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MINI-REVIEW

Advances in the enzymatic production of L-hexoses

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Abstract Rare sugars have recently drawn attention because of their potential applications and huge market demands in the food and pharmaceutical industries. All L-hexoses are considered rare sugars, as they rarely occur in nature and are thus very expensive. L-Hexoses are important components of biologically relevant compounds as well as being used as precursors for certain pharmaceutical drugs and thus play an important role in the pharmaceutical industry. Many general strategies have been established for the synthesis of L-hexoses; however, the only one used in the biotechnology industry is the Izumoring strategy. In hexose Izumoring, four entrances link the D- to L-enantiomers, ketose 3-epimerases catalyze the C-3 epimerization of L-ketohexoses, and aldose isomerases catalyze the specific bioconversion of L-ketohexoses and the corresponding L-aldohexoses. In this article, recent studies on the enzymatic production of various L-hexoses are reviewed based on the Izumoring strategy.

Keywords Bioconversion · L-hexose · Izumoring · Monosaccharide · Rare sugar

Introduction

Hexose is a typical monosaccharide and classified into the D- or L-configuration, with the chemical formula $C_6H_{12}O_6$. The D-form is usually the isomer found in nature, and the biotechnological production of various D-hexoses has recently been reviewed in detail elsewhere (Mu et al. 2015). Recently, L-hexoses have recently garnered attention because of their potential applications in the pharmaceutical industry (Table 1). L-Hexoses can be categorized to include four L-ketohexoses including L-sorbose, L-psicose, L-tagatose, and L-fructose, and each L-ketohexose corresponds to two L-aldohexoses, giving rise to eight different sugars including L-gulose, L-idose, L-galactose, L-talose, L-altrose, L-allose, L-mannose, and L-glucose.

L-Sugars have often been recognized as important components of biologically relevant compounds and precursors of certain pharmaceutical drug molecules (Ahmed 2001). L-Sorbose has been used as an intermediate for industrial synthesis of L-ascorbic acid (vitamin C) for decades (Pappenberger and Hohmann 2014). L-Tagatose is used as a starting material for synthesis of deoxygalactonojirimycin (DGJ), a pharmacological chaperone, with synergistic activity that has potential implications for treating lysosomal storage disorders (Jenkinson et al. 2011). L-Fructose is a potential nonnutritive sweetener (Levin et al. 1995) and an effective inhibitor of various glycosidases (Muniruzzaman et al. 1996). L-Gulose is an important component of Bleomycin A_2, which is employed clinically as an antitumor antibiotic (Saitta et al. 2008), and its 6-deoxy derivative, 6-dexoy-L-gulose, is contained in yet another anti-tumor antibiotic, zorbamycin (Wang et al. 2007), while L-gulosamine is a key component of adenomycin, a potential antibacterial agent (Hung et al. 2001). The L-idose derivative L-iduronic acid is an important component of the repeating unit of some glycosaminoglycans (GAGs), including heparin, heparin sulfate, and dermatan sulfate (Seeberger and Werz 2007). L-Talose has been used as substrate to synthesize 9-α-L-talopyranosyladenine, a slow-reacting substrate for calf intestinal adenosine deaminase (EC 3.5.4.4), which inhibits the growth of leukemia L1210 cells

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Table 1 L-Hexoses serve as important components or precursors of bioactive or pharmaceutical molecules

