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Research review paper

Enzymatic approaches to rare sugar production

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ABSTRACT

Rare sugars have recently attracted much attention because of their potential applications in the food, nutraceutical, and pharmaceutical industries. A systematic strategy for enzymatic production of rare sugars, named Izumoring, was developed >10 years ago. The strategy consists of aldose-ketose isomerization, ketose C-3 epimerization, and monosaccharide oxidation-reduction. Recent development of the Izumoring strategy is reviewed herein, especially the genetic approaches to the improvement of rare sugar-producing enzymes and the applications of target-oriented bioconversion. In addition, novel non-Izumoring enzymatic approaches are also summarized, including enzymatic condensation, phosphorylation-dephosphorylation cascade reaction, aldose epimerization, ulosonic acid decarboxylation, and biosynthesis of rare disaccharides.

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1. Introduction

Currently, the incidences of some diseases have increased rapidly throughout the world, including obesity, hyperlipidemia, hypertension and diabetes. The major reason for this increase is the excessive intake of high-fat and high-sugar foods. As this result, low-calorie rare sugars have attracted much attention from researchers. Rare sugars are defined as monosaccharides and their derivatives that rarely exist in nature, according to the International Society of Rare Sugars (ISRS). By definition, most monosaccharides are rare sugars; only seven are known to be common sugars that abundantly occur in nature, including D-glucose, D-fructose, D-galactose, D-mannose, D-ribose, D-xylose, and L-arabinose. Although existing in nature rarely, rare sugars have been evaluated extensively for biological and functional uses. Rare sugars have great potential use in the food and pharmaceutical industries. Many sugar alcohols, such as xylitol, mannitol, and erythritol, have been widely used as low-calorie sweeteners in health care (Park et al., 2016). Recently, the US Food and Drug Administration approved D-tagatose and D-allulose (previously known as D-psicose) to be 'generally recognized as safe' (GRAS). These promising, low-calorie sucrose substitutes will

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probably change the future sweetener market. D-Tagatose is also a potentially new antidiabetic and obesity control drug (Lu et al., 2008). Pharmaceutical activities of D-allulose have been widely studied and found to include anti-tumour, anti-inflammatory, anti-hypertensive, cryoprotective, and immunosuppressant effects (Lim and Oh, 2011). L-Monosaccharides are often recognized as important precursors of pharmaceutical drug molecules (Frihed et al., 2015). For example, L-tagatose is a starting material for deoxygalactonojirimycin (DGJ) synthesis (Jenkinson et al., 2011); L-sorbose is an intermediate for L-ascorbic acid (Vitamin C) synthesis (Pappenberger and Hohmann, 2014); L-fructose is an effective glycosidase inhibitor (Muniruzzaman et al., 1996). Chemical synthesis of rare sugars generally the forms chemical waste and by-product, and requires multi-step reactions and functional group protection-deprotection manipulations (Emmadi and Kulkarni, 2014). Using an enzymatic technique for synthesis of rare sugars, however, is more environmentally friendly. In addition, enzymatic techniques have many advantages that include moderate reaction conditions and high specificity, efficiency, and sustainability.

In 2002, Prof. Izumori at the Rare Sugar Research Center (Kagawa University, Japan), creatively established a novel and complete strategy to synthesize rare sugars. By using this method, termed Izumoring strategy, all monosaccharides could be cyclically converted by enzymatic epimerization, isomerization, and oxidization-reduction (Granstrom et al., 2004; Izumori, 2002, 2006). In the past two decades, most studies on the production of rare sugars were based on this classical strategy (Fig. 1). However, a few non-Izumoring enzymatic techniques have recently emerged, including aldose epimerization, enzymatic condensation (Alajarin et al., 1995), phosphorylation-dephosphorylation cascade reaction (Wen et al., 2015), decarboxylic reaction (Bao and Solheim, 2005), and biosynthesis of rare disaccharides by sucrose phosphorylase (Morimoto et al., 2015) and transglucosidase (Oshima et al., 2006). In this article, the non-Izumoring enzymatic techniques to synthesize rare sugars are reviewed. The synthesis of deoxy sugars is not considered in this review.

2. Izumoring strategy and its recent development

2.1. Izumoring strategy

Four types of enzymes are used in the Izumoring strategy, including ketose 3-epimerase, aldose isomerase (AIase), polyol dehydrogenase (PDH), and aldose reductase (ARase) (Fig. 2A). KEase catalyses reversible C-3 epimerization between ketoses. Each ketose corresponds to two aldoses by enzymatic isomerization and two polyols by corresponding PDHs (Fig. 2B). ARase and PDH catalyses the reduction of aldoses and ketoses, respectively, to corresponding polyols. Some polyols are identical to others, such as D-glucitol/L-gulitol and D-altritol/D-talitol, when the chemical structures are flipped 180° in the horizontal relative to one another (Fig. 2C). In this case, each polyol corresponds to two ketoses by corresponding PDHs. Based on these rules, the Izumoring strategy is constructed in a perfect ring, such that the relationship between any two monosaccharides is easily found and the bioconversion approach is easily designed (Fig. 2D) (Izumori, 2006).

