-ribose (36%), which was isolated in 46% yield as the anilide. This catalyst did not give significant amounts of side reaction products compared with molybdic acid. Ichikawa and Iwane discovered that the compounds of metals such as Ni, Co, Sr, Ca, and diamines, such as tetramethylethylenediamine, converted L-arabinose to L-ribose at a high rate of epimerization.[27] Tachibana reported that the combination of molybdic acid and bases such as pyridinemethanol also effectively improved the selectivity.[28] Ichikawa et al. additionally reported that sodium tungstate showed higher catalytic activity than molybdanate.[29]

The choice of counter cations of the ion-exchange resins, which are used in the separation of the epimerization mixture, is also important. Jumppanen et al. improved the separation efficiency, especially the separation from L-ribulose, by use of ion-exchange resin in Pb form instead of Ba form, and succeeded in obtaining high purity crystalline L-ribose.[30] Angyal also improved the yield of L-ribose by an ion-exchange resin in Nd form.[31] These epimerization technologies have a potential role in the industrial preparation of L-ribose; however, separation equipment using an ion-exchange resin and having a recovery step for the starting material is necessary.

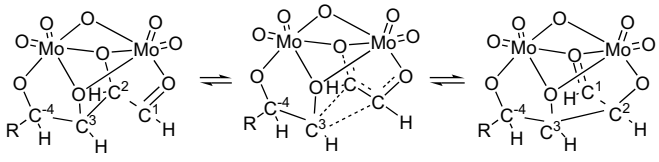
Barker et al. examined the mechanistic study of epimerization[32] by investigating the reaction mechanism of the molybdate-catalyzed C-2 epimerization of aldoses using ^{13}C- and ^{2}H-enriched compounds and ^{13}C NMR spectroscopy, and found that epimerization involves rearrangement of the carbon skeleton, including C-2 and C-3 of aldose, via a 1,2-endiol intermediate (Scheme 6).

Table 1
Metal-catalyzed epimerization of L-arabinose



Catalyst	Conditions	Yield (%)	Reference
H_2MoO_4	95 °C, 9 h	26	Bilik[23]
resin-CH_2N+Me_3MoO_4	95 °C, 12 h	25[a]	Arena et al.[24]
resin-CH_2N+Me_3MoO_4	95 °C, 5 h	54	Kubala and Burdatsova[25]
$MoO_2(acac)_2$	50 °C, 25 h	36[a]	Abe et al.[26]
$NiCl_2$/TMEDA	60 °C, 1 h	25	Ichikawa and Iwane[27]
MoO_3/3-pyridinepropanol	95 °C, 2 h	17	Tachibana[28]

[a] Epimerization ratio with L-arabinose.



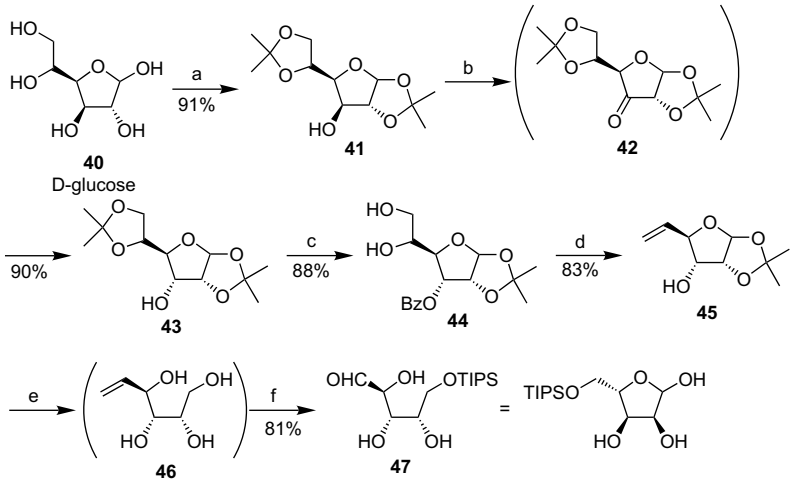
Scheme 6. Reaction mechanism of epimerization.

