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Review

Recent progress of sugar amino acids: Synthetic strategies and applications as glycomimetics and peptidomimetics

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ABSTRACT

In order to meet the increasing demands for the development of large varieties of new molecules for discovering new drugs and materials, organic chemists are developing many novel multifunctional building blocks, which are assembled rationally to create 'nature-like' and yet unnatural organic molecules with well-defined structures and useful properties. Sugar amino acids (SAAs), the carbohydrate derivatives bearing both amino and carboxylic acid functional groups, are important ones of these multifunctional building blocks, which can be used to create novel materials with potential applications as glycomimetics and peptidomimetics. This review will focus on recent synthetic strategies of SAAs and their applications in creating large number of structurally diverse glycomimetics and peptidomimetics.

1. Introduction

As demand for discovering new molecules is increasing day by day, the requirements are not adequately met by the traditional methods, which have prompted chemists to work on alternative concepts to create new molecules at much faster rate as they can [1]. Both carbohydrates and amino acids are widely used in nature as fundamental building blocks to build its vast repertoire of biomolecules, which can be amalgamated to create nature-like and yet unnatural new molecules with multifunctional groups anchored on a single of ensemble [2]. Sugar amino acids (SAAs), the carbohydrate derivatives bearing both amino and carboxylic acid functional groups, represent an important class of such new molecules that can be used to create novel materials with potential applications as glycomimetics, artificial amino acids and peptidomimetics [3].

In this review, we describe recent synthetic strategies of SAAs as a novel class of building blocks and their applications in creating large number of structurally diverse glycomimetics and peptidomimetics. The term SAAs was used for compounds that are basically hybrids of carbohydrate and amino acids where carboxyl and amino functional groups have been incorporated at the two termini of regular 2,5- or 2,6-anhydrocarbohydrate frameworks (Fig. 1).

2. Naturally occurring SAAs

SAAs and their derivatives occur in nature in various forms (Fig. 2). The most prominent example is sialic acid (**1**), a family of *N*- or *O*-substituted derivatives of neuraminic acid, containing over 50 derivatives of the nine-carbon backbone. These structures unusually appear free in nature, but present as components of oligosaccharide chains of mucins, glycoproteins and glycolipids occupying terminal, non-reducing positions of complex carbohydrates on both external and internal membrane areas where they are very exposed and develop important functions [4]. Glucosaminuronic acid (**2**), which has many biological functions such as being a component of many typical bacterial cell walls, exists naturally as an acetyl derivative [5]. The naturally occurring 2-acetamido-2-deoxygalacturonic acid (**3**) is one of bacterial Vi-antigen components of *Escherichia coli* [5]. 2-Amino-2-deoxy-D-mannouronic acid (**4**) is found in bacterial polysaccharide

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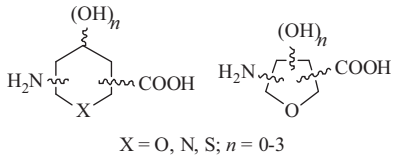

Fig. 1. General structures of SAAs.

sequences. Derivatives of 3-amino-3-deoxy-D-gulopyranuronic acid (**5**) and 3-amino-3,4-dideoxy-D-xylohexopyranuronic acid (**6**) are found in ezomycin A [5]. Naturally existing 4-amino-4-deoxy-glucuronic acid (**7**) is found in gougerotin, a product isolated from *Streptomyces* bacteria [6]. SAA **8** is found as the residue of the cell wall O-antigen in *Plesiomonas shigelloides* O51 [7]. Peptidyl nucleoside antibiotics polyoxin (**9**), nikkomycin (**10**) are other kinds of natural SAAs [8]. Hydroxylated prolines (**11**) and hydroxylated pipecolic acids (**12**) are azasugar-based SAAs, whose endocyclic oxygen atom in the ring is replaced with a nitrogen atom [9]. The naturally occurring SAA **13** is the α,α-disubstituted hydantoin derivative, exhibiting potent selective anti-herbal activity with no toxicity to microorganisms or animals [10].

3. Synthetic strategies of SAAs

In recent years, a number of research groups have designed and synthesized many unnatural SAAs and used them to create novel structural entities. The synthesis of SAAs is always accomplished in a few steps starting from commercially available or easily accessible monosaccharides, such as glucose, galactose, glucosamine, diacetone glucose *ect*. In order to obtain synthetic SAAs, amino and carboxylic functional groups are required to be introduced. The amino functional group can be introduced as azide, cyanide, nitromethane, followed by subsequent reduction. The carboxylic group can be constructed by selective oxidation of a primary alcohol, or by Wittig reaction and subsequent oxidation, or directly as carbon dioxide, or as a hydrolyzable cyanide and subsequent hydrolysis reaction.

