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Transforming monosaccharides: Recent advances in rare sugar production and future exploration

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ABSTRACT

Rare sugars are defined as monosaccharides and their derivatives that do not exist in nature at all or that exist in extremely limited amounts despite being theoretically possible. At present, no comprehensive dogma has been presented regarding how and why these rare sugars have deviated from the naturally selected monosaccharides. In this minireview, we adopt a hypothesis on the origin and evolution of elementary hexoses, previously presented by one of the authors (Hirabayashi, Q Rev Biol, 1996, 71:365–380). In this scenario, monosaccharides, which constitute various kinds of glycans in nature, are assumed to have been generated by formose reactions on the prebiotic Earth (chemical evolution era). Among them, the most stable hexoses, *i.e.*, fructose, glucose, and mannose remained accumulated. After the birth of life, the "chemical origin" saccharides thus survived were transformed into a variety of "*bricolage* products", which include galactose and other recognition saccharides like fucose and sialic acid through the invention of diverse metabolic pathways (biological evolution era). The remaining monosaccharides that have deviated from this scenario are considered rare sugars. If we can produce rare sugars as we wish, it is expected that various more useful biomaterials will be created by using them as raw materials. Thanks to the pioneering research of the Izumori group in the 1990′s, and to a few other investigations by other groups, almost all monosaccharides including L-sugars can now be produced by combining both chemical and enzymatic approaches. After briefly giving an overview of the origin of elementary hexoses and the current state of the rare sugar production, we will look ahead to the next generation of monosaccharide research which also targets glycosides including disaccharides.

1. Origin of monosaccharides

Monosaccharides, the simplest forms of carbohydrates, serve as the fundamental units from which more complex carbohydrate chains are constructed. Two monosaccharides linked by a glycosidic bond form disaccharides, 2–10 monosaccharides form oligosaccharides, and several >10 monosaccharides form polysaccharides. These sugar chains play crucial roles in cell wall structure and surface functionality. Beyond the common "constitutive" monosaccharides, such as D-glucose (D-Glc), a fascinating class of rare sugars exists: monosaccharides and their derivatives are found in nature at much lower abundances. Kiliani-Fischer synthesis [1–3], a powerful method for synthesizing aldohexoses (6-carbon aldoses), exemplifies the generation of isomers (diastereomers) from the smallest sugar, D-glyceraldehyde (Fig. 1). Among D-aldohexoses, D-Glc, D-mannose (D-Man), and D-galactose (D-Gal) are ubiquitous, while D-allose (D-All), D-altrose (D-Alt), D-idose (D-Ido), D-gulose (D-Gul), and D-talose (D-Tal) are classified as rare sugars. This observation raises a basic question: how and why have these rare sugars deviated from the naturally selected constitutive monosaccharides?

In this review, we adopt a hypothesis on the origin and evolution of elementary hexoses, which has previously been presented by one of the authors [5,6]. Fig. 2 summarizes the essence of the proposed scenario [for more recent reviews, *see* Ref. 7]. As the first important point, the formose reaction, starting with formaldehyde (CH_2O) provides the foundation of carbohydrate chemistry. In the complex features of the reaction, key reactions include aldol condensation between glyceraldehyde and dihydroxyacetone, which produces a ketohexose, fructose. Once the fructose is produced, it is easily transformed under a basic

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condition into glucose (plus mannose in a trace amount) by the mechanism known as the classic glycochemistry "Lobry de Bruyn rearrangement-Alberda van Ekenstein transformation" (referred to as the Lobry de Bruyn transformation: [8–15]), and this happened before the first life was born (chemical evolution era). Recent advances in astrobiology provide evidence that formaldehyde is also available in interstellar space, where the reaction occurs between carbon monoxide (CO) and hydrogen (H_2) on the surface of ice grains [16]. Therefore, the origin of carbohydrates could be traced back to interstellar space, not restricted to Earth alone [17,18].

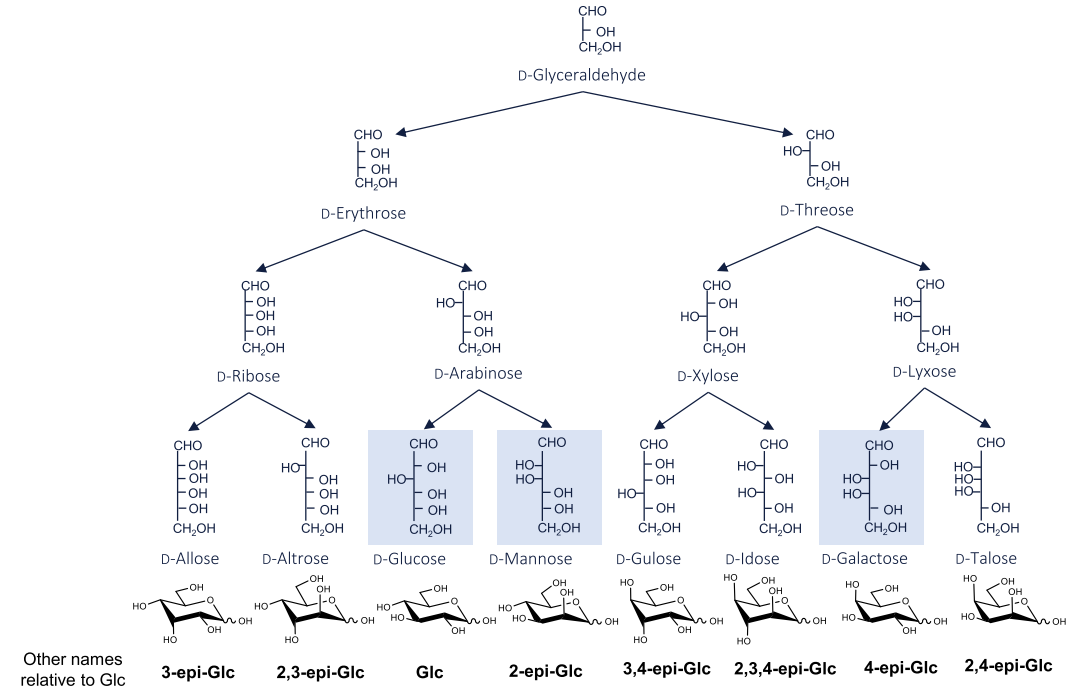
Among the formose reaction products, glucose is considered most stable with its pyranose form of $^4C_1$ conformation (see box in Fig. 1). In other words, no significant 1,3-diaxial interaction occurs in glucose, which destabilizes the $^4C_1$ conformation, and thereby shifts the equilibrium exclusively from an open ring structure (aldehyde form) to a closed pyranose form. On the other hand, such a hindrance is more significant in other aldohexoses. Notably, current life systems adopt only limited aldohexoses (i.e., glucose, mannose and galactose) with the minimal number (one, if any) of such interactions in their $^4C_1$ conformation. Thus, the second important point is that nature only uses stable aldohexoses with respect to 1,3-diaxial interaction. The effect of 1,3-diaxial interactions is still more severe in idose (regarded as 2,3,4-epi-glucose) > talose (2,4-epi-glucose) > gulose (3,4-epi-glucose) > altrose (2,3-epi-glucose). For this reason, these rare sugars have difficulty in being isolated as free monosaccharides, while they are often found in glycosides (described later).

