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Monosaccharide and Disaccharide Mimics: New Molecular Tools for Biology and Medicine

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Abstract: Intercellular communication is governed by interactions between surface oligosaccharides and glycoproteins. The biosynthesis of these molecules involves glycosidations catalyzed by glycosyltransferases and hydrolysis of O-glycosyl linkages catalyzed by glycosidases. Monosaccharide and disaccharide mimics such as carbasugars, iminosugars and C-linked disaccharides can be glycosidase or glycosyltransferase inhibitors. They are leads as new drugs to treat infective diseases and cancer. The preparation of a conduramine, a pentahydroxyindolizidine, and two C-linked disaccharides are outlined.

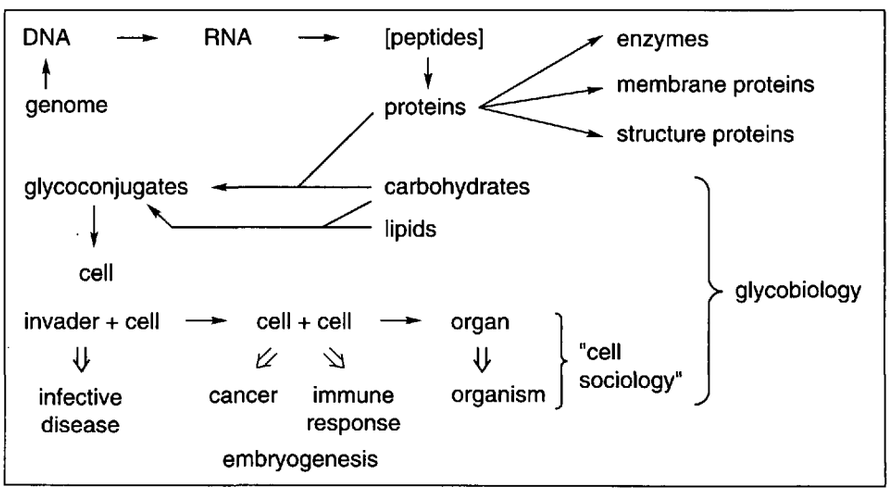
Keywords: Anticancer vaccine · Carbasugar · Conduramine · C-Disaccharide · Glycosidase inhibitor · Glycosyltransferase inhibitor · Iminosugar · Isolevoglucosenone · 'Naked sugar' · Pentahydroxyindolizidine

1. Introduction

Modern molecular biology views biological information as flowing from DNA to RNA, then from RNA to protein, then to cells and organisms (Scheme 1). With the completion of the genomic sequences of humans and other organisms, a deeper understanding of biological systems is anticipated. In fact, creating a cell requires two other major classes of molecules: lipids and carbohydrates [1]. These molecules can serve as intermediates in storage and generating energy, as signaling molecules, or as structural components. Carbohydrates regulate the sociology of cells and play a crucial role in the construction of multicellular organs and organisms [2]. Oligosaccharides have been neglected by classical biology, perhaps because of their molecular complexity. Nucleotides and proteins are linear polymers that can each have only one basic type of linkage. In contrast, each monosaccharide can generate an α or a β-linkage (anomeric C(1) center) to any one of several positions of another monosaccharide give a chain or branched type of structure. Whereas three nucleotides or three amino acids can only generate six possible trinucleotides, or tripeptides, three hexoses can produce 27 648 different trisaccharides! As the number of units in the polymer increases, the difference in complexity between oligonucleotides and oligopeptides on the one hand, and the oligosaccharides, on the other, becomes even greater. For instance, six hexoses can have more than one trillion ($1.05 \cdot 10^{12}$) possible combinations [3].

1.1. *Cell Communication*

The first glycoprotein to be studied was the 'glycogenous matter' of liver identified in 1855 by Claude Bernard as a storage form of glucose. Now it is recognized that glycoproteins and glycolipids found at the surface of cells are the words and the phrases cells use to communicate with each other, with viruses and bacteria [4]. The glycocalyx of cells has thickness of 60 to 100 Å. It is thus thicker than the cytoplasmic membrane (40 Å for the lipidic bilayer). The oligosaccharides (glycans) attached to matrix molecules such



Scheme 1. Paradigm of molecular biology.