3.1.3. Transformation of other sugars

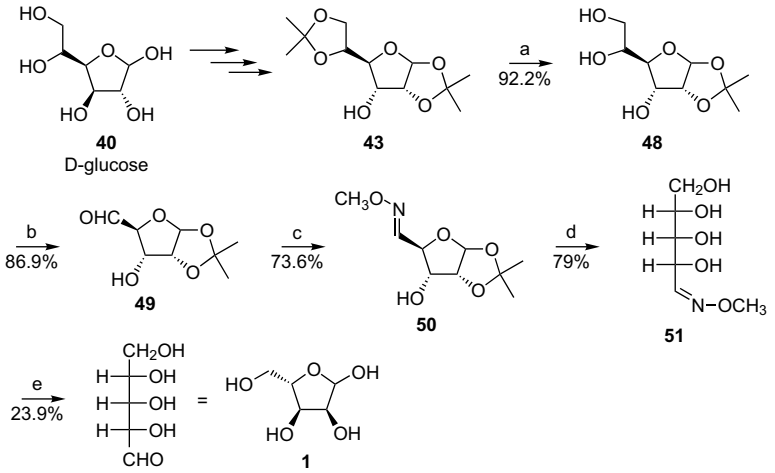
Several groups report that L-ribose can be synthesized from other available sugars. D-Glucose is one of the cheapest sugars available and is widely used as the starting material of unnatural sugars. Pitsch developed a synthetic route to L-ribose from D-glucose for the preparation of an oligoribonucleotide containing L-ribose (Scheme 7).[33] The inversion of 3-OH by the oxidation–reduction step and transformation of C-5 to the carbonyl group are the key steps. D-Glucose protected by the ketal group was oxidized by PDC and reduced by sodium borohydride to give 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose **43** selectively. Benzoylation and selective cleavage of the primary ketal group of **43** provided diol **44**. This diol was transformed to the corresponding di-*O*-mesylate, from which olefin **45** was obtained by treatment with NaI followed by debenzoylation. Acid-catalyzed hydrolysis of the remaining ketal group in **45**, followed by reduction of the resulting hemiacetal, yielded the hexenetetraol **46**, which was selectively *O*-triisopropylsilylated at the primary OH group. Ozonization of the resulting intermediate, followed by reductive workup and perbenzoylation, led to an α-L/β-L-mixture of the differentially protected L-ribose derivative **47** in an overall yield of 48% (based on D-glucose). Synthesis was carried out on a 0.1–0.5-mol scale and required only five purification steps. Qi et al. improved Pitsch's method by direct conversion of triol **48** to aldehyde **49**. Acid-catalyzed hydrolysis of the remaining ketal group in **50**, followed by reduction of the resulting hemiacetal, yielded L-ribose oxime **51**. Deprotection of **51** by titanium trichloride gave L-ribose **1** (Scheme 8).[34]

D-Galactose **52** has the same configuration at C-3 and C-4 as L-ribose, but they differ at C-2. Shi et al. employed a two-key-step strategy: chemoselective oxidative cleavage of the 5–6 diol of D-galactose, and then nucleophilic inversion of the 2-hydroxyl group. According to this strategy, Shi et al. prepared L-ribose from 1,2,5,6-di-*O*-isopropylidene-D-galactofranose **53** via nine steps (Scheme 9).[35] One carbon degradation of **52** and oxidation of the aldehyde followed by protection gave L-arabinose derivative **57**. Mesylation of **57** and acetolysis produced 1,5-diacetate **59**. Hydrolysis of **59** followed by inversion of the configuration of the 2-hydroxyl group via 1,2-epoxide intermediate **60** using NaOMe/MeOH gave protected L-ribose **61**.

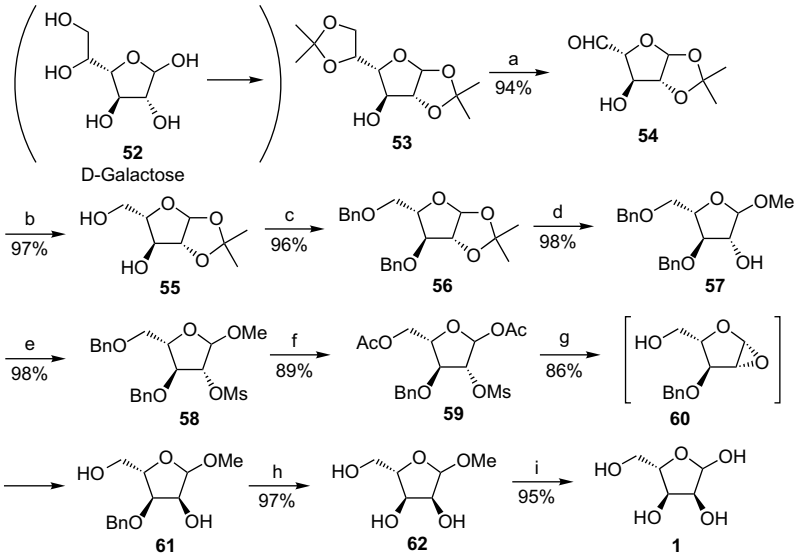
D-Ribose and L-ribose differ from each other only in the groups at C-1 and C-5, and those at C-2, C-3, and C-4 are unchanged. Therefore, L-ribose can be prepared by the interconversion of the ends of D-ribose. Based on this strategy, Jung and Xu prepared



Scheme 7. Preparation of protected L-ribose from D-glucose (source: Pitch[33]). Reagents: (a) acetone, $ZnCl_2$, H_3PO_4, rt; (b) (i) pyridinium dichromate, Ac_2O, CH_2Cl_2, 50 °C, 2 h; (ii) $NaBH_4$, H_2O/EtOH, rt, 2 h; (c) (i) BzCl, DMAP, pyridine, CH_2Cl_2, rt, 2 h; (ii) AcOH, HCO_2H, H_2O, rt, 1 h; (d) (i) MsCl, Et_3N, CH_2Cl_2, 4 °C, 20 min; (ii) NaI, pentan-3-one, 100 °C, 2.5 h; (iii) NaOH, MeOH, rt, 30 min; (e) (i) ion-exchange resin (H^+ form), H_2O/THF, 80 °C, 3.5 h; (ii) $NaBH_4$, H_2O, rt, 2 h; (f) (i) TIPS-Cl/1*H*-imidazole, DMF, rt, 2 h; (ii) O_3, MeOH, −78 °C, then Me_2S/MeOH, 4 °C, 14 h.