The third important point of the scenario is that galactose is not included in the chemical origin monosaccharides (fructose, glucose and mannose) considering its biosynthetic features (i.e., epimerized via a 4-keto-intermediate using the coenzyme NAD^+) clearly distinct from those of chemical origin monosaccharides. From a mechanistic viewpoint, galactose cannot easily be transformed from fructose by the Lobry de Bruyn transformation, but from tagatose, which is absent in nature. Thus, galactose is regarded as a "late-comer" saccharide relative to the chemical origin saccharides with many other "*bricolage* products" [for details, *see* Refs. 5-7,19]. Actually, all of these *bricolage* saccharides (e.g., D-Gal, L-Fuc, L-Rha, sialic acid, various dideoxy saccharides) are biosynthesized from either glucose or mannose, but rare sugars are not.

2. Foundation of rare sugar synthesis

A breakthrough came with Izumori group demonstrating the microbial production of D-tagatose (D-Tag) [20] and D-sorbose (D-Sor) [21] from galactitol (the structures of a series of ketohexoses are shown in Supple. Fig. S1). This was followed by the discovery of D-tagatose-3-epimerase (DTE), an enzyme that converts D-fructose (D-Fru) to D-allulose (D-Alu) [22]. This enzymatic conversion paved the way for the production of D-type ketohexoses from readily available galactitol and D-Fru. Subsequently, L-rhamnose isomerase (LRI) enabled the production of D-All from D-Alu in 1997 [23,24], further highlighting the potential of enzyme-mediated rare sugar production [25,26].

Now that rare sugar standards are commercially available [22], unique properties of rare sugars, including their potential as low-calorie sweeteners (due to reduced digestibility) have garnered significant interest in the food, pharmaceutical, and nutraceutical industries [27–31]. Consequently, the mass production of these rare sugars is actively



1,3-diaxial interactions in $^4C_1$ conformation	2 × (OH–H)	3 × (OH–H)	0	1 × (OH–H)	3 × (OH–H)	1 × (OH–OH)+ 2 × (OH–H)	1 × (OH–H)	1 × (OH-OH)
Potential Energy increase relative to Glc	>1.0 kcal/mol	>1.5 kcal/mol	-	0.5 kcal/mol	>1.5 kcal/mol	2.9 kcal/mol	0.5 kcal/mol	1.9 kcal/mol

Fig. 1. A series of D-aldoses. Monosaccharide structures are shown as Fischer projections. For hexoses, generally accepted stable chair forms, i.e., $^4C_1$, are also shown for systematic comparison in terms of 1,3-diaxial interaction. The number of 1,3-diaxial interactions and relevant pairs are shown in a *box* at the bottom. Note that the energy increase caused by the 1,3-diaxial interaction between OH and OH groups (1.9 kcal/mol) is much larger than that between H and OH groups (0.5 kcal/mol; original data are from Ref. 4).

investigated, with various methodologies being reported [32–51].

The features of these enzymes represented by DTE and LRI are summarized in Fig. 3: *red* arrows indicate interconversion between ketoses catalyzed by DTE, while *blue* arrows indicate that between ketoses and aldoses catalyzed by LRI. The latter interconversion essentially follows the same reaction mechanism as that of the Lobry de Bruyn transformation, proceeding via a 1,2-enediol intermediate, while the former is regarded as an extended version of the Lobry de Bruyn transformation which proceeds via a 2,3-enediol intermediate Supple. Fig. S2).

Another important strategy to synthesize rare sugars is to utilize the redox scheme with alditol-2-dehydrogenase (Supple. Fig. S3). For example, D-Glc is chemically or enzymatically reduced to an alditol (D-glucitol = L-gulitol), then it is oxidized by alditol-2-dehydrogenase to generate D-Fru and L-Sor. Although this redox scheme is useful to generate various monosaccharides, including l-sugars, the reactions are complex, and the products are in most cases a mixture, forcing laborious work for further purification.

In any case, for most rare sugars, in particular L-sugars, large-scale production methods suitable for industrial applications remain to be established. Moreover, the lack of knowledge regarding rare sugars in nature as well as in processed foods hinders our understanding of their potential biological significance.

Having in mind the presented scenario on the origin and evolution of elementary hexoses, this review further focuses on methods for the supply and analysis of rare sugars, particularly aldohexoses (D, L-All, D, L, L-Alt, L-Gal, L-Glc, D, L, L-Gul, D, L, L-Ido, L-Man, D, L, L-Tal) and ketohexoses (D, L, L-Alu, L-Fru, D, L, L-Sor, D, L, L-Tag). We will also explore examples of naturally occurring rare sugars that have been reported to date.

3. Naturally occurring sugars and rare sugars

Rare sugars identified to date in nature are summarized in Table 1. All have been detected as free monosaccharides or their derivatives. On the other hand, neither D/L-Ido nor D/L-Gul, known to be unstable in their free forms, have been reliably reported in nature. Furthermore, attempts were made to utilize these plants and fruits as sources of rare sugars; however, these attempts were mostly unsuccessful due to the insufficient quantity of extraction and the considerable time and effort required. These reports also indicate that rare sugars are scarce in nature.

Additionally, there are reports indicating the existence of rare sugars present as glycosides or in complex carbohydrates. D-Tal has been expressed in antibiotics [62,63] and polysaccharides [64]; D-All in microbial glycolipids [65] and microbial [66] and plant [67] polysaccharides; D-Gul in microbial glycolipids [68] and antibiotics [69,70]; and L-Sor [71] in plant polysaccharides.

Reports of deoxygenated rare sugars exist —including 6-deoxy-D-altrose (dAlt) [72–75] and 6-deoxy-talose (dTal) [76–80] in which the 6-position of the sugar is deoxygenated. In glycoconjugates, there are numerous reports of rare sugars with low stability in aqueous solutions, including gulose, talose, and altrose (D/L not determined). In particular, numerous additional rare sugars have undergone deoxygenation, the reason for which has not been mentioned in the aforementioned reports. However, this suggests that the closed ring structure (i.e., non-linear structure) makes even unstable, free rare sugars (e.g., gulose, idose, talose) available as a result of 6-deoxygenation and are present at the cell surface for unknown reasons.