L-Hexose		CAS no.	Application	Reference
L-Ketohexose	L-Sorbose	87-79-6	An important intermediate for industrial production of L-ascorbic acid	Pappenberger and Hohmann (2014)
	L-Tagatose	17598-82-2	A starting material for synthesis of deoxygalactonojirimycin (DGJ), a pharmacological chaperone for treatment of lysosomal storage disorders	Jenkinson et al. (2011)
	L-Psicose	16354-64-6	Not found	
	L-Fructose	7776-48-9	A potential inhibitor of various glycosidases	Muniruzzaman et al. (1996)
L-Aldohexose	L-Gulose	6027-89-0	A chemical component of Bleomycin A_2, a broad-spectrum anti-tumor drug	Saitta et al. (2008)
	L-Idose	5934-56-5	L-Iduronic acid is a major uronic acid component of glycosaminoglycans (GAGs).	Hallak et al. (2000)
	L-Galactose	15572-79-9	A glycosyl component of the side chain of rhamnogalacturonan II; a structurally complex pectic polysaccharide	O'Neill et al. (2004)
	L-Talose	23567-25-1	The starting material to produce 9-α-L-talopyranosyladenine, an inhibitor of the growth of leukemia L1210 cells in vitro	Lerner and Mennitt (1994)
	L-Altrose	1949-88-8	A specific component of extracellular polysaccharide from the anaerobic microorganism *Butyrivibrio fibrisolvens* strain CF3	Ferreira et al. (1997)
	L-Allose	9392-62-6	The derivative 6-deoxy-L-allose is contained in tetracyclic triterpene datiscoside C isolated from *Datisca glomerata*.	Sasamori et al. (1983)
	L-Mannose	10030-80-5	Contained in a polysaccharide capsule from *Sphingomonas* strain S88, used as a gelling agent in the food industry	Yamazaki et al. (1996)
	L-Glucose	921-60-8	An important component of littoralisone, a natural bioactive agent from *Verbena littoralis*, enhances NGF-induced neurite outgrowth in PC12D cells	Li et al. (2001)

in vitro (Lerner and Mennitt 1994). L-Glucose is a major component of littoralisone, a natural bioactive product from *Verbena littoralis*, which plays a role in enhancing nerve growth factor (NGF)-induced neurite outgrowth in PC12D cells (Li et al. 2001). These findings have greatly increased the interest in research regarding the synthesis of L-hexoses.

By definition, all L-hexoses are classified as rare sugars and are thus very expensive (Granstrom et al. 2004). Limited availability and high costs limit the research and application of L-hexoses. General methodologies for L-hexose synthesis have been widely studied. Chemical synthesis of L-hexoses has recently been reviewed in detail (D'Alonzo et al. 2009; Frihed et al. 2015), while the Izumoring strategy is the preferred method in the biotechnology industry (Granstrom et al. 2004; Izumori 2002). In this article, recent advances in the studies of enzymatic production of various L-hexoses are reviewed. However, due to the scope of this review, L-hexitols were not included.

Entrances to form L-hexoses from D-hexoses

Based on the hexose Izumoring strategy, there are four entrances to form L- from D-hexoses via four D, L-series of hexitols, including D-glucitol (L-gulitol, D-sorbitol), allitol (D-allitol, L-allitol), galactitol (D-galactitol, L-galactitol, dulcitol), and D-gulitol (L-glucitol, L-sorbitol) (Izumori 2006). These four hexitols can be converted to L-ketohexoses by polyol dehydrogenases and are then inevitable passing points to enter the L-hexose world (Fig. 1).

L-Sorbose production from D-sorbitol

L-Sorbose is the most studied L-hexose not only because it is used as an important intermediate for L-ascorbic acid (Pappenberger and Hohmann 2014) but also because the substrate for L-sorbose synthesis, D-sorbitol, is very cheap and easy to obtain. D-Sorbitol can be industrially produced from