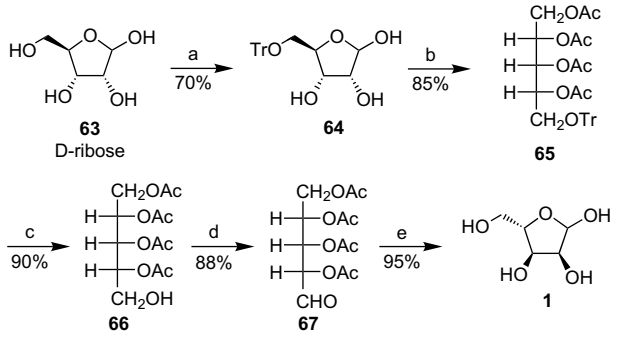


Scheme 8. Improved synthesis of L-ribose from D-glucose (source: Qi et al.[34]). Reagents: (a) dil. H_2SO_4; (b) $NaIO_4$, $NaHCO_3$; (c) CH_3ONH_2/HCl, CH_3ONa; (d) (1) 001X resin, (2) $NaBH_4$; (e) $TiCl_3$, THF.



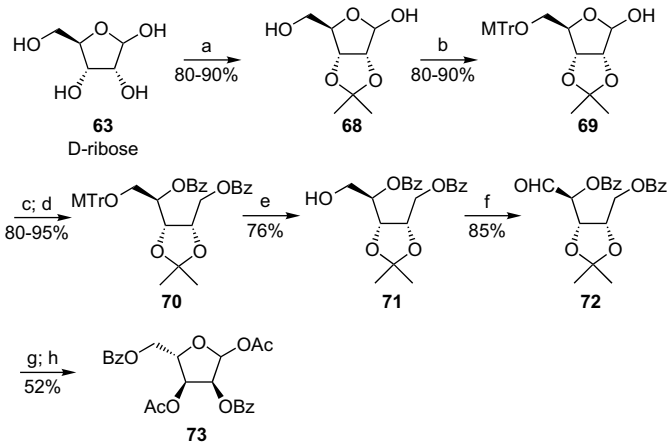
Scheme 9. Degradation and nucleophilic inversion from D-galactose (source: Shi et al.[35]). Reagents: (a) $NaIO_4/H_5IO_6$, EtOAc, rt, 5 h; (b) $NaBH_4$, MeOH, rt, 2 h; (c) KOH, BnCl, 1,4-dioxane, reflux, 2 h; (d) 10% HCl/MeOH, rt, 3 h; (e) MsCl, Et_3N, rt, overnight; (f) Ac_2O, AcOH, H_2SO_4, 4 °C, overnight; (g) NaOMe, MeOH, rt, 6 h; (h) 10% Pd/C, MeOH, H_2, 2 h; (i) Dowex-H^+, H_2O, 50 °C, 24 h.

L-ribose from D-ribose (Scheme 10).[36] Selective protection of the 5-hydroxyl group by trityl chloride gave 5-*O*-trityl-D-ribose **64** in 70% yield. Reduction of the aldehyde with sodium borohydride and acetylation of alcohol gave tetraacetate **65**. Hydrolysis of the trityl ether could be carried out in high yield by treatment with formic acid, and the resulting alcohol **66** was transformed to L-ribose tetraacetate **67** by Swern oxidation under cryogenic conditions. Finally, L-ribose was prepared by basic hydrolysis using potassium carbonate in six steps in 45% overall yield from D-ribose. Recently, Meng et al. reported that oxidation of tetraacetate could be carried out at room temperature using pyridinium chlorochromate.[37]



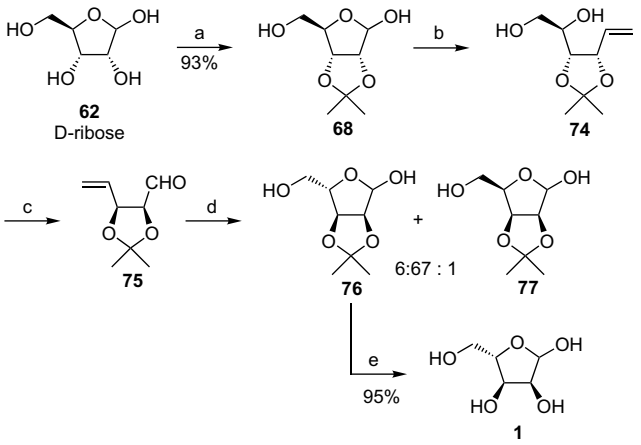
Scheme 10. Interconversion between C1 and C5 of D-ribose (source: Jung and Xu[36]). Reagents: (a) TrCl, pyridine; (b) $NaBH_4$, then Ac_2O, pyridine; (c) formic acid, Et_2O; (d) DMSO, TFAA, Et_3N, −78 °C; (e) K_2CO_3, EtOH.