4. Analysis of rare sugars

Until now, it was not known at all how many rare sugars existed in

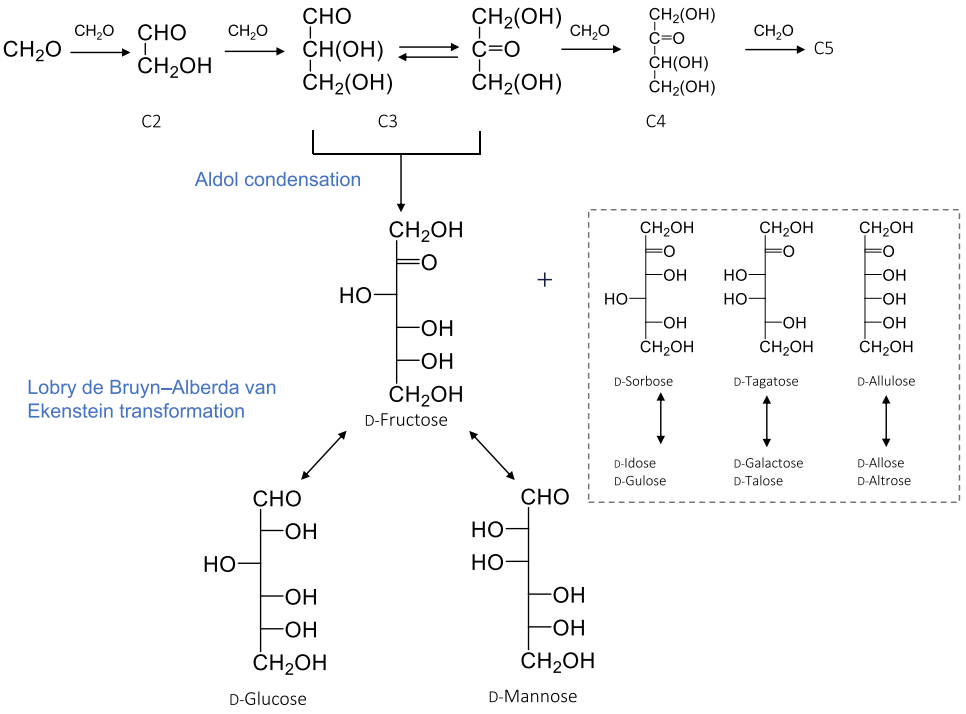


Fig. 2. A core scheme of the formose reaction from which elementary hexoses are considered to have originated in the chemical evolution era. The provided scenario is according to Hirabayashi [5]. The formose reaction is assumed to be a sole prebiotic synthesis of carbohydrates possibly having occurred on prebiotic Earth. Starting with formaldehyde (C1), it proceeds under a basic condition, repeating condensation to form C2, C3 and C4 sugars, while it also comprises aldol condensation between C3 sugars (glyceraldehyde and dihydroxyacetone) under the same basic condition. The condensation results in the generation of an important ketohexose (fructose), which is then slowly converted to aldohexoses (glucose and mannose) in equilibrium by the classic glycochemistry known as Lobry de Bruyn transformation-Alberda van Ekenstein transformation [8]. Mechanistically, however, other ketohexoses (sorbose, tagatose, allulose) cannot produce stable aldohexoses found in nature except for galactose (also *see* Fig 1). Formaldehyde is also available in interstellar space [16].

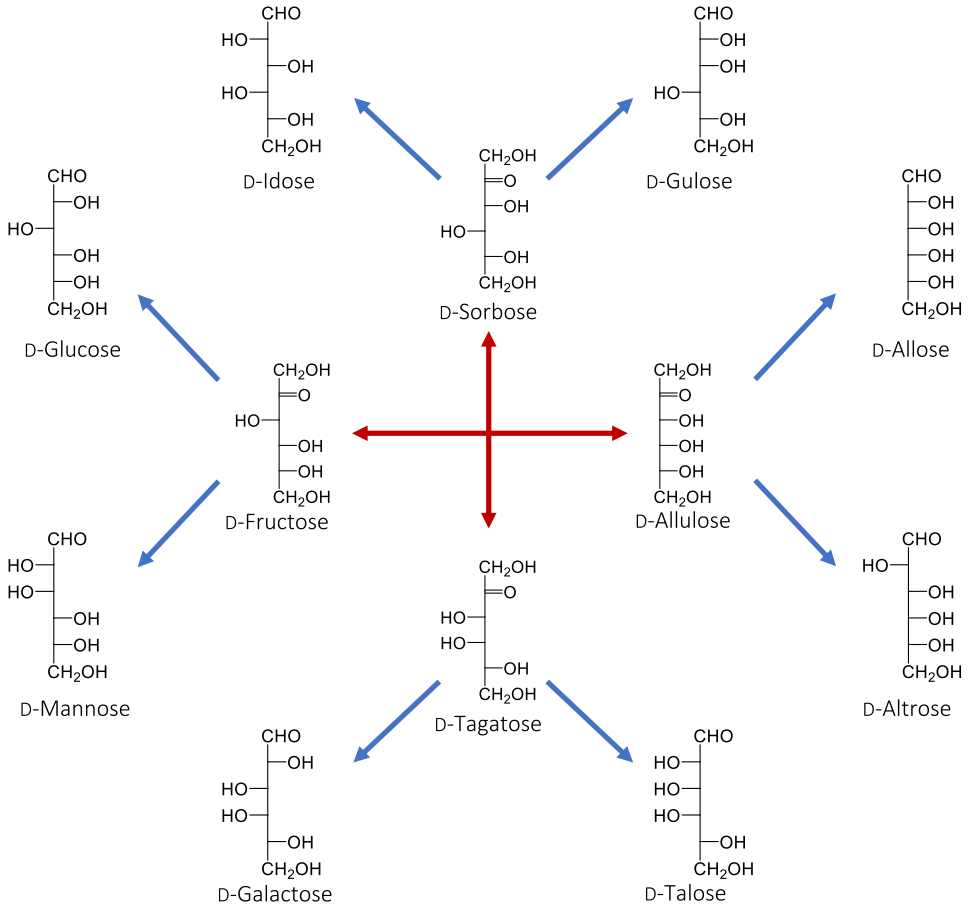


Fig. 3. Schemes of transformation between D-aldohexoses and D-ketohexoses. *Red* arrows represent reactions mediated by DTE (3-epimerization) via 2,3-enediol intermediates, while *blue* arrows represent those mediated by LRI (Lobry de Bruyn transformation) via 1,2-enediol intermediates.

Table 1
Naturally occurring rare sugars.

Rare sugars	Origins	References
D-Tagatose	*Sterculia setigera* Leaves	[52]
D-Allulose	Psicofuranine	[53]
	Itea ilicifolia	[54]
	Itea virginica	[54]
	Itea yunnanensis.	[54]
L-Sorbose	*Sorbus aucuparia*	[55]
	Passiflora edulis	[56]
	Avicennia marina	[57]
	Leaves	[57]
	Smilax china L., *Salix alba* L.	
D-Talose	*Avicennia marina*	[57]
	Leaves	[58]
	Mangifera indica Kernel	
D-Allose	*Passiflora edulis*	[59]
	Acalypha hispida	[60]
	Lavandula angustifolia	[61]
	Mill, Leaves	
D-Altrose	*Lavandula angustifolia* Mill, Leaves	[62]

nature, and there was no definitive method for how to measure them. This is because there were almost no standards for rare sugars. A range of rare sugars is now commercially available, thereby facilitating their detection. The D/L identification method for rare sugars is mainly based on the optical rotation method [81–83]. However, given the necessity of high purity and substantial sample volumes for analysis, there is a clear need to develop more sensitive and practical methods. Commercial products were employed as authentic standards in the search for rare sugars. At present, the majority of reports on the detection of rare sugars in natural products have employed analytical techniques based on gas chromatograph–mass spectrometry (GC–MS) [84–96]. In many cases, rare sugars are identified as metabolites in vivo through metabolomic analysis. However, the quantities detected by metabolomic analysis are generally very small and are only detected when increased or decreased expression levels occur.