3.1. Introduction of amino group

3.1.1. Introduction of azide

As shown in Scheme 1, addition of hydrazoic acid to the α,β-unsaturated aldehyde derived from methyl 3,4-di-*O*-acetyl-D-glucuronal (**14**), followed by glycosylation of methanol, yielded a mixture of products that were separated and identified as methyl (methyl 4-*O*-acetyl-3-azido-2,3-dideoxyhexopyranosid)uronates (-α-D-*arabino* (**15a**), -β-D-*ribo* (**15b**), -α-D-*ribo*- (**15c**), and -β-D-*arabino* (**15d**)) [11]. Compounds **15a–d** were each *O*-deacetylated with sodium methoxide in methanol (0.1 mol/L) to yield the corresponding methyl (methyl 3-azido-2,3-dideoxyhexopyranosid)uronates, which were then reduced by hydrogenation (10% Pd/C) of the azide to yield methyl (methyl 3-amino-2,3-dideoxy-α-D-*arabino*- (**16a**), -β-D-*ribo*- (**16b**), -α-D-*ribo*- (**16c**) -β-D-*arabino*-hexopyranosid)uronates (**16d**). Treatment of **16a** and **16d** with 1 mol/L aq. NaOH led to completely unprotected SAAs **17a** and **17b** [12].

3.1.2. Introduction of cyanide

The substitution of an anomeric *O*-acyl group with cyanide of trimethylsilyl cyanide (TMSCN) in the presence of a mild catalyst was reported by Gross P.H. [13]. As shown in Scheme 2, treatment with excess TMSCN and 0.1 mol equiv. of $HgBr_2$ in CH_3NO_2, β-D-glucopyranose **18** was converted into β-D-glucosyl cyanide **19** in

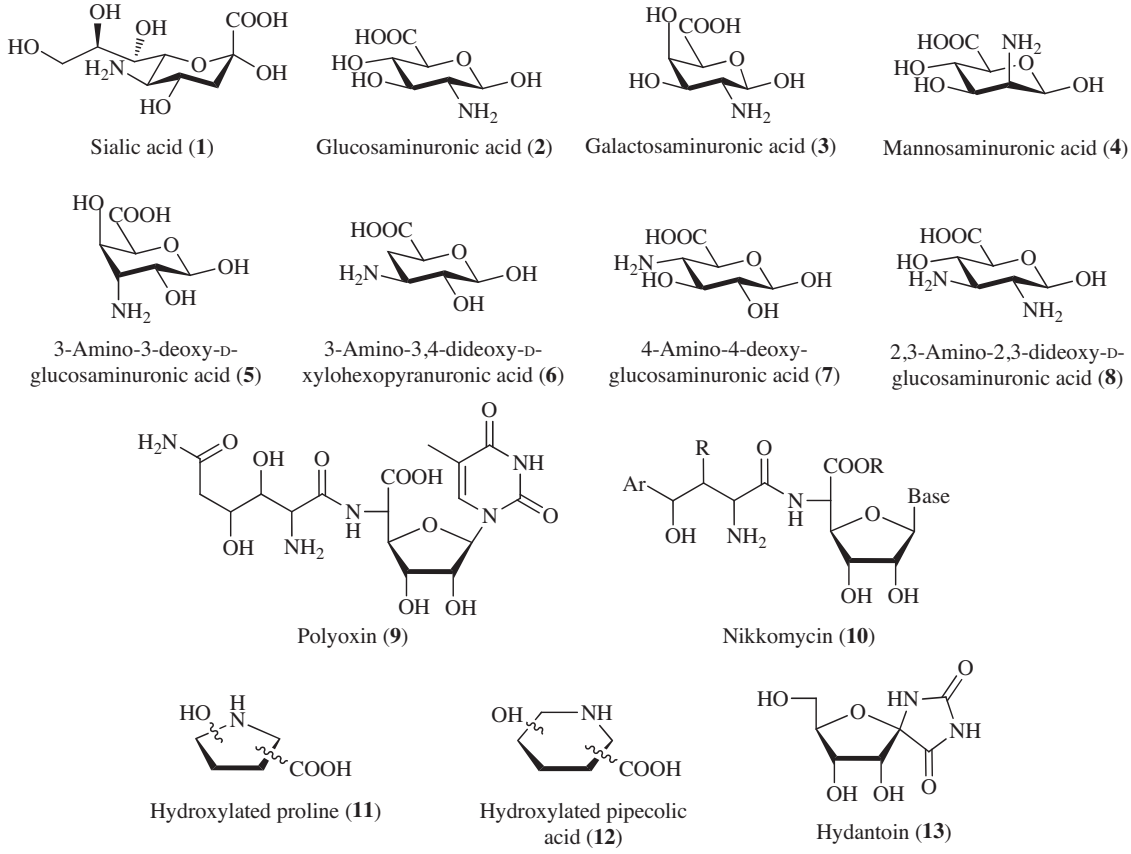

Fig. 2. Examples of naturally occurring SAAs.