

Sugar Mimetics: Why and How

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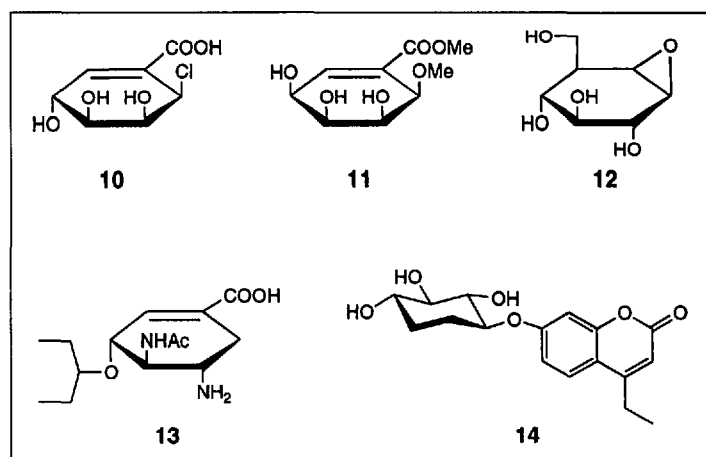
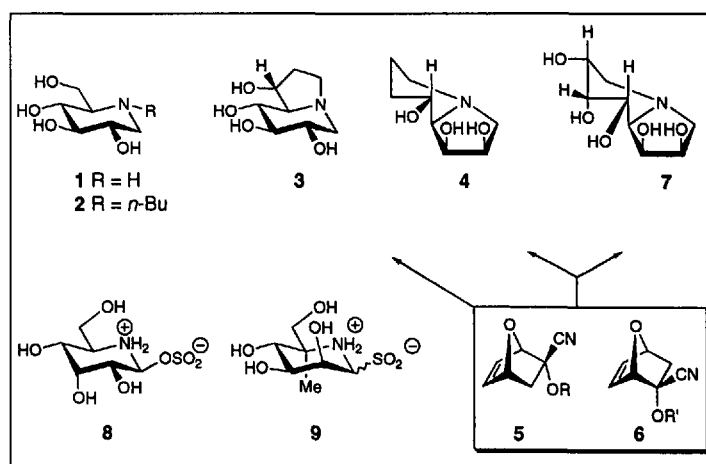
Besides their role in energy storage, carbohydrates contribute to the structural framework of cells and tissues. Conjugates with proteins (glycoproteins) or lipids (glycolipids) are the words, the phrases used in cell–cell and cell–pathogen communications [1]. Cell-surface oligosaccharides control cell adhesion, fertilization, inflammation, the immune responses and metastasis. Their biosynthesis implies sequences of reactions catalyzed by glycosyltransferases (enzymes that catalyze the glycosidation of sugars or of other substrates) and glycosidases (enzymes that catalyze the cleavage of mono-, disaccharides or oligosaccharides from larger oligosaccharides) [2]. Inhibitors of these enzymes are potential antibacterial, antiviral, antimetastatic, antidiabetes, antihyperglycemic, antiadhesive, or immunostimulatory agents [3]. Sugar (monosaccharide, disaccharide, oligosaccharide) mimetics can be such inhibitors. Furthermore, they are tools to study the mechanisms of cellular interactions, the biosynthesis of glycoproteins and glycolipids, the catabolism of glyconjugates [3], and the mechanisms of digestion [4].

Monosaccharide Mimetics

Pyranose and furanose analogues, in which nitrogen replaces oxygen in the ring (imino-sugars), are inhibitors of glycosidases. *In vivo* they are N-protonated and thus imitate in terms of charge and shape the transition structures, or the intermediates that follow, of the glycosidase-catalyzed hydrolyses of O-glycosides. These compounds have been found in Nature [5]. For instance, 1-deoxynojirimycin (**1**), an α -glucosidase I inhibitor, inhibits syncytia formation with HIV1 [6]. Its *n*-butyl derivative (**2**) prevents Tay-Sachs disease [7], it reduces human hepatitis B [8] and retards HIV entry [9]. Castanospermine (**3**), a natural α -glucosidase inhibitor has a synergic effect with AZT in inhibiting HIV1 and HIV2 growth [10]. It also prolongs renal allograft survival in rats [11]. Swainsonine (**4**), another indolizidine found in Nature, contains an iminofuranoside moiety. It is a α -mannosidase II inhibitor that blocks Golgi oligosaccharide processing. Clinical trials have shown that **4** reduces solid tumors and hematological malignancies [12] (Scheme 1).