Peracylated derivatives of ribofuranose are generally used as the starting materials for the synthesis of nucleosides. However, the synthetic preparation of peracylated derivatives comprises multiple steps (acetalization, acylation, and acetolysis), and requires careful control to reduce the by-product, especially at acetolysis. In order to avoid problems during acetolysis, Mikhailopulo et al. developed the synthesis of peracylated derivatives of β-L-ribofuranose from D-ribose (Scheme 11).[38] Conventional acetonide protection and p-monomethoxytritylation of D-ribose led to the respective 5-*O*-protected furanosides **69** in high yield. Reduction of carbonyl function, followed by acylation gave the fully blocked D-ribitol **70**. Detrytilation by aqueous acetic acid in THF, followed by silica gel chromatography gave **71**. Oxidation of the primary hydroxyl group of acylates **71** with PCC resulted in the corresponding aldehyde **72**. Deprotection of the 3,4-diol function of **72** with aqueous trifluoroacetic acid, followed by standard acetylation gave 1,3-di-*O*-acetyl-2,5-di-*O*-benzoyl-β-L-ribofuranose **73**. This intermediate was transformed to β-L-nucleosides by condensation with a silylated base, such as thymine or cytosine.



Scheme 11. Preparation of L-ribose tetraacetate from D-ribose (source: Mikhailopulo et al.[38]). Reagents: (a) acetone, *p*-TsOH, CaH_2; (b) MTrCl, pyridine; (c)$NaBH_4$, EtOH; (d) BzCl, pyridine; (e) 90% aq HOAc, THF; (f) PCC, CH_2Cl_2; (g) 85% aq CF_3CO_2H; (h) Ac_2O, pyridine.

Jeong et al. prepared L-ribose by a combination of carbon homologation and degradation of D-ribose (Scheme 12).[39] D-Ribose was converted to its 2,3-acetonide **68** and transformed to vinyl diol **74** by treatment with methyltriphenylphosphonium bromide. Oxidative cleavage of **74** with sodium metaperiodate produced vinyl aldehyde **75**. Dihydroxylation of the vinyl group of **75** by osmium tetroxide and *N*-methylmorpholine-*N*-oxide gave a desirable isomer of 2,3-*O*-isopropyridene-L-ribose after separation by silica gel column chromatography. L-Ribose was obtained from D-ribose over five steps and in 50% overall yield by hydrolysis of **76** using acidic resin.



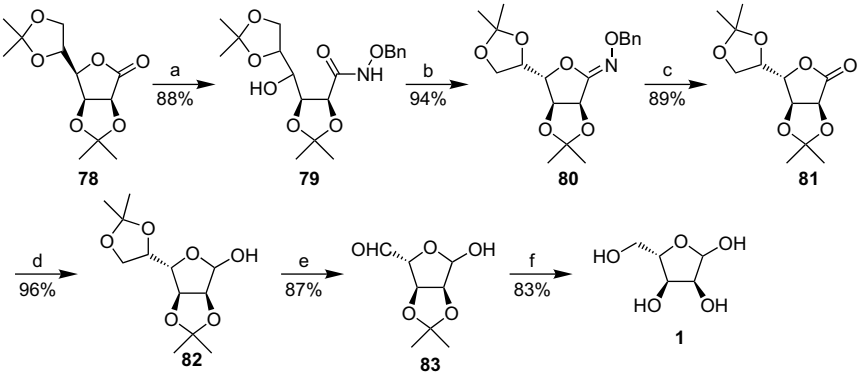
Scheme 12. Carbon homologation and degradation of D-ribose (source: Jeong et al.). Reagents: (a) acetone, concd H_2SO_4, rt, 2.5 h; (b) Ph_3PCH_3Br, KO-*t*-Bu, THF, rt, 15 h; (c) $NaIO_4$, H_2O, CH_2Cl_2, rt, 15 min; (d) OsO_4, NMO, H_2O; (e) Dowex-H^+ resin, dioxane/H_2O.

D-Mannono-1,4-lactone is readily prepared from D-mannose and has the same configuration at C-2 and C-3 as L-ribose, but that of C-4 is inverse. Ikegami et al. prepared L-ribose by inversion at C-4 of D-mannono-1,4-lactone using intramolecular O-alkylation of σ-hydroxyalkoxamates (Scheme 13).[40] The acetonide of D-mannono-1,4-lactone was converted into the γ-hydroxyalkoxamate. Treatment of **78** with *O*-benzylhydroxylamine followed by trimethylaluminium afforded the corresponding γ-hydroxybenzyloxamate **79**. The cyclization of **79** under Mitsunobu conditions gave **80** via O-alkylation. Treatment of the *O*-cyclized oxime **80** with TsOH gave L-gulono-1,4-lactones **81**. The carbonyl moiety of **81** was reduced by DIBAL to provide L-gulofuranose **82**. Compound **82** was partially hydrolyzed to the diol, which was treated with $NaIO_4$ to provide **83**. The aldehyde of **83** was reduced by H_2/PtO_2 and deprotected to afford L-ribose.