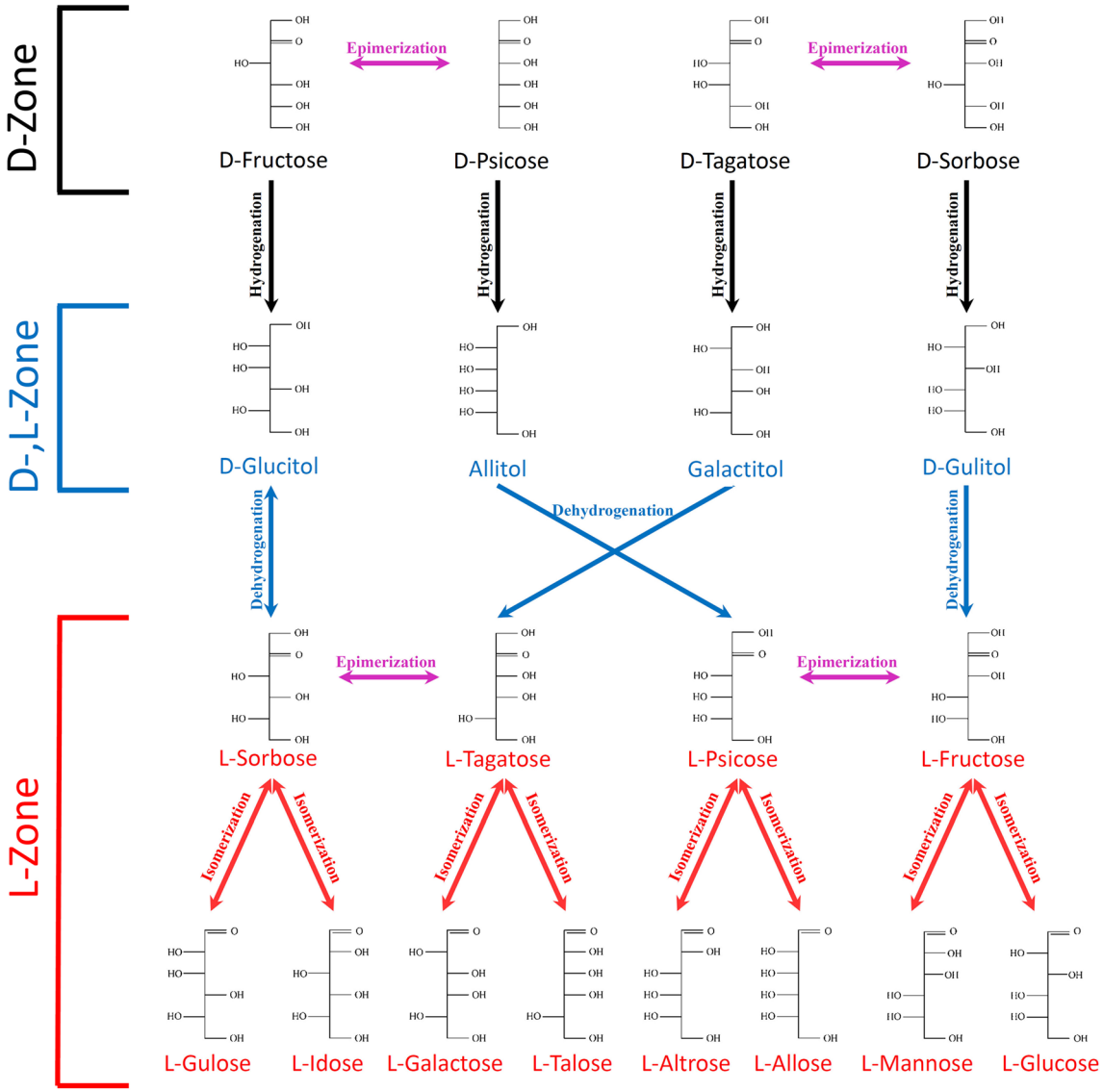

Fig. 1 Enzymatic production of L-hexoses based on the hexose Izumoring strategy. Entrances to form L- from D-hexoses are included, and the enzymatic epimerization and isomerization of L-hexoses are shown

D-glucose, with theoretically 100 % yield by simple chemical hydrogenation (Zhang et al. 2013a).

L-Sorbose production was firstly reported by Reichstein et al., stating that L-sorbose could be biotechnically synthesized by oxidation of D-sorbitol using *Gluconobacter oxydans* (previously called *Acetobacter suboxydans*) pyrroloquinoline quinone (PQQ) enzymes (Reichstein et al. 1933). Since then, bulk L-sorbose production has been widely studied using microbial fermentation by *G. oxydans* (Giridhar and Srivastava 2001a; Giridhar and Srivastava 2001b; Macauley-Patrick et al. 2005). Furthermore, D-sorbitol 2-dehydrogenase (EC 1.1.1.14) is very responsible for converting D-sorbose to L-sorbose (Shinjoh et al. 2002). Immobilized whole cells were used for efficient production of L-sorbose from D-sorbitol (Kim et al. 1999; Spassov et al. 1995; Wang et al. 2013), and the fermentation of L-sorbose could be significantly enhanced by improving the mRNA abundance of D-sorbitol 2-dehydrogenase in these cells (Xu et al. 2014).