Starting from our 'naked sugars of the first generation' (e.g. **5**, **6** obtained by Diels-Alder addition of furan to enantiomerically pure 1-cyanovinyl esters [13]), we have prepared the first examples of pentahydroxyindolizidines [14]. Derivative **7**, like swainsonine (**4**), is a potent inhibitor of α -mannosidase but, unlike **4**,

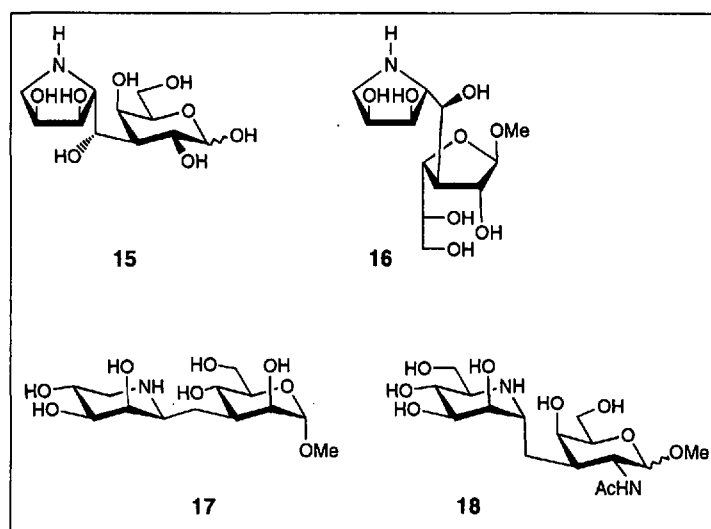
Scheme 1



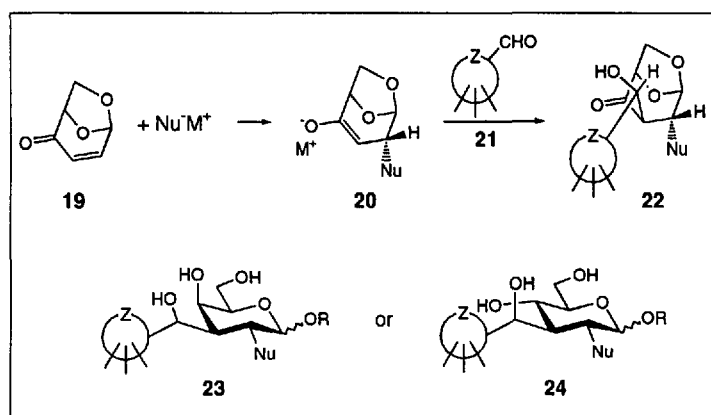
does not inhibit other glycosidases [15]. Applying the same methodology, we have prepared for the first time allononjirimycin (**8**) [16] and analogue **9** [17] (Scheme 1).

Pyranose and furanose analogues, in which carbon replaces oxygen in the ring (carba-sugars), can have interesting biological activities. Natural derivatives such as the pericosines A (**10**) and B (**11**) are antitumor agents [18]. Cyclophellitol (**12**) and its synthetic stereoisomers are glycosidase inhibitors [19]. Synthetic carba-sugars are potential leads in all kinds of therapeutic application. For instance, the potent neuraminidase inhibitor GS4071 (**13**) is an active drug (administered by nasal spray) for the treatment and prophylaxis of influenza infection [20]. The 'naked sugar' methodology has been applied to prepare **12** [21] and other carba-sugars such as **14**, a new orally active venous antithrombotic agent [22]. Its advantage is that it is more resistant toward *in vivo* hydrolysis than the corresponding O- or S-xylosides.

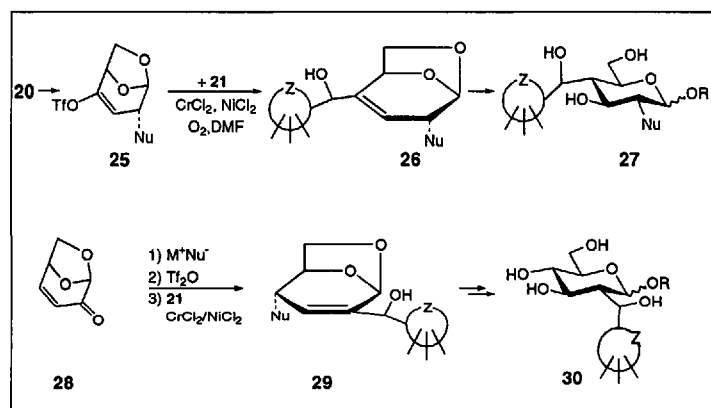
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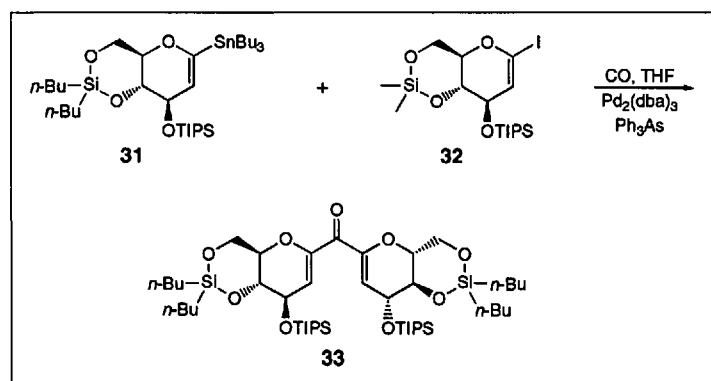
Scheme 2