Other analytical methods include high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) [97–100], as well as a combination of fluorescently labeled sugars and HPLC [101,102]. In the HPAEC-PAD method, the eluent is ionized under high pH conditions using a solvent, such as sodium hydroxide (OH groups of monosaccharides generally have p*K*a values of 12–13), and they are separated using an ion-exchange resin. This separation was made by measuring the oxidation current specific for each sugar in the solution. Moreover, this method can be used to analyze unlabeled rare sugars. However, it has not been used in the search for rare sugars derived from natural products due to the following problems: i) the use of sodium hydroxide solution as eluent, which requires careful handling; ii) the elution time is easily affected by carbon dioxide in air or in solution; and iii) the separation is not good (a small difference in p*K*a

occurs).

Rare sugars can be labeled by monoamine-coupling using reagents with amino groups that are commonly used for labeling oligosaccharides; e.g., 2-aminopyridine (2-AP), 2-aminobenzamide, 2-aminobenzoic acid, 4-aminobenzoic acid ethyl ester). The analysis of the labeled rare sugars was performed by HPLC connected with a fluorescence detector. When reacting with the aldehyde or ketone group of monosaccharides, they form a Schiff base. By reducing the double bond of the Schiff base with an appropriate reducing agent (e.g., borane dimethylamine complex, sodium borohydride), stable fluorescently labeled sugars can be prepared (Fig. 4). Fluorescent groups such as Fluorescein, Cy3, and Rhodamine have high fluorescence intensity, but are not suitable for separation of monosaccharides of equal molecular weight, because they are hydrophobic enough to cancel the water solubility of monosaccharides. In this method, however, it is possible to detect 1 fmol of fluorescently labeled glycans using a commercially available fluorescence detector [101,102]. When applying the monoamine-coupling method for ketoses, caution is necessary, because this reaction is very slow compared with aldoses [102]. Moreover, each ketose provides a pair of diastereomers regarding at the C3 position after reduction of the Schiff base. It should also be noted that when 2-AP is utilized, 2-AP acts as a base catalyst and promotes the Lobry-de Bruyn transformation to produce corresponding aldoses [103] (Fig. 4).

The analysis of rare sugars using a combined fluorescence-labeling and HPLC method is highly quantitative and sensitive because the fluorescent groups are introduced stoichiometrically at the reducing end terminal monosaccharide and a highly sensitive fluorescence detector is used. In addition, due to the incorporation of a hydrophobic fluorescently labeled group, the labeled sugars can be separated by a reversed-phase column with a much better resolution compared to other modes of chromatography (e.g., ion-exchange, normal-phase/hydrophilic, size-exclusion).

Nevertheless, there is a paucity of reports on the utilization of such methodologies. The abundance of rare sugar found in natural environments is a topic of significant interest. Additional research may potentially yield the identification of biomaterials that could facilitate the preparation of rare sugars from natural sources. It is anticipated that methodologies will be devised in the future that will facilitate the straightforward and sensitive detection of rare sugars.

5. Synthetic approaches to rare sugars

The production of rare sugars was previously carried out by Kiliani-Fischer synthesis and organic synthesis methods [1–3]. Later, two enzymes (DTE and LRI) discovered by Izumori *et al.* made it possible to produce both aldohexoses and ketohexoses [22,23], and some rare sugars can now be produced in quantities compatible with industrialization (Fig. 3). Enzymatic methods for rare sugar production are summarized in Table 2. Their reaction schemes are categorized based on the carbon atoms at the reaction center with respect to isomerization/epimerization and use a designated "Strategy nomenclature" (e.g., C1–C2 strategy). Notably, these reactions commonly proceed via key intermediate structures represented by keto-enol tautomerism and enediol intermediates, reflecting the classic glycochemical reaction, the Lobry de Bruyn transformation [8–15]. These schemes are summarized as "Reaction scheme" in the center of the Table 2.

The following subsections describe the production methods (enzymatic, organic, and chemical conversion methods) for each of the rare sugars (D-All, D-Alt, D-Alu, D-Gul, D-Ido, D-Sor, D-Tag, D-Tal, and ketohexoses) along with relevant research articles.

5.1. D-Allose (D-All)

D-All is the 3-epimer of D-Glc (the hydroxyl group at position 3 is oriented toward the axial side in the $^4C_1$ conformation); it is particularly abundant in some natural plant extracts and bacterial metabolites [104]. Its potential uses include anticancer [28,105–107], antioxidant [29], antiaging [30], antihypertensive [108], cryoprotective, and immunosuppressive [109,110] agents. Chemical synthesis methods use redox to change the arrangement of various sugars to synthesize D-All, but the procedure is laborious and produces many byproducts [111–114].

In the enzymatic production method, LRI is used for the production of D-All from D-Alu (Table 2, C1–C2 strategy), the scheme of which is essentially the same as the Lobry de Bruyn transformation. The enzyme was discovered in 1997 [23] and has been cloned from various microorganisms due to its usefulness for D-All production [115–119].