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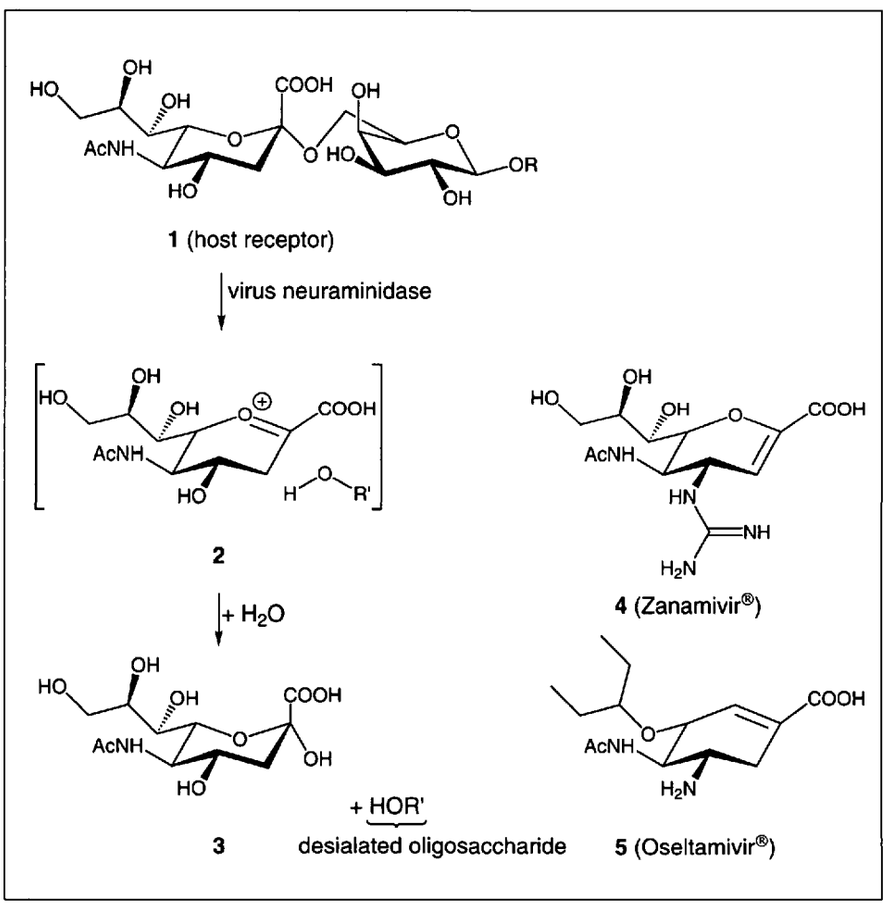
as collagens and proteoglycans can represent a physical barrier for other cells. They play an important role in the maintenance of tissue structure, porosity and integrity. Glycans are also involved in the proper folding of newly synthesized polypeptides in the endoplasmic reticulum (ER) and/or in the subsequent maintenance of protein solubility and conformation [5]. Glycosylation can modulate the interaction of proteins with one another.

1.2. *Monosaccacharide Mimics against Influenza*

Many microbial interactions with mammals involve attachment to epithelial cells lining the respiratory track or the gastrointestinal track [6]. For an infection to occur, the invader (virus, bacteria) must penetrate the glycocalyx of the host cell. The first step involves adhesion, a process controlled by specific proteins or glycoproteins on the surface of the microorganism called bacterial adhesins or viral heamagglutinins. They bind to ligands of the host cell surface called receptors. In many cases these ligands are oligosaccharides. Thus mimics of these oligosaccharides can be envisioned as anti-infective drugs, able to lure the invaders. Binding of the invader to the host cell can lead to cell invasion, tissue destruction, and infection. In the case of the influenza A and B viruses, their heamagglutinins bind to oligosaccharides [7] of the host cells. Then a neuraminidase of the virus catalyzes the hydrolysis of a terminal sialic acid unit of the host receptor (Scheme 2) [8][9]. Thus the receptor oligosaccharide **1** is desialated into a shorter oligosaccharide, liberating sialic acid **3**. The desialated oligosaccharide facilitates the transport of the virus through the mucus within the respiratory tract. The virus neuraminidase thus plays an essential role in the infection [10]. Inhibitors of this enzyme such as Zanamivir® (**4**) and Oseltamivir® (**5**) are currently used for the treatment of influenza viral infection [11]. These compounds are mimics of the glycosyl cation intermediate **2** supposed to be formed during hydrolysis of the terminal sialic acid unit of the host receptor. Compound **5** can be seen as a 'carbasugar' in which the oxygen of the pyranosic ring of **3** has been replaced by a carbon center. It can also be considered as a diaminoconduritol derivative.