2.2. Recent studies on the enzymes for rare sugar production

Numerous rare sugars have been enzymatically produced by the Izumoring strategy. Earlier studies mainly focused on isolation, identification and immobilization of rare sugar-producing enzymes. KEase was first identified by the Rare Sugar Research Center, at Kagawa University 20 years ago. To date, at least twelve KEases have been screened and identified showing high substrate specificity towards D-tagatose (Itoh et al., 1994), D-allulose (Kim et al., 2006a), D-fructose (Zhang et al., 2009), or L-ribulose (Uechi et al., 2013b). Based on the different optimal substrate, these KEases could be divided into three types, including D-tagatose 3-epimerase, D-psicose 3-epimerase and L-ribulose 3-epimerase. AIases generally exhibit broad substrate specificities, and at least ten AIases have been exploited for the production of various rare sugars (Mu et al., 2015). Typically, L-rhamnose isomerase catalyses reversible isomerization of more than ten pairs of aldoses-ketoses (Xu et al., 2016) and is used for production of D-allose (Lin et al., 2011), D-gulose (Bhuiyan et al., 1999), L-lyxose (Granstrom et al., 2005), L-mannose (Park, 2014), L-talose (Takata et al., 2011), and L-galactose (Leang et al., 2004). L-Arabinose isomerase (L-AI) has been extensively used for D-tagatose production from D-galactose (Xu et al., 2014a). D-Arabinose isomerase (D-AI) (Menavuvu et al., 2006) and L-fucose isomerase (L-FI) (Ju and Oh, 2010) are able to catalyse the bioconversion between D-allulose and D-altrose. Immobilization of rare sugar-producing enzymes is investigated to a cost efficient method for rare sugar production. For example, 441 g/L D-allulose could be obtained from 700 g/L D-fructose, by immobilization of *Agrobacterium tumefaciens* KEase on Duolite A568 beads with borate (Lim et al., 2009). The immobilized *Geobacillus stearothermophilus* L-AI on packed-bed reactor (PBR) loading alginate, could produce 54 g/L h^{-1} for D-tagatose (Ryu et al., 2003). The L-ribose isomerases immobilized on DIAION HPA25L beads could also be used in the production of L-allose, by which 33 g/L of L-allose could be gained from 100 g/L of L-allulose after a 1 day (Terami et al., 2015).

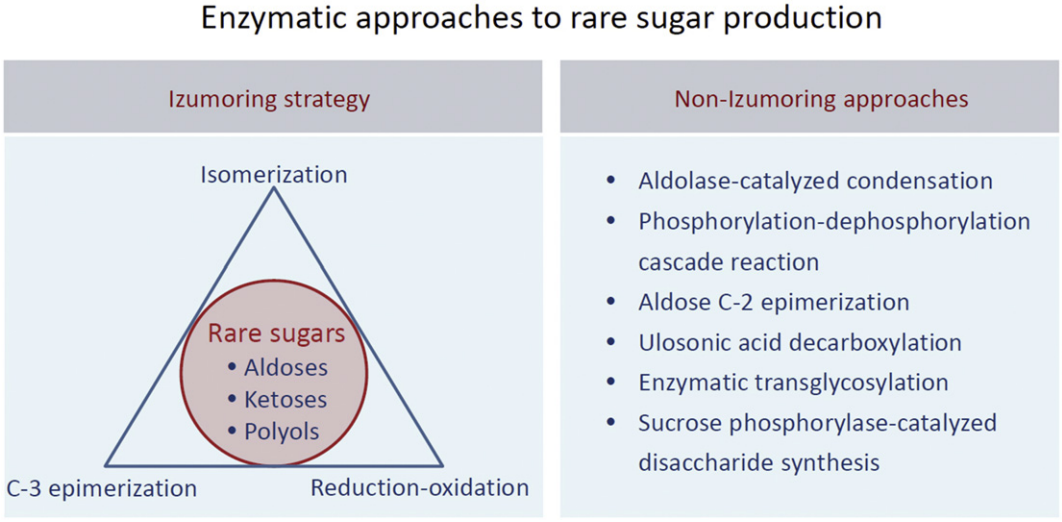

Fig. 1. Enzymatic approaches to rare sugar production.