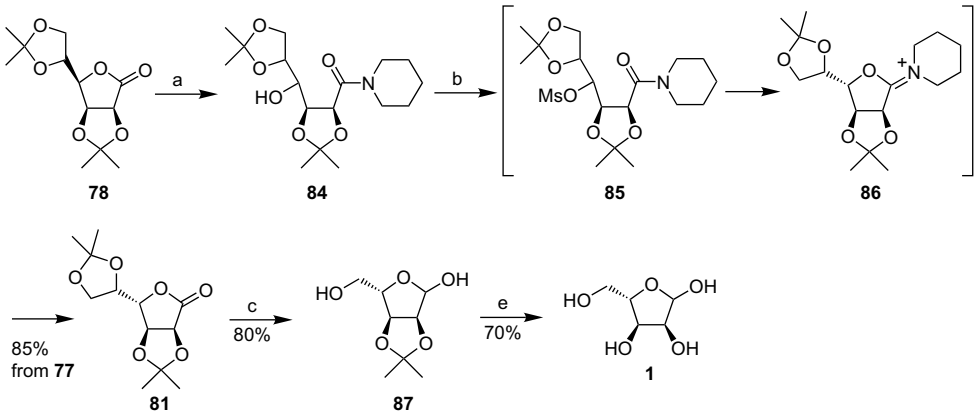
Kim et al. improved Ikegami et al.'s method using a readily available reagent (Scheme 14).[41] They found that piperidine opens γ-lactone smoothly under mild conditions to liberate the hydroxyl group. Amide **84** was reacted with methanesulfonyl chloride to afford mesylate **85**, and in situ attack of the carbonyl group furnished the inversed stereochemistry, yielding L-gulono-1,4-lactones **81**. Cleavage of the diol moiety by periodic acid, reduction of the resulting aldehyde by DIBAL-H, and deprotection of **87** by acidic hydrolysis gave L-ribose in good yield.

3.2. Chemical synthesis from non-sugar compounds

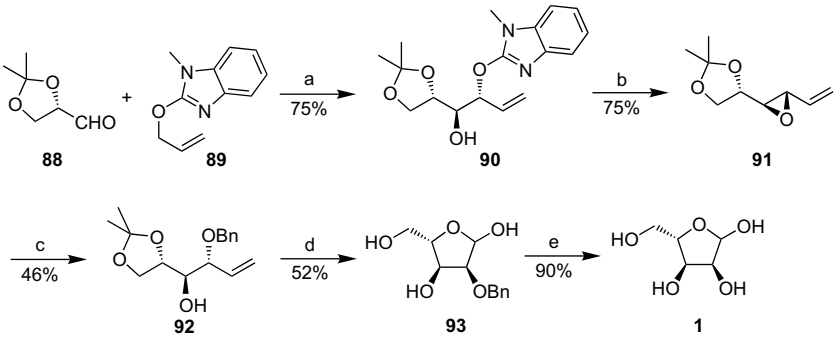
Asymmetric synthesis, which includes chiral pool and catalytic methods, has the advantage of readily preparing both enantiomers of the target molecule, when both enantiomers of the chiral source are available. Various asymmetric syntheses of L-ribose from various non-sugar compounds are reported. Mukaiyama investigated the stereoselective addition of an allyl cadmium reagent to an aldehyde and applied this methodology to the stereoselective synthesis of L-ribose (Scheme 15).[42] L-2,3-*O*-Isopropyrideneglyceraldehyde **88** was reacted with allyloxyimidazole **89** in the presence of *n*-BuLi and CdI_2 and alcohol **90** was stereoselectively transformed. Stereoinversion by oxirane formation, followed by nucleophilic attack by



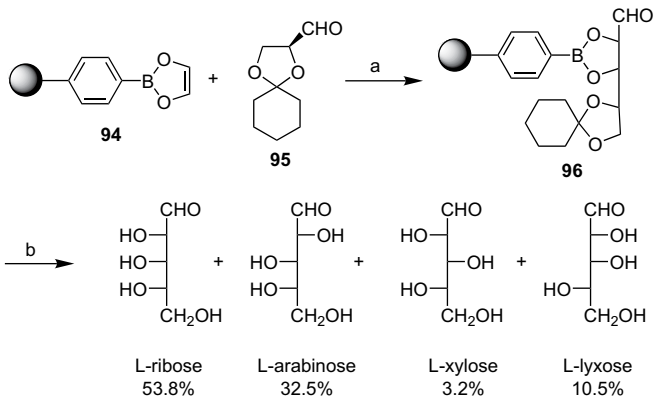
Scheme 13. Cyclization of a γ-hydroxyalkoxamate (Ikegami et al.[40]). Reagents: (a) $BnONH_2$, Me_3Al, CH_2Cl_2; (b) PPh_3, DEAD, THF; (c) TsOH/H_2O, acetone; (d) DIBAL, CH_2Cl_2; (e) (i) TFA, THF, (ii) $NaIO_4$, CH_2Cl_2; (f) (i) H_2, PtO_2, THF, (ii) Amberlite IR-120.