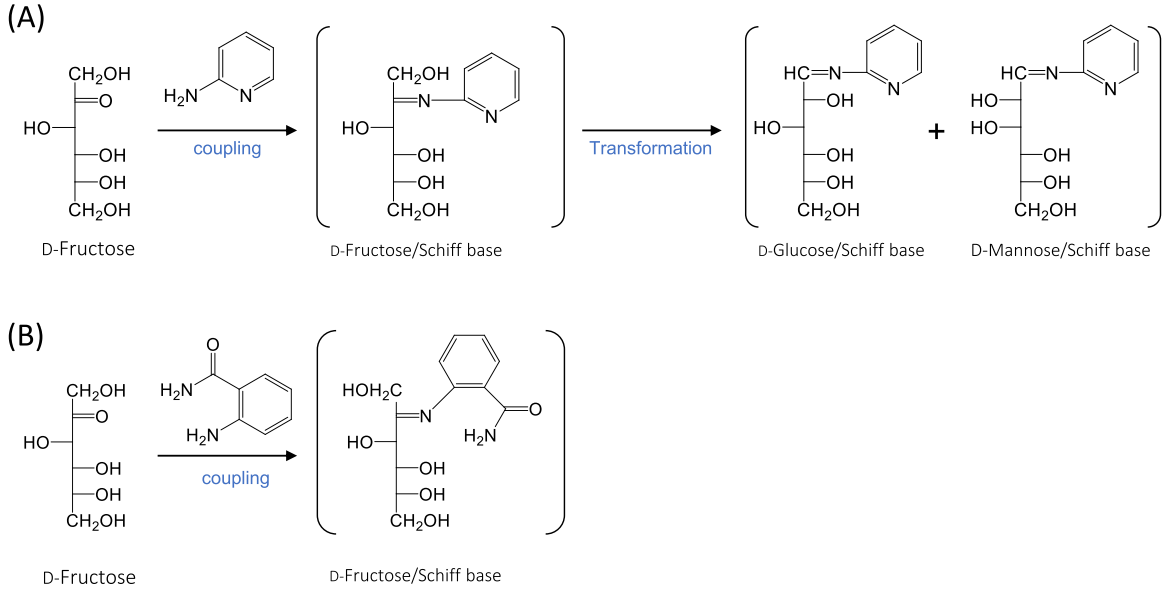
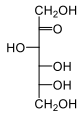
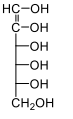
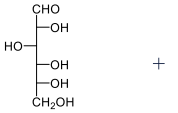
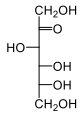
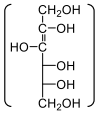
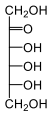
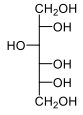
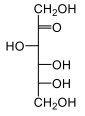
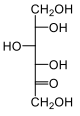
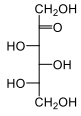
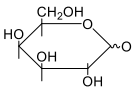
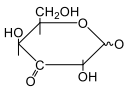
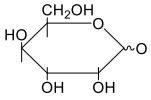
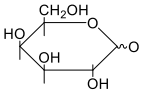
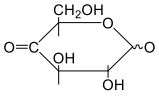
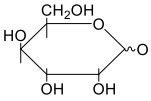
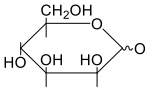
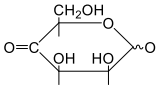
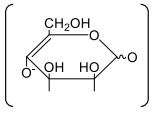
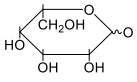
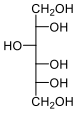
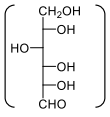
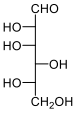


Fig. 4. Different behaviors of ketohexoses on monoamine coupling using 2-aminopyridine and 2- aminobenzamide. When a ketohexose, e.g., D-fructose is reacted with the 2-aminopyridine, which is used for fluorescent labeling of oligosaccharides, the ketose is subjected to Lobry de Bruyn-Alberda van Ekenstein transformation with the reagent acting as a base catalyst (A), while 2-aminobenzamide is used for fluorescent labeling, it does not induce the transformation and a Schiff base product is obtained as expected. The derived Schiff base products are reduced to generate more stable fluorescently labeled ketohexoses. Note that Lobry de Bruyn-Alberda van Ekenstein transformation is observed only when ketoses are reacted with 2-aminopyridine, but not with aldoses.

Table 2
Key strategies to produce rare sugars.

Strategy nomenclature	Reaction scheme				
C1-C2 (Classical Lobry)		→		→	
	D-Fructose		1,2-Enediol		D-Glucose + D-Mannose
C2-C3 (Extended Lobry)		→		→	
	D-Fructose		2,3-Enediol		D-Allulose
C2 keto (C5 keto)		→		+	 = 
	D-Glucitol/ L-Gulitol		D-Fructose (2-keto)		(5-keto) L-Sorbose
C3 keto (3-epi)		→		→	
	D-Galactose		3-Keto-D-Galactose		D-Gulose
C4 keto (4-epi)		→		→	
	D-Glucose		4-Keto-D-Glucose		D-Galactose
C4 keto (3,5-epi)		→		→	 → 
	D-Mannose		4-keto-D-Mannose		4,5-Enol L-Gulose
C6 aldo		→		=	
	D-Glucitol/ L-Gulitol		Aldehyde		L-Gulose

Additionally, ribose/galactose isomerase has been cloned as an enzyme that may catalyze the isomerization of D-Alu to D-All [120–122]. When D-All is produced using these enzymes, the substrate (D-Alu) and the products (D-All and D-Alt) must be separated, which presents a challenge for industrialization.

5.2. D-Allulose (D-Alu)

D-Alu, the 3-epimer of D-Fru, is found in the *Itea* (*Itea ilicifolia, Itea virginica, Itea yunnanensis*) plant [54] and also in heated foods, possibly as an artifact resulting from D-Fru [98]. D-Alu is 70 % as sweet as sucrose but is not an energy source [27]. It also has insulin-secreting properties [123]. Moreover, GLP-1 (whose secretion is enhanced by D-Alu) was found to improve overeating, obesity, and diabetes [124]. Additionally, it exhibits plant growth inhibitory properties [125] and is one of the rare sugars that have attracted industrial attention.

Most methods used for the production of D-Alu incorporate microbial enzymes (Table 2, C2–C3 strategy)—only a few reports describe: a chemical synthesis method [126]. In enzymatic methods, D-Fru is used as a substrate, and epimerization is carried out using an

epimerase—DTE—discovered in 1993 [127]. This enzyme showed rather broad substrate specificity and later proved to be useful even for the production of D-Alu [128]. Subsequently, epimerases for the production of D-Alu were cloned from various microorganisms [129–132]. Hence, various methods of immobilizing DTE on columns to perform isomerization reactions [133–143], as well as production using microorganisms without enzyme purification [144–150], have been developed.

In addition to DTE methods, those using aldol condensation [151,152] and NAD(H)-dependent alcohol dehydrogenase [153,154] have also been reported. Regarding the purification of D-Alu, methods such as separation using simulated moving bed chromatography [155–157] and converting unreacted substrates to ethanol and removing the ethanol using yeast [158–160] have also been developed, thus making industrial production of D-Alu possible based on these procedures.

5.3. D-Altrose (D-Alt)

D-Alt is the 2,3-epimer of D-Glc. Little is known about the function of D-Alt as a monosaccharide. D-Alt has been synthesized by organic chemical methods, but the procedure is complex [161]. Other reports include its polymerization [162] and incorporation into antimicrobial agents [163]. Microbial production methods allow its synthesis from D-Alu or D-All (Table 2, C1–C2 strategy, Fig. 3) with the same reaction strategy of isomerization by LRI [164]. Synthesis from D-Alu using arabinose isomerase has also been reported [165].

5.4. D-Gulose (D-Gul)

D-Gul is the 3,4-epimer of D-Glc. Little is known about the function of D-Gul as a monosaccharide. D-Gul has been synthesized using organic chemical methods [166,167], and microbial production has also been attempted. However, because the structure is prone to Lobry de Bruyn transformation, the synthesis (Table 2, C-3 keto strategy) has been carried out using a glycoside (e.g., lactose) as a substrate, in which the non-reducing terminal D-Gal is subjected to modification [168,169].