L-Psicose production from allitol

Through specific polyol dehydrogenase, L-psicose could be produced from allitol, which is a scare hexitol and converted from D-psicose. Enzymatic oxidation of allitol to L-psicose was first reported using *Acetomonas oxydans* (Carr et al. 1968). However, the process was lengthy and required 2 weeks for L-psicose production. Consequently, Takeshita et al. developed a highly efficient production of L-psicose from allitol using the whole cells of *Gluconobacter frateurii* IFO 3254. The conversion rate was approximately 98 % when 100-g L^{-1}

allitol was used; however, the enzyme responsible for catalyzing this reaction is still unknown (Takeshita et al. 1996).

L-Tagatose production from galactitol

Bioconversion of galactitol to L-tagatose is the third of the four entrances to form L- from D-hexoses (Fig. 1). However, only two publications have focused on L-tagatose production from galactitol. Shimonishi et al. used an isolated L-tagatose-producing bacterial strain from soil, *Klebsiella pneumoniae* strain 40b, to produce L-tagatose, with a yield of higher than 60 % from 0.5 to 2 % galactitol (Shimonishi et al. 1995). Huwig et al. developed a strategy for enzymatic production of L-tagatose from galactitol using a specific galactitol dehydrogenase from *Rhodobacter sphaeroides* D, with NADH regeneration by L-lactate dehydrogenase (EC 1.1.1.27) and with the overall yield of L-tagatose reaching 78 % (Huwig et al. 1998).

L-Fructose production from L-glucitol

L-Fructose can theoretically be produced from L-glucitol by enzymatic dehydrogenation and the latter can be produced by dehydrogenation of D-sorbose (Fig. 1). Unfortunately, there are no reports concerning these two steps, but interestingly, the reverse reactions of these two steps have been documented. The L-glucitol dehydrogenase responsible for catalyzing the conversion of L-glucitol to D-sorbose was first identified from *Pseudomonas* sp. Ac (Mayerskuntzer et al. 1994), and the whole cells produced D-sorbose from L-glucitol, with a yield of higher than 95 % (Huwig et al. 1996). Through hydrogenation, *Aureobasidium pullulans* LP23, isolated from a soy sauce mash, could convert L-fructose to L-glucitol (Sasahara and Izumori 2005).

C-3 epimerization between L-ketohexoses

Ketose 3-epimerase catalyzes the epimerization of various ketoses at the C-3 position to produce their C-3 epimers. The enzyme generally exhibits a broad specificity toward many ketoses including ketohexoses and ketopentoses, and theoretically, is able to catalyze the epimerization between L-sorbose and L-tagatose and between L-psicose and L-fructose.

In 1993, the enzyme was first reported by Izumori et al., which they isolated from *Pseudomonas cichorii* (Izumori et al. 1993). The purified enzyme showed C-3 epimerization activity toward various ketoses with the optimum substrate being D-tagatose, and thus, it was classified as D-tagatose 3-epimerase (EC 5.1.3.31) (Itoh et al. 1994). Twelve years later, a second ketose 3-epimerase was identified from *Agrobacterium tumefaciens* (Kim et al. 2006a), showing the highest activity toward D-psicose and was named D-psicose 3-epimerase (EC 5.1.3.30). In 2009, the third ketose 3-epimerase, with D-fructose being the optimum substrate, was characterized from *R. sphaeroides* (Zhang et al. 2009). Recently, D-psicose 3-epimerases were identified from *Clostridium cellulolyticum* (Mu et al. 2011), *Ruminococcus* sp. 5_1_39BFAA (Zhu et al. 2012), *Clostridium scindens* (Zhang et al. 2013b), *Desmospora* sp. 8437 (Zhang et al. 2013c), *Clostridium* sp. BNL1100 (Mu et al. 2013), *Clostridium bolteae* (Jia et al. 2014), *Dorea* sp. CAG317 (Zhang et al. 2015), and *Treponema primitia* (Zhang et al. 2016). Finally, a ketose 3-epimerase with the optimum substrate of L-ribulose, named L-ribulose 3-epimerase (EC 5.1.3.31), was first identified from *Mesorhizobium loti* (Uechi et al. 2013b).