Scheme 14. Nucleophilic inversion from D-mannono-1,4-lactone (Kim et al.[41]). Reagents: (a) piperidine, EtOAc; (b) MsCl, Et_3N, EtOAc, H_2O; (c) (i) H_5IO_6, EtOAc, (ii) DIBAL-H, toluene; (d) 1 N HCl, dioxane.



Scheme 15. Stereoselective aldol-type reaction with 2,3-*O*-isopropyrideneglyceraldehyde (source: Mukaiyama and Yamaguchi[42]). Reagents: (a) *n*-BuLi, CdI_2; (b) NaH; (c) BnOH, Al_2O_3; (d) O_3, Me_2S, silica gel; (e) H_2, 10% Pd/C.



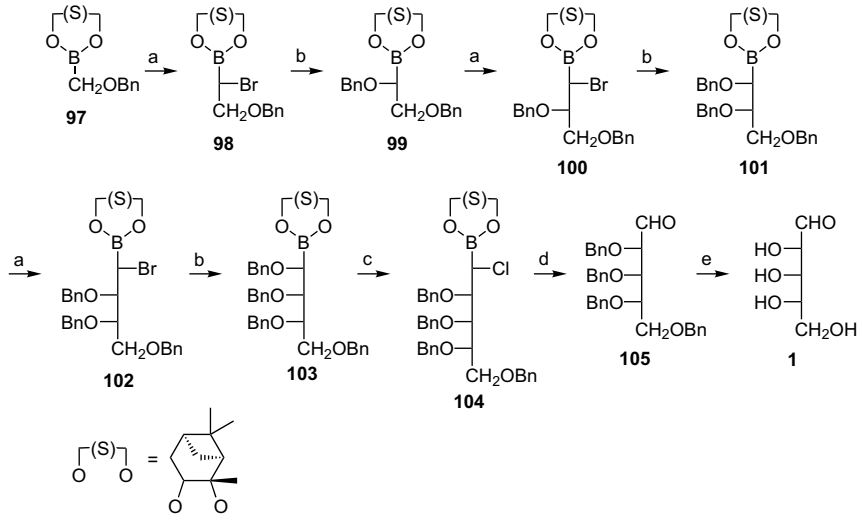
Scheme 16. C2 elongation of glyceraldehyde (source: Wulff and Hansen [43]). Reagents: (a) CH_2Cl_2, rt; (b) (i) MeOH, H_2O, (ii) ion exchanger.

benzylalcohol gave hexenetetraol **92**, which has the same stereochemistry as L-ribose. Ozonolysis of olefin, followed by deprotection afforded L-ribose.

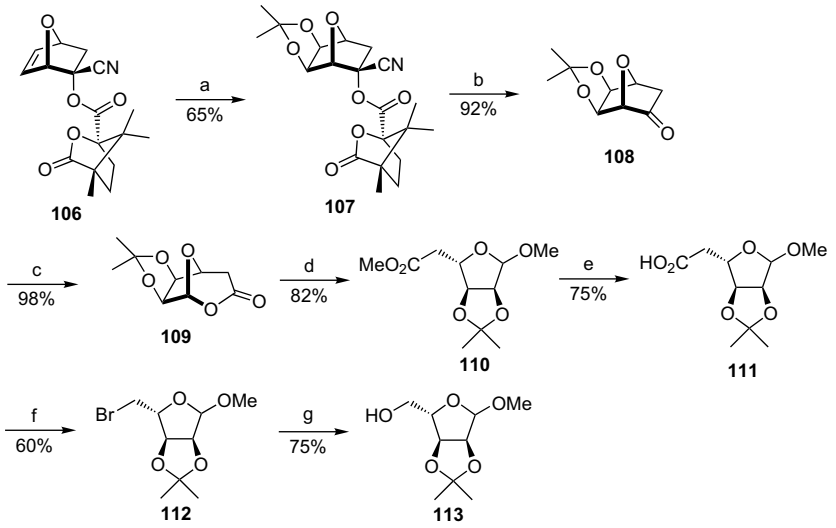
If stereoselective elongation by two carbon atoms to glyceraldehyde was possible, it would be a general method for the synthesis of pentose. However, this reaction is difficult using an anion of glycolaldehyde because a polycondensation material is generated under basic conditions. Wulff and Hansen found that 1,3,2-dioxaboroles function as synthetic equivalents of the anion of glycolaldehydes, and applied these intermediates to the synthesis of L-ribose (Scheme 16).[43] 2,3-Cyclohexylidene-(*S*)-glyceraldehyde **95** was allowed to react with the polymer-bound dioxaborole **94** at room temperature. The resulting pentose mixture was removed by treatment with an acidic ion exchanger and separated by liquid chromatography. L-Ribose was isolated as the main product.