5.5. D-Idose (D-Ido)

D-Ido is the 2,3,4-epimer of D-Glc. Little is known about the function of D-Ido as a rare sugar, particularly because of its instability. D-Ido has been synthesized using only organic chemical methods [170].

5.6. D-Sorbose (D-Sol)

D-Sor is the 3,4-epimer of D-Fru. Although little is known about the function of this monosaccharide, D-Sor has been synthesized using microbial methods [14]. Enzymatic methods have also been reported for its synthesis from D-Tag using DTE and D-psicose-3-epimerase [171,172] (Table 2, C2–C3 strategy). Alternatively, its production has also been achieved by aldol condensation between dihydroxyacetone phosphate and glyceraldehyde using aldolase [151,152].

5.7. D-Tagatose (D-Tag)

D-Tag is the 4-epimer of D-Fru. The function of D-Tag as a monosaccharide has been reported for caries prevention [173–177]. D-Tag has been synthesized using microbial methods [20,178–183]. Enzyme-based methods, including production with L-arabinose isomerase [184–193] (Table 2, C1 strategy) or ketose-3-epimerase [194] (Table 2, C1 strategy) using D-Gal as a substrate, and L-ribose isomerase [195] (Table 2, C2–3 strategy) using D-Tal as a substrate, have been reported. Recently, methods using tagatose-4-epimerase [196,197] and (de)phosphorylation cascade [198,199] have also been reported.

Synthetic methods using D-Gal as a raw material and chemical processing methods have also been reported [200,201] (Table 2, C1 strategy) in numerous reports. Chemical synthesis (Lobry de Bruyn transformation) is more efficient than enzymatic methods, and D-Tag is currently produced by chemical synthesis.

5.8. D-Talose (D-Tal)

D-Tal is the 2,4-epimer of D-Glc; little is known about the function of D-Tal as a monosaccharide. For its production, however, both organochemical [202] and enzymatic methods have been reported (Table 2, C1-C2 strategy). For the latter, L-arabinose isomerase [203], L-ribose isomerase [194,204], and cellobiose 2-epimerase [204] have been used with D-Gal and D-Tag as substrates. In the production of D-Tal using epimerase, D-Man and D-Gal are possible substrates. However, the only reported case is with D-Gal as the substrate [205], suggesting that epimerization at position 4 may be difficult. In addition, a synthetic method (Table 1, C1 strategy), in which D-Gal is chemically treated, has also been reported [206].

6. Summary of the current state-of-the-art of rare sugar synthesis

6.1. D-Series hexoses

Reaction schemes to produce a series of D-hexoses mediated by DTEs (D-tagatose-3-epimerase [22], D-psicose-3-epimerase [106]) and LRIs (LL-rhamnose isomerase [23], L-ribose isomerase [169], L-arabinose isomerase [140], D-xylose isomerase [75]) are summarized in Fig. 3. The central *red* arrows indicate the reactions catalyzed by DTEs, and the peripheral *blue* arrows indicate those catalyzed by LRIs reactions. The DTEs are ketose-ketose converting enzymes, and LRIs are ketose-aldose converting enzymes; in other words, the former reaction proceeds via 2,3-endiol intermediates, while the latter proceeds via 1,2-enediol intermediates. Both DTEs and LRIs recognize all four types of ketohexoses as substrates; i.e., they have rather broad specificity, and thus can convert them to their respective products.

Commonly available monosaccharides are D-Glc, D-Man, D-Gal, and D-Fru, among which the ketose substrate for DTEs is D-Fru, and the product is D-Alu (3-epi-D-Fru) [22]. D-Sor and D-Tag cannot be synthesized directly from the available monosaccharides, but they can be converted from their respective alditols. In fact, it is possible to convert galactitol (the alditol form of galactose) to D-Tag using a microbial system [20], subsequently, D-Tag was converted by the action of DTEs to D-Sor, which is in a sense "3-epi-D-Tag" [21]. Therefore, it is possible to prepare all D-ketohexoses.

D-Aldohexoses are converted using LRIs with D-ketohexose as a substrate. D-Glc and D-Man are obtained from D-Fru (classic Lobry de Bruyn transformation). On the other hand, D-All and D-Alt are obtained from D-Alu [120,164], D-Gul is obtained from D-Sor [207], and D-Gal and D-Tal are obtained from D-Tag [204]. Despite the broad specificity of the enzymes, D-Ido cannot be easily obtained. As the enzymatic reaction is weakly basic at pH 7–9, D-Ido is readily converted to a more stable D-Sor by a Lobry de Bruyn transformation mechanism, which is known to proceed under equilibrium conditions [8]. Also, D-Gul, D-Tal, and D-Alt showed low conversion rates, possibly due to their instability in aqueous solutions. In fact, D-Ido has three hydroxyl groups with axial configuration, and D-Gul, D-Tal, and D-Alt have two (*see* box of Fig. 1). These axial hydroxyl groups significantly contribute to the destabilization of the structure by 1,3-diaxial interactions [5,6].

6.2. L-Series hexoses

At present, the only L-hexose that can be readily available is L-Sor, which is produced by the procedure known as "L-sorbose fermentation" [208–218] (Fig. 5). As a substrate, L-Sor is then converted to L-Tag (possibly expressed as "3-epi-L-Sor") by the action of DTEs.

On the other hand, neither L-Fru nor L-Alu, can be produced by DTEs

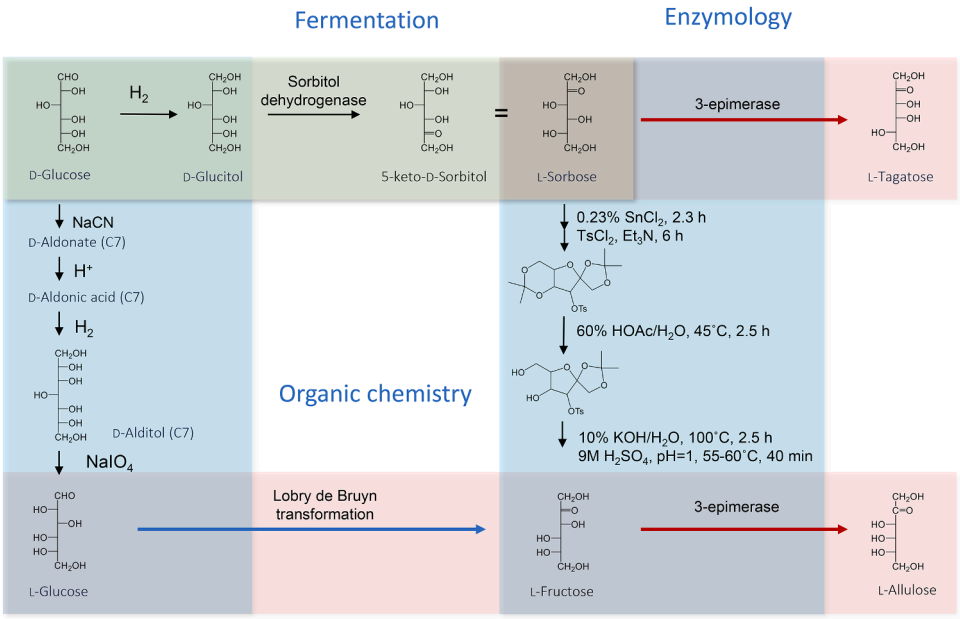


Fig. 5. Synthetic strategy for L-series hexoses.