Ketose 3-epimerases have attracted considerable attention, because they have a very important role in the Izumoring strategy (Izumori 2006) and in the biological production of D-psicose (Mu et al. 2012). These enzymes are also used for the production of deoxyketohexoses (Gullapalli et al. 2010; Rao et al. 2009), methyl-ketohexoses (Jones et al. 2008; Rao et al. 2008), and some other rare sugars, including D-sorbose (Itoh et al. 1995), L-xylulose (Uechi et al. 2013b), L-tagatose, and L-fructose (Itoh and Izumori 1996). Although they exhibit broad substrate specificity toward various ketoses, the activities of many ketose 3-epimerases toward L-sugars have not been measured, probably due to the difficulty in obtaining L-sugars as substrates commercially. Only the D-psicose 3-epimerase from *P. cichorii* (Izumori et al. 1993) and the L-ribulose 3-epimerase from *M. loti* (Uechi et al. 2013b), identified by the Rare Sugar Research Center at Kagawa University, have been used to measure the epimerization activity toward L-ketohexoses. The epimerase isolated from *P. cichorii* not only displayed 20 % of the relative activity toward L-psicose, compared to the optimum substrate D-tagatose, but also showed trace activity toward L-tagatose, L-sorbose, and L-fructose (Itoh et al. 1994). The epimerase isolated from *M. loti* exhibited specific activities of 31, 10, and 5.5 U mg^{-1} toward L-psicose, L-fructose, and L-tagatose, respectively, and by comparison, showed a specific activity of 230 U mg^{-1} toward the optimum substrate L-ribulose and only trace activity toward L-tagatose (Uechi et al. 2013b).

Except for the oxidative dehydrogenation by polyol dehydrogenase, C-3 epimerization is an efficient approach to biological production of L-ketohexoses. However, only isolated *P. cichorii* has been used for the enzymatic production of L-ketohexoses. The enzyme was first immobilized on Chitopearl beads BCW 2510, and the immobilized enzyme produced 20 % L-tagatose and 65 % L-fructose from 40 g L^{-1} of L-sorbose and 20 g L^{-1} of L-psicose, respectively (Itoh and Izumori 1996). The crystal structure of ketose 3-epimerases from *P. cichorii* (PDB: 2QUL) (Yoshida et al. 2007), *A. tumefaciens* (PDB: 2HK0) (Kim et al. 2006b), *C. cellulolyticum* (PDB: 3VNI) (Chan et al. 2012), and *M. loti* (PDB: 3VYL) (Uechi et al. 2013a) has been determined and is available in the Protein Data Bank. Based on

already known crystal structure information, a molecular modification made to these epimerases would be expected to improve the substrate specificity and enzymatic activity toward L-ketohexoses, and thus, the enzymatic production of L-ketohexoses could be more efficient and widely utilized in the near future.

Isomerization between L-ketohexoses and L-aldohexoses

L-Ketohexoses can be biologically produced through the same entrances from D-hexoses mentioned above. Enzymatic isomerization is an important approach in the production of L-aldohexoses from L-ketohexoses (Fig. 1). Each L-ketohexose corresponds to two different L-ketoaldoses by isomerization. Many aldose isomerases and aldose phosphate isomerases have been identified to catalyze the isomerization between various ketoses and their corresponding aldoses. Unfortunately, none of the reported isomerases shows a high activity toward L-hexoses. Still, some aldose isomerases have been used for L-aldohexose production, including L-rhamnose isomerase (EC 5.3.1.14) (Bhuiyan et al. 1997; Leang et al. 2004a; Takata et al. 2011), L-ribose isomerase (EC 5.3.1.B3) (Terami et al. 2015), and D-arabinose isomerase (EC 5.3.1.3) (Leang et al. 2003). Some aldose phosphate isomerases have also shown potential for the application of L-aldohexose production, including D-ribose-5-phosphate isomerase (EC 5.3.1.6) (Park et al. 2010), D-glucose-6-phosphate isomerase (EC 5.3.1.9) (Yoon et al. 2009b), D-mannose-6-phosphate isomerase (EC 5.3.1.8) (Yeom et al. 2009a), and D-galactose-6-phosphate isomerase (EC 5.3.1.26) (Park et al. 2007). However, for practical industrial applications, it is essential to obtain enzymes that utilize L-hexoses as an optimum substrate, or the specific activity needs to be vastly improved using molecular modification.