Chirality-controlled homologation of boronic esters to α-halo boronic esters is used for the synthesis of various sugars. Matteson and Peterson synthesized L-ribose in 13% yield by the reaction of a benzyloxy-substituted boronic ester bearing (*S*)-pinanediol **97** as a chiral auxiliary by homologation with Br_2CHLi and repeated subsequent replacement of the α-bromo group by a benzyloxy group (Scheme 17).[44]

Furan structures in optically pure 7-oxanorbornenes can be viewed as precursors of furanose. Both enantiomers can be prepared from 7-oxanorbornenes, because those of chiral 7-oxanorbornens are available from natural sources. Vogel et al. prepared an L-ribose derivative from a chiral 7-oxanorbornene derivative of (+)-camphanic acid.[45] (1*S*,2*R*,4*S*)-2-*exo*-Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1′*R*)-camphanate **106** was subjected to stereospecific cis-bishydroxylation with H_2O_2 under the presence of OsO_4 and transformed into the corresponding 5-*exo*,6-*exo*-diol acetonide **107**. Hydrolysis of **107**, followed by treatment with formalin gave ketone **108**. Baeyer–Villiger oxidation followed by lactone opening afforded methyl uronate **110**. Hydrolysis of the ester and oxidative decarboxylation with red HgO and bromine gave bromide **112**. The hydrolysis of bromide gave partially protected L-ribose **113** (Scheme 18).



Scheme 17. Asymmetric chain elongation of dibromomethyllithium (source: Matteson and Petterson[44]). Reagents: (a) Br_2CHLi, ZnCl; (b) BnOLi; (c) Cl_2CHLi, ZnCl; (d) H_2O_2; (e) H_2, Pd/C.



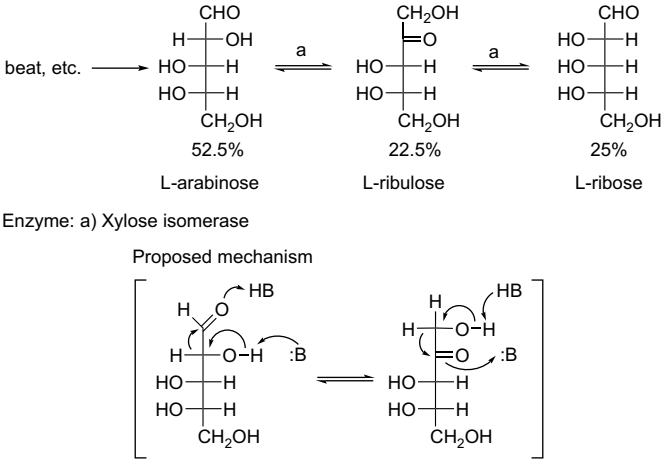
Scheme 18. Chiral-pool method from 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivative (source: Vogel et al.[45]). Reagents: (a) (i) H_2O_2, OsO_4, (ii) acetone, 2,2-dimethoxypropane, TsOH; (b) (i) KOH, H_2O, THF, (ii) 40% aq HCHO; (c) *m*-CPBA; (d) MeOH, 2,2-dimethoxypropane, MsOH; (e) KOH, H_2O, THF; (f) red HgO, Br_2; (g) HMPA, H_2O, $NaHCO_3$.

3.3. Biotransformation from sugars

Glycolysis is the metabolism of D-glucose for energy production in vivo and is conducted by many kinds of enzymes in the living system. Following the discovery of enzymes that conduct glycolysis, the enzymatic transformation of carbohydrates has been utilized in the preparation of sugars in industry from the 1960s.[46] Generally, enzymatic transformation of carbohydrates can proceed at mild conditions, directly from the substrate without a protecting group. Recently, various enzymatic transformations have been applied in the preparation of L-ribose, and each process is commercialized or in development at fine chemical companies.

3.3.1. Epimerization of L-arabinose

Since the 1960s, D-xylose isomerase (EC 5.3.1.5, XI) has been utilized for the isomerization of D-glucose to D-fructose in the industrial production of 'isomerized sugar' in the food industry.[47] The natural substrate of XI is D-xylose; however, Leisola et al. reported in 1999 that many kinds of L-pentose, including L-arabinose, are substrates for *Streptomyces rubiginosus* xylose isomerase.[48] Leisola et al. found that *S. rubiginosus* xylose isomerase catalyzed slow isomerization of L-arabinose to L-ribulose and epimerization to L-ribose. In equilibrium, the reaction mixture contained 52.5% arabinose, 22.5% ribulose, and 25% ribose. They used crystalline cross-linked xylose isomerase in a packed-bed reactor for simultaneous catalytic reaction and separation of substrates from reaction products.[49] This biocatalytic C-2 epimerization is considered to proceed by an 'oxidation–reduction' mechanism, which involves the transfer of one hydrogen as a proton via a catalytic base from O2 to O1; however, the reaction rate is very low. In order to clarify the reason for the low reaction rate, Leisola et al. explored X-ray analysis of the reaction center of the enzyme and found that the hydrogen bond that binds L-arabinose to the enzyme is incomplete compared with the binding structure of D-glucose. He engineered mutation of the binding site of XI to change the amino acid, and improved the catalytic efficiency for the epimerization of L-arabinose.[50] In order to isolate L-ribose from the equilibrium mixture, Leisora et al. developed a recycle process using a continuous flow reactor bearing a cross-linked D-xylose isomerase column. L-Ribose is separated chromatographically from the reaction mixture and the parent solution is recycled.[51] Now several companies with L-arabinose in their product line, such as Danisco (Finland) and BioRefining (USA), produce L-ribose from L-arabinose (Scheme 19).[52]

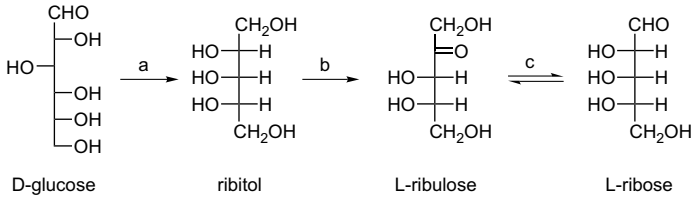


Scheme 19. Biocatalytic epimerization of L-arabinose (source: Leisola et al.[48]).