Scheme 2.

1.3. *Glycosidase and Glycosyltransferase Inhibitors as New Drugs*

The biosynthesis of membrane bound glycoproteins and glycolipids occurs in the endoplasmic reticulum (ER) and the Golgi apparatus. This process requires activated monosaccharides (Leloir sugar nucleotides) as glycosyl donors and enzymes called glycosyltransferases that catalyze the glycosylation of a specific acceptor at a specific position. Glycosidase enzymes (like the neuraminidase of the influenza virus presented above) specialized in the catalysis of the hydrolytic cleavage of glycosidic linkages are also involved. Inhibitors of these enzymes are potential antibacterial, antiviral, antimetastatic, antidiabetes, antihyperglycemic, antiadhesive, or immunostimulatory agents [12]. Sugar (monosaccharide, disaccharide, oligosaccharide) mimetics can be such inhibitors. Furthermore, such molecules are useful tools to study the mechanisms of cellular interactions, the biosynthesis of glycoproteins and glycolipids, the catabolism of glycoconjugates [12], and the mechanisms of digestion [13].

1.4. *Monosaccharide Mimics*

Pyranose and furanose analogs in which nitrogen replaces oxygen in the ring (imino-sugars) are inhibitors of glycosidases. *In vivo* they are N-protonated and thus imitate the charge and shape of the transition structures of the glycosidase-catalyzed hydrolyses of O-glycosides or the intermediates that follow. These compounds have been found in nature [14]. For instance, 1-deoxynojirimicyn ((+)-**6**), an α-glucosidase I inhibitor, inhibits syncytia formation with HIV1 [15]. Its *n*-butyl derivative (**7**) prevents Tay-Sachs disease [17], it reduces human hepatitis B [17] and retards HIV entry [18]. Castanospermine ((+)-**8**), a natural α-glucosidase inhibitor has a synergistic effect with AZT in inhibiting HIV1 and HIV2 growth [19]. It also prolongs renal allograft survival in rats [20]. Swainsonine ((–)-**9**), another indolizidine found in nature, contains an iminofuranoside moiety. It is a α-mannosidase II inhibitor that blocks oligosaccharide processing in the Golgi. Clinical trials have shown that (–)-**9** reduces solid tumors and hematological malignancies [21] (Fig. 1). These findings have spurred the search for synthetic analogs. We have found that the perhydroxylated indolizidine (–)-**10**, like swainsonine ((–)-**9**), is a potent inhibitor of α-mannosidases, but unlike the natural alkaloid it does not inhibit β-galactosidases [22], thus making (–)-**10** a possible

candidate for an anti-tumor drug. The synthesis of (–)-**10** [23] will be reviewed below. Our group has also presented total syntheses of castanospermine ((–)-**8**) [24] and 1-deoxynojirimycin (**6**) and analogs [25].

1.5. *Anticancer Vaccines*

Tumor cells have other oligosaccharides than normal cells on their surface [26]. They include T_N, sialyl-T_N and T antigens, as well as Lewis-x and Lewis-a blood group determinant trisaccharides (Fig. 2). Furthermore, increased β1,6-GlcNAc-branching of N-linked glycans and a general increase in sialylation and fucosylation are commonly observed. These altered glycan structures provide a means to distinguish between cancer cells and normal cells. The immune system which eradicates non-self structures perpetually eliminates most tumor cells, unless the immune response is too low.

Conjugation of sugar epitopes to immunogenic carrier proteins such as keyhole limpet hemocyanine (KLH) or bovine serum albumin (BSA) has been shown to elicit an immune response that was directed against the synthetic glycopeptide hapten as well as the tumor cells [27]. This opens the possibility of synthetic glycopeptides becoming anticancer vaccines [28].