Isomerization of L-sorbose to L-gulose and L-idose

To the best of our knowledge, there is no existing literature concerning the biological production of L-gulose and L-idose from L-sorbose. However, it was discovered that the *Pyrococcus furiosus* D-glucose-6-phosphate isomerase (Yoon et al. 2009b), the *Serratia proteamaculans* D-lyxose isomerase (EC 5.3.1.15) (Park et al. 2010), and the *Cellulomonas parahominis* L-ribose isomerase (Morimoto et al. 2013) exhibit isomerization activity toward L-sorbose. Using L-sorbose as the substrate, the *P. furiosus* D-glucose-6-phosphate isomerase could convert L-sorbose to L-idose and L-gulose by a two-step isomerization mechanism. The final equilibrium ratio of L-sorbose/L-idose/L-gulose is 60:26:14. (Yoon et al. 2009b). In contrast, the *S. proteamaculans* D-lyxose isomerase and *C. parahominis* L-ribose isomerase only catalyze one-step isomerization between L-gulose and L-sorbose (Park et al. 2010; Morimoto et al. 2013).

Isomerization of L-tagatose to L-talose and L-galactose

Many aldose and aldose phosphate isomerases can catalyze the isomerization between L-tagatose and L-talose (Table 2). Most of the isomerases produce L-talose as a sole product from L-tagatose. However, *P. furiosus* D-glucose-6-phosphate isomerase produces two aldo-isomers from L-tagatose, giving a conversion ratio of L-tagatose/L-talose/L-galactose of 80:15:5 (Yoon et al. 2009b). The L-rhamnose isomerase from *Pseudomonas stutzeri* also produces both L-talose and L-galactose from L-tagatose (Leang et al. 2004b). However, the *M. loti* L-rhamnose isomerase only catalyzes one-step isomerization between L-tagatose and L-talose (Takata et al. 2011).

Production of L-tagatose from L-talose

The *P. furiosus* D-glucose-6-phosphate isomerase shows the highest activity toward L-talose among all the tested aldoses, giving the specific activity of 620 U mg^{-1}, and therefore has great potential for L-tagatose production (Yoon et al. 2009b). *Streptococcus pneumoniae* D-ribose-5-phosphate isomerase, another potential L-tagatose-producing enzyme, catalyzed the isomerization between L-talose and L-tagatose, which could produce 450 g L^{-1} of L-tagatose from 500 g L^{-1} of L-talose after a 5-h reaction (Park et al. 2011).

Production of L-talose from L-tagatose

L-Talose production was performed by an *M. loti* L-rhamnose isomerase immobilized on Chitopearl beads BCW 2510, which converted 300 g L^{-1} of L-tagatose to 30 g L^{-1} of L-talose without any byproducts after 12 h of reaction (Takata et al. 2011). The *P. stutzeri* L-rhamnose isomerase immobilized on BCW 2603 beads was also used for L-talose production, and it produced L-talose from 200 g L^{-1} of L-tagatose, with a conversion ratio of 12 % (Bhuiyan et al. 1999). However, the *P. stutzeri* L-rhamnose isomerase normally produces both L-talose and L-galactose from L-tagatose (Leang et al. 2004b), which makes it an unlikely candidate in the production of L-talose on the industrial level.

Production of L-galactose from L-tagatose

The *P. stutzeri* L-rhamnose isomerase has also been used for L-galactose production. The enzyme immobilized on BCW 2510 beads produced approximately 7.5 g L^{-1} of L-galactose from 25 g L^{-1} of L-tagatose, with L-talose production as a minor byproduct during the reactions (Leang et al. 2004a).

Table 2 Summary of the isomerases catalyzing bioconversion between L-talose and L-tagatose