3.3.2. Biotransformation of ribitol

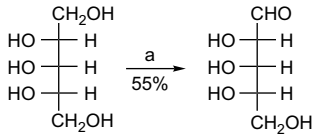
While XI is a useful enzyme for scale-up production, its weak point is that the equilibrium ratio leans toward L-arabinose. In 1996, Izumori et al. discovered an L-ribose isomerase (L-RI) in *Acinetobacter* sp. strain DL-28 and demonstrated that L-ribose can be prepared from L-ribulose in high yield.[53] The purified enzyme catalyzed the isomerization of D-mannose, D-lyxose and L-ribose, with the highest catalytic activity observed during the conversion of L-ribose to L-ribulose. This enzyme does not require cofactor recycling and can prepare L-ribose by isomerization of L-ribulose in 70% yield.

L-RI has a potential usefulness for the industrial production of L-ribose. L-Ribulose does not exist in nature and therefore has been unavailable on a commercial scale; however, L-ribulose has long been known to be prepared by bioconversion[54] from ribitol by bacteria of the genus *Acetobacter*. Izumori et al. developed the microbial oxidation of ribitol to L-ribulose by the reaction of washed cells of *Acetobacter aceti* IFO 3281, and the following step involves the production of L-ribose from L-ribulose by L-RI.[55] Ribitol is known to be produced by fermentation[56] from D-glucose. Kawaguchi of Mitsubishi Chemical found that some microorganisms, which belong to *Trichosporonoides*, produce ribitol with high yield during the oxidative fermentation of glucose.[57] Kawaguchi combined these technologies and developed the production process of L-ribose



Enzyme: a) ribitol fermentaion, b) *Gluconobacter oxydans,* c) L-RI (L-ribulose:L-ribose=30:70)

Scheme 20. Preparation of L-ribose from D-glucose (source: Izumori et al.,[53,56] Kawaguchi et al.[57]).



Enzyme: a) mannitol-1-dehydrogenase

Scheme 21. Selective oxidation of ribitol via enzymatic desymmetrization (source: Wymer et al.[63]).

from D-glucose.[58] In order to develop the industrial process, they found that L-ribulose could be produced from the crude ribitol, which is prepared by the oxidative fermentation of glucose.[59] The industrial processing of L-ribose was developed by Mitsubishi Chemical by combining the three types of biotransformation. In 2006, API Corporation, a subsidiary of Mitsubishi Chemical, began the commercial production of L-ribose at ton scale (Scheme 20).

After the discovery of L-ribose isomerase, many groups have reported the improvement of each enzyme. Muynck et al. reported on the optimization of the ribitol dehydrogenation procedure to L-ribulose with washed cells of *G. oxydans*.[60] Kawaguchi et al. found that new microorganisms belonging to *Cellulomonas*, *Microbacterium*, and *Stenotrophomonas* could isomerize L-ribulose to L-ribose.[61] Recently, thermostable L-ribose isomerase was reported by two groups. Pyun et al. reported a novel thermostable L-ribose isomerase derived from *Paenibacillus* RI-39 (KCCM 10653), which has an optimal reaction temperature of 60–80 °C,[62] and Izumori et al. found that the thermostable L-ribose isomerase derived from *Raoultella ornithinolytica* MB426 is stable up to 45 °C during heat treatment at pH 9.0 for 10 min.[63]

The structure of L-ribose corresponds to a shape that indicates oxidation of the terminal carbon of ribitol. Ribitol is in *meso*-form, therefore, if selective oxidation of ribitol via enzymatic desymmetrization occurs, L-ribose can be prepared from ribitol directly. Recently, Wymer et al. reported the selective oxidation of ribitol via enzymatic desymmetrization of ribitol by mannitol-1-dehydrogenase.[64] They constructed the gene encoding mannitol-1-dehydrogenase (MDH) from *Apium graveolens* for optimal expression in *Escherichia coli*, and found that the MDH enzyme catalyzes the interconversion of several polyols and their L-sugar counterparts, including the conversion of ribitol to L-ribose. The optimized conditions at a 1-l scale resulted in 55% conversion of 100 g/L ribitol in 72 h (Scheme 21).

4. Conclusion

L-Ribose synthesis has received increasing attention in recent years because of the growing recognition of its importance as a key intermediate in the pharmaceutical industry, especially in the development of nucleoside and oligonucleotide drugs. Among the various routes, biotransformation using enzymes is a feasible method for the industrial production of L-ribose. However, diverse methodologies using organic synthesis will also provide new possibilities in the chemistry of L-sugars.

Acknowledgements

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