Scheme 3



Scheme 4



Disaccharide Mimetics

Monosaccharide mimetics often inhibit more than one enzyme *in vivo*. Selectivity should be increased if the imino-sugar included not only the steric and charge information of the glycosyl moiety, which is liberated during the glycosidase-catalyzed hydrolysis, but also that of the aglycon which is attached to it. Such inhibitors could be dideoxy-imino-alditols linked to other sugars through non-hydrolyzable links such as in the C-linked imino-disaccharides. These disaccharide mimetics could also be candidates as haptens for the generation of catalytic antibodies [23]. The comparison of inhibitory activities toward glucoamylase between acarbose (a tetrasaccharide mimetic of the non-reducing end of amylase, $K_i \approx 10^{-12}$ M [24]) and (+)-lentiginosine, a 1,2-dihydroxyindulizidine; $K_i \approx 10^{-6}$ M [25]) demonstrates that inhibition is greatly enhanced if the glycosyl-cation mimetic is attached to a mimetic of the aglycon, the compound from which a monosaccharide is cleaved. Linking isofagomine and methyl α -D-glycopyranoside generates a better glucoamylase inhibitor than isofagomine [26]. The first example of a C-linked imino-disaccharide (1,5-dideoxy-1,5-D-mannitol linked at C(6) of D-galactose through a CH_2 unit) was prepared by Johnson and co-workers [27]. Other examples of 'linear' C-linked imino-disaccharides were obtained by the groups of Martin [28] and Van Boom [29]. We have prepared the first examples of 'branched' C-linked imino-disaccharides [30] [31]. Further examples were reported by Johnson and co-workers [32] and by our group [33] [34]. Brandi and co-workers [35] have obtained the first examples of (1 \rightarrow 2)-linked pseudo imino-C-disaccharides in which 2,3-dihydroxypyrrolidine or 2-hydroxypyrrolidine is linked at C2 and D-glucose *via* a single C-C bond. Robina and our group have been working on the synthesis of homo-(1 \rightarrow 3)-C-linked imino-disaccharides in which an imino-sugar is attached to another sugar through a two-carbon linker [36].

We have found that **15**, a pyrrolidine-3,4-diol attached at C(3) of galactose *via* a hydroxymethylene linker is a weak, but specific inhibitor of Jack bean α -mannosidase [31]. Derivative **16** is an anti-leukemic agent [37]. Compound **17** is a moderate inhibitor of α -L-fucosidase from bovine liver ($K_i = 100 \mu\text{M}$) [34]. The neutral C-disaccharide **18** (α -D-ManpCH₂(1 \rightarrow 3)-D-GalNAc) inhibits β -galactosidase from Jack bean ($\text{IC}_{50} = 9.4 \mu\text{M}$, $K_i = 7.5 \mu\text{M}$) [38], demonstrating for the first time that C-disaccharides that do not incorporate an imino-sugar or an aminocyclitol can be potent glycosidase inhibitors. The C-disaccharide **18** is also an inhibitor of human α -1,3-fucosyltransferase VI [39]. The C-linked disaccharides **15**–**18** were derived from our 'naked sugar of the first generation' [40]. The methods are highly stereoselective but require several steps.

We are developing [41] new approaches to the synthesis of C(1 \rightarrow 3)-disaccharides and analogues based on the cross-aldolization of aldehydes **21**, derived from monosaccharides or azasugars, with enolates **20** obtained by nucleophilic addition of isolevoglucosenone (**19**), an enone derived from D-glucose in four steps [42]. In principle, libraries of aldols **22** can be obtained in one or two steps. Stereoselective reductions of **22**, alcoholysis and deprotection provides the corresponding C-disaccharides **23** or **24** [41] (Scheme 2).

Quenching enolates **20** as triflates **25**, followed by Nozaki-Kishi couplings with aldehydes **21** generate the corresponding eno-C-disaccharides **26**, the hydroboration of which and deprotection produces the corresponding C(1 \rightarrow 4)-disaccharides **27**. Similarly, starting from levoglucosenone, the product of cellulose pyrolysis, the same method allows the generation of C(1 \rightarrow 2)-disaccharides **30** (Scheme 3). Thus libraries of C(1 \rightarrow 2), C(1 \rightarrow 3),

C(1→4)-disaccharides can be obtained starting with the same sublibraries of enones (**19**, **28**), nucleophiles (MNU) and aldehydes (**21**) [43].

For the synthesis of C(1→1)-disaccharides, the carbonylative Stille condensation of stannylated glycol and iodoglycol derivatives **32** is the shortest and most flexible approach we have to propose [44] (Scheme 4).

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