Enzyme	Microbial source	Specific activity (U mg^{-1})		Equilibrium ratio (L-talose/L-tagatose, %)	K_m (mM)		k_{cat}/K_m (mM^{-1} min^{-1})		Reference
		L-Talose	L-Tagatose		L-Talose	L-Tagatose	L-Talose	L-Tagatose	
D-Glucose-6-phosphate isomerase	*Pyrococcus furiosus*	620[a]	404[a]	15:80:5 (L-talose/L-tagatose/L-galactose)	133	NR	215	NR	Yoon et al. (2009b)
L-Rhamnose isomerase	*Mesorhizobium loti*	5.23[a]	NR	10:90	5.25	NR	80	NR	Takata et al. (2011)
D-Mannose-6-phosphate isomerase	*Geobacillus thermodenitrificans*	26[a]	NR	NR	NR	NR	NR	NR	Yeom et al. (2009b)
	Bacillus subtilis	0.47[b]	0.08[b]	NR	NR	NR	NR	NR	Yeom et al. (2009a)
D-Ribose-5-phosphate isomerase	*Clostridium thermocellum*	7363[a]	720[a]	11:89	37	125	368	15	Yoon et al. (2009a)
	Streptococcus pneumoniae	19[b]	1.3[b]	10:90	NR	NR	NR	NR	Park et al. (2011)
	Clostridium difficile	28[b]	14[b]	NR	520	NR	18	NR	Park et al. (2010b)
	Thermotoga maritima	307[b]	55[b]	NR	190	NR	420	NR	Park et al. (2010b)

NR not reported

[a] One unit (U) is defined as the enzyme amount producing 1-μmol product from substrate per minute

[b] One unit (U) is defined as the enzyme amount producing 1-nmol product from substrate per minute

Isomerization of L-psicose

Isomerization between L-psicose and L-altrose

There are scarce reports in the literature regarding the isomerization between L-psicose and L-altrose. The *P. furiosus* D-glucose-6-phosphate isomerase can catalyze the conversion between L-psicose and L-altrose, with specific activities of 251 and 67 U mg^{-1}, respectively. However, the reactions with both substrates produced L-allose as a very minor byproduct (Yoon et al. 2009b).

Isomerization between L-psicose and L-allose

L-Ribose isomerases have potential to be used in the isomerization between L-psicose and L-allose. An L-ribose isomerase isolated from *C. parahominis* catalyzed L-psicose/L-allose isomerization, with an equilibrium ratio of 65:32 (Morimoto et al. 2013). The enzyme was also used for L-allose production from L-psicose via immobilization on DIAION HPA25L beads. The immobilized enzyme produced 33 g L^{-1} of L-allose from 100 g L^{-1} of L-psicose after a 1-day reaction (Terami et al. 2015).

Isomerization of L-fructose

Isomerization between L-fructose and L-mannose

Most of the reported L-rhamnose isomerases prefer L-rhamnose and L-lyxose, respectively, as the first and second aldose substrates, with the third preference toward the production of L-fructose from L-mannose. The specific activities of the enzymes isolated from *P. stutzeri*, *Caldicellulosiruptor saccharolyticus* (Lin et al. 2011), *Thermotoga maritime* (Park et al. 2010), *Thermoanaerobacterium saccharolyticum* (Hung et al. 2014), *Bacillus pallidus* (Poonperm et al. 2007), *M. loti* (Takata et al. 2011), and *Bacillus subtilis* (Park 2014) toward L-mannose were 81.6, 38, 15, 6, 4.52, 2.27, and 0.92 U mg^{-1}, respectively. In addition, L-fructose has also been produced from L-mannose with a conversion ratio of approximately 25 % by an enzyme reactor packed with cross-linked *Streptomyces rubiginosus* D-glucose isomerase crystals (Jokela et al. 2002).

Certain L-rhamnose isomerases are also used for L-mannose production. The enzyme isolated from *P. stutzeri* converted L-fructose to L-mannose, with a yield of 30 % via immobilization on BCW 2603 beads (Bhuiyan et al. 1997). The free enzyme from *B. subtilis* produced 25 g L^{-1} of L-mannose

from 100 g L^{-1} of L-fructose after a reaction of 80 min (Park et al. 2010), and the enzyme isolated from *T. maritime* produced 175 g L^{-1} of L-mannose from 500 g L^{-1} of L-fructose after 5 h (Park 2014).

Isomerization between L-fructose and L-glucose

There have been few reports regarding the enzymatic isomerization between L-fructose and L-glucose. An L-glucose-producing D-arabinose isomerase was isolated from *Klebsiella pneumoniae*, and the enzyme empirically produced 0.35 g of L-glucose from 1.0 g of L-fructose, with an overall yield of 35 % (Leang et al. 2003).

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Compliance with ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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