or LRIs alone. Possible methods include: *i*) oxidation of D-sugar-derived alditols to ketose by alditol dehydrogenase [219,220] (Table 2, C-6) and *ii*) condensation using aldolase between 1,3-dihydroxyacetone phosphate (DHAP) and L-glyceraldehyde (GA) as substrates [221–223]. In the method *i*), L-Alu (and D-Alu) are produced from D-All, which is reduced, and then the derived "allitol" is oxidized to form corresponding ketohexoses by the action of alditol dehydrogenase [224,225]. Alternatively, D-Sor is reduced, and the derived "D-gulitol" (=L-glucitol) and "D-iditol" react with alditol dehydrogenase to produce L-Fru and D-Sor, respectively (Supple. Fig. S3). However, both of these methods *i*) and *ii*) are very laborious and require many processes. Alternatively, *iii*) either of L-Fru, L-Glc, or L-Man are synthesized by organic chemistry (Scheme 1). Once L-Fru [226] or L-Glc [167,227] is produced, it can be readily converted to L-Man and other L-sugars using the appropriate enzymes described above.

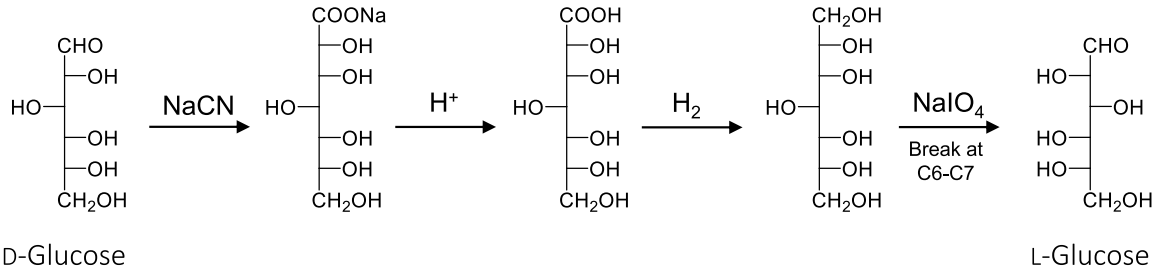
7. Future perspectives: from free monosaccharides to glycosides

As described above, a series of D-hexoses can now be obtained by using common monosaccharides (D-Fru, D-Glc, D-Man, and D-Gal) and their alditols (D-glucitol, D-mannitol, and galactitol) as raw materials. D-Tag and D-Sor can be synthesized from galactitol using fermentation technology. D-Alu, D-All, and D-Alt can also be synthesized from D-Fru, D-Gul from D-Sor, and D-Tal from D-Tag using DTEs and LRIs. Only D-Ido is difficult to produce by enzymatic conversion. This is because D-Ido is unstable in a basic aqueous solution and is converted to a more stable D-Sor *via* Lobry de Bruyn transformation.

On the other hand, the only possible raw material for L-hexoses is L-Sor, which can be obtained by fermentation technology. Starting with L-Sor and using DTEs and LRIs, its derivatives (L-Gul, L-Tag, L-Tal, and L-Gal) can be synthesized according to an analogous scheme shown in Fig. 3. On the other hand, neither L-Glc nor L-Fru can be produced by the present enzymes to the extent of an industrial scale. However, by using organic chemical procedures L-Glc can be produced in a satisfactory yield and scale (Scheme 1). Hence, by combining with DTEs and LRIs, the remaining L-series hexoses (L-Man, L-All, and L-Alt) can be produced (Fig. 5).

Taken together, a comprehensive strategy for hexose synthesis has been established: if any of the two key ketohexoses (i.e., Fru/Alu and Sol/Tag) or any of the four aldohexose (Glc/Man, All/Alt, Gal/Tal, and Gul/Ido) for each of the D and L-series monosaccharides is given, all of the other hexoses can be produced with good productivity by the action of DTE and LRI (Suppl. Fig. 4), albeit with limitations regarding: the natural monosaccharides. For their industrialization, a successful combination of organic chemical and biological methods (enzyme engineering, genetic engineering and synthetic biology) will be a better solution. Discovering an enzyme that can more efficiently convert L-glucitol to L-Fru after the reduction of D-Sor would be a breakthrough in the production of L-series hexoses. Thus, the groundwork for developmental research on rare sugars has been laid.

By the way, it is also important to grasp the potential diversity of carbohydrates consisting of not only natural but also non-natural monosaccharides. It is known that current life systems utilize only a part of the possible component monosaccharides despite the vast theoretical possibilities. In other words, a chemical scheme represented by Kiliani-Fischer synthesis [1–3] has not been achieved yet in the scope of



Scheme 1. Chemical synthesis of L-Glc from D-Glc.

"chemical space" [228]. In this context, RA Laine once attempted to calculate the structural diversity of hexasaccharides consisting of natural saccharides and estimated it to be as large as 1.02×10^{12} [229]. However, this figure must be much smaller than the potential diversity of all carbohydrates. The basic question is: how many isomers are possible when all aldohexoses form disaccharides?

Fig. 6 illustrates a portfolio of the theoretical scheme for this question. For instance, if the non-reducing end is fixed to D-Glc, its reducing terminal aldohexoses are composed of 8 D-aldohexoses and 8 L-aldohexoses. When considering the disaccharide structure of non-reducing terminal D-Glc and the reducing terminal D-sugars, there are two anomers for each of the five glycosidic linkages (α/β1–1/2/3/4/6), which results in $2 \times 5 = 10$ combinations. In the case of disaccharides, we must take into consideration non-reducing disaccharides, which are formed by linkages *via* α1–1α, α1–1β, β1–1α, and β1–1α. However, if the same monosaccharides form the non-reducing end of the disaccharides, two of them should be identical; i.e., D-Glcα1–1βD-Glc = D-Glcβ1–1αD-Glc. So, in the case of homodimers, there are 11 structural variations (Fig. 6, upper part), while in the other case there are 12 structural variations (Fig. 6, lower part).

If we consider only naturally occurring aldohexoses (D-Glc, D-Man, and D-Gal), $3\times (11+12\times2) = 105$ disaccharide isomers can be formed, among which the number of disaccharides that naturally occur is still worth discussing [230]. On the other hand, if we consider all of the theoretical aldohexoses including rare sugars, the structural diversity reaches $8 \times 2\times (11+12\times15) = 3056$. For comparison, in the case of amino acids, the number of isomers when 20 amino acids form a dipeptide is $20\times20=400$.

What about the possibility of synthesizing such non-natural disaccharides? Carbohydrates or glycans potentially have enormous structural diversity compared to polynucleotide (DNA and RNA) and polypeptide (protein). This is largely attributed to a variety of glycosidic linkages (as many as 12 in the case of disaccharides). However, the current life system only utilizes a part of the monosaccharide components; at the level of aldohexose, only 3 (i.e., D-Glc, D-Man, and D-Gal) as described for an evolutionary reason [5,6]. This is precisely the point at which the "*raison d'etre*" of rare sugars is questioned.

Sugars, rigorously defined as carbo-hydrate (C—H_2O), hold multiple asymmetric carbons; therefore, chemical synthetic approaches are technically difficult; However, by utilizing the transglycosylation activity of a variety of glycosidases, which combines a monosaccharide with a *p*-nitrophenly group (*p*NP group) and exoglycosidases, a monosaccharide (*p*NP-linked monosaccharide) can be introduced at the non-reducing terminal end [231–233]. In that case, however, the linkage position is difficult to control, but four isomers (1–2, 1–3, 1–4, and 1–6) can be prepared in a single reaction, as the linkage mode is significantly influenced by the substrate specificity of the exoglycosidases. Thus, rare sugars have great potential as raw materials for future bioscience, encompassing medicine, food and material sciences by providing both unexplored structural modalities and high-water solubility [234].

8. Conclusion

A possible scenario on the origin and evolution of elementary saccharides was presented more than a quarter of a century ago [5,6]. To the best of the authors' knowledge, this is the only scenario to explain

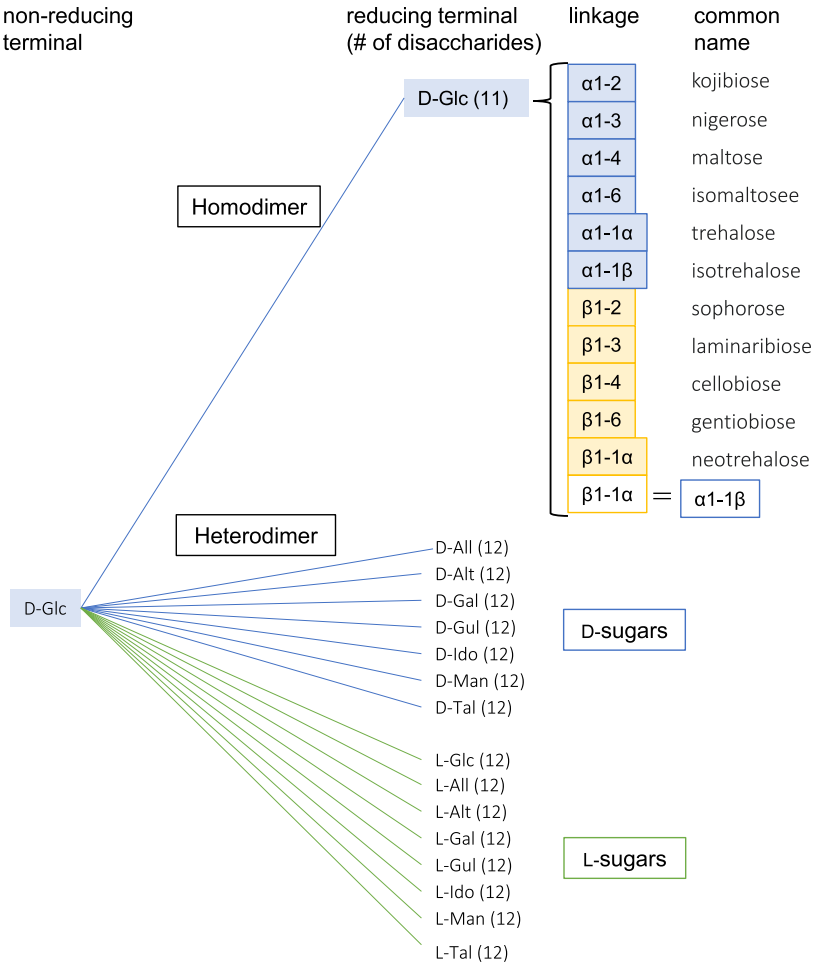


Fig. 6. Structural diversity of disaccharides with D-glucose at the non-reducing end.

the origin of carbohydrates and evolutionary process at the level of monosaccharides [7]. Formose reaction is the most probable prebiotic synthesis of carbohydrates on the primitive Earth [235], for which raw material, formaldehyde, has recently been shown by analysis to be available even in interstellar space [7]. After the emergence of the first life, chemical derived monosaccharides (i.e., fructose, glucose and mannose) were maximally utilized to produce a number of *bricolage* products, represented by "recognition" saccharides like D-Gal, L-Fuc and sialic acid [5,19].

In this minireview, the authors attempt a consistent explanation of how and why rare sugars have deviated in accordance with the proposed scenario. In our conclusion, 1,3-diaxial interaction had great influence on the selection of monosaccharides produced on the primitive Earth, because free monosaccharides readily react with amine (e.g., ammonia), which were assumed to be relatively rich in the primitive atmosphere on the prebiotic Earth. Among products of formose reaction, glucose is most stable owing to its $^4C_1$ conformation of the pyranose form, while the other aldohexoses are less stable with multiple 1,3-diaxial interactions so that they had difficulty in surviving on the prebiotic Earth. It is hardly expected that less stable, minor compounds had a better chance to be selected by life for making *bricolage* products, because they are neither abundant nor inexpensive; only glucose does*.

* The authors do not discuss the issue of enantiomeric selection (how and why D-sugars were selected on Earth, because it is beyond the scope of this paper, although there have been advanced researches in D/L-amino acids in the theoretical physics (e.g., [236]).

Although the systematic Kiliani synthesis may give us the impression that the carbohydrate series is totally homogeneous, a comparison of the $^4C_1$ conformations among isomers shows that they are by no means homogeneous or similar, at least in terms of 1,3-diaxial interactions. This is a real reflection of which sugars are present in nature (constituent) or absent. Apparently, rare sugars belong to the latter. Life has the ability to create various substances from a small number of inexpensive and abundant tools, such as glucose, through a *bricolage* strategy. However, as the Kiliani synthesis method shows, there is no need to synthesize all diastereomers that satisfy the carbohydrate formula (according to the Occam's razor principle). If that is the case, will glycosides containing monosaccharides called rare sugars, which are the subject of this mini-review, become meaningless compounds for life? No, they must be waiting for the day when they are unlocked by "science," which is the ability of humanity. Since disaccharides containing all kinds of rare sugars have a hitherto unrealized "chemical space" the combinations of monosaccharides containing rare sugars (synthetic glycomics) are infinite and must contain the key to creating future life. The authors believe that this is the true intention of this special issue, "Expanded Glycomics: A Bridge over Future Glycoscience".

CRediT authorship contribution statement

Shin-ichi Nakakita: Writing – review & editing, Writing – original draft. **Jun Hirabayashi:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bbadva.2025.100143.

Data availability

Data will be made available on request.

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