2. Application of the 'Naked Sugars' to the Synthesis of Sugar Mimics

2.1. *Total Synthesis of (-)-Conduramine C*

The first syntheses of enantiomerically pure conduramines were described by Paulsen and co-workers in 1981 [29]. In 1992, Johnson and co-workers [30] reported the first synthesis of (–)-conduramine C_1 ((–)-**18**) and of its enantiomer following a process involving the microbial oxidation of benzene into cyclohexa-3,5-diene-1,2-diol. We have applied our 'naked sugar methodology' [31] to the synthesis of (–)-**18** (Scheme 3). The enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivative (+)-**11** was photolyzed in the presence of *tert*-butyl azidoformate to give an aziridine intermediate that was benzoylated into **12** [32]. Under acidic treatment a highly regioselective isomerization of **12** into **13** occurs due to the participation of the *endo* camphanoyloxy group. After saponification of **13** (recovery of the chiral auxiliary (1*S*)-camphanic acid), ketone (+)-**14** is obtained in 46% yield based on (+)-**11**. Reduction of ketone (+)-**14** followed by acetylation gives (–)-**15**. For steric reasons, oxa ring opening by HBr in AcOH provides (–)-**16** with high regioselectivity. DBN-induced HBr elimination provides the protected conduramine (–)-**17**. Acidic treatment of (–)-**17** gives the unprotected (–)-conduramine C_1 ((–)-**18**). Using the Diels-Alder adduct (-)-**19** (Scheme 4), derived from furan and 1-cyanovinyl (1*R*)-camphanate, as starting materials, (+)-conduramine C_1 ((+)-**18**) can be obtained with equal ease [33].

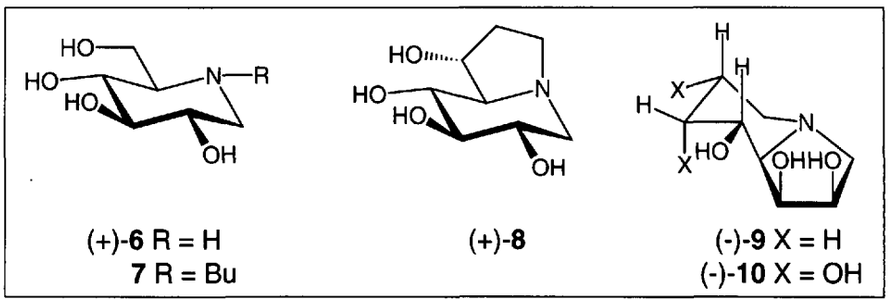


Fig. 1. Glycosidase inhibitors.

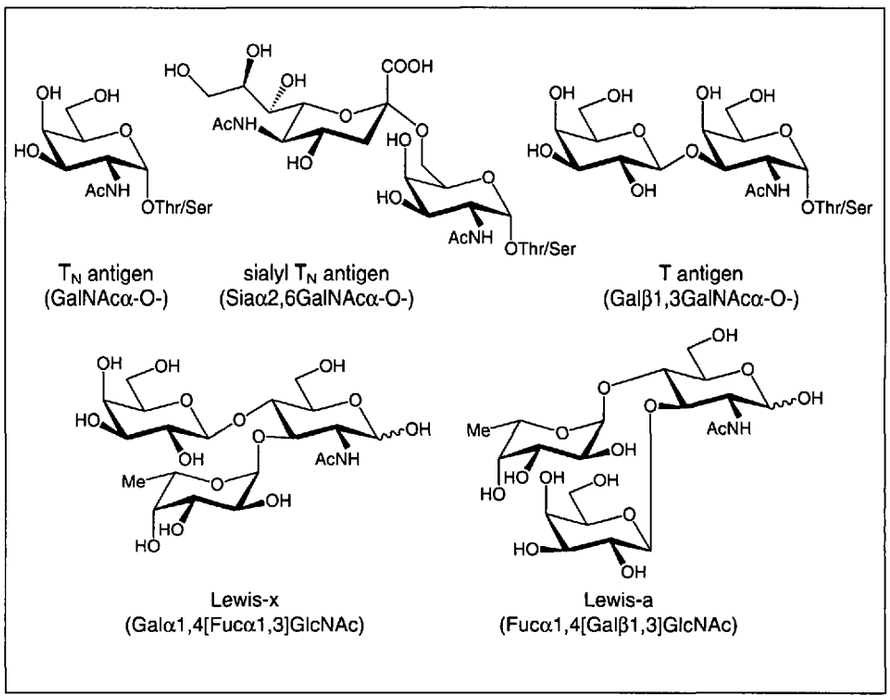


Fig. 2. Sugar epitopes of cancer cells. Gal = D-galactopyranose, GlcNAc = 2-acetylamino-2-deoxy-D-glucopyranose, Fuc = L-fucopyranose, Sia = sialic acid, GalNAc = 2-acetylamino-2-deoxy-D-galactopyranose.

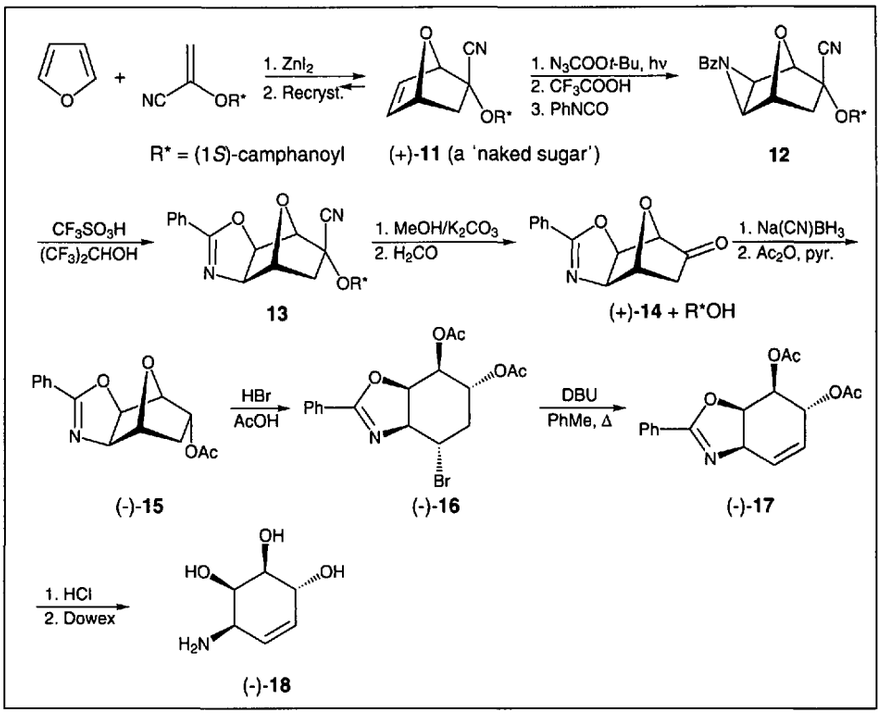
2.2. *Synthesis of a Pentahydroxyindolizidine Specific Inhibitor of α-Mannosidases*

The 'naked sugar' (–)-**19** was dihydroxylated to give a diol that was protected as an acetonide (Scheme 4). Saponification gave ketone (–)-**20** with ((1*R*)-camphanic acid). Mukaiyama cross-aldol reaction of (–)-**20** with (*R*)-2,3-O-isopropylideneglyceraldehyde gave a single aldol that was oxidized regioselectively into uronolactone (+)-**21**. Treatment of (+)-**21** with benzyl alcohol in DMSO in the presence of CsF provided (+)-**22** which was silylated to afford (+)-**23**. Debenzylation liberated the uronic acid which was converted into the fully protected 5-amino-5-deoxyoctose **24** *via* a Curtius rearrangement. Desilylation and debenzylation liberated an amino-furanose which equilibrated with an imine intermediate that was hydrogenated to (–)-**25**. Acidic hydrolysis liberated the unprotected 1,5-dideoxy-1,5-iminooctitol (–)-**26** that was converted without selective protection into the 1,2,6,7,8-pentahydroxyindolizidine (–)-**10** in a single step [23].

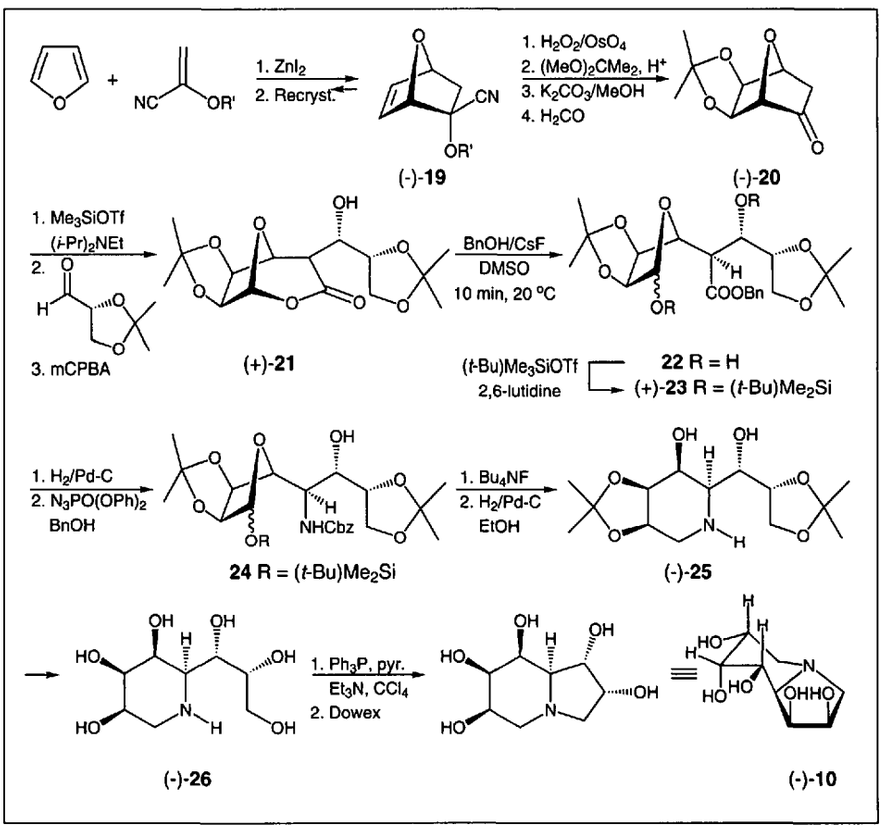
It is interesting to note that whereas (–)-**10** is a specific α-mannosidase inhibitor, the 1,5-dideoxy-1,5-iminooctitol precursor (–)-**26** is not, and the latter does not inhibit other glycosidases either [22].

3. The First C-Disaccharide Inhibitor of Human α-1,3-Fucosyltransferase VI

Fucosylated glycoconjugates play important roles in physiological and pathological processes such as fertilization, embryogenesis, lymphocyte trafficking, immune response, and cancer metastasis [34]. Among the eight Fuc-Ts cloned to date [35], five of them catalyze the transfer from GDP fucose to N-acetylglucosamine in an α-1,3 linkage. These Fuc-Ts are designated Fuc-TIII to Fuc-TVII and differ in substrate specificity, cation requirement, sensitivity to inhibitors, and tissue distribution [36]. Cell surface α-1,3-fucosylated structures including the trisaccharide Lewis x (Le^x) and the tetrasaccharide sialyl-Lewis x (sLe^x) (Fig. 2) are involved in a variety of cell–cell interactions such as inflammation [37] and tumor metastasis [38]. Indeed, α-1,3-fucosylated glycoconjugates have been identified as ligands for E- and P-selectins, cell-adhesion molecules involved in recruitment of leukocytes into the site of inflammation [39]. Furthermore, many studies have shown that invasiveness of tumor cells correlates with an increase in serum Fuc-T activity or with fucose incorporation into certain surface glycoproteins [40]. Many glycosidase inhibitors can behave as inhibitors of glycosyltransferases. This was shown for fucosyltransferases which are inhibited moderately by some fucosidase inhibitors such as 1-deoxy-L-fuconojirimycin and homofuconojirimycin [41–43]. Some inhibitors of glycosyltransferases based on acceptor substrates have been developed, but their potency is generally low with K_i values in the millimolar range [41][42]. Fucosyltransferase inhibitors prepared by Jefferies and Bowen [43] require GDP to be fully active. They are composed of 1-deoxy-L-fucononojirimycin linked to D-galactose, a disaccharide mimetic related to the transition state of the reaction. The group of Hindsgaul [44] has prepared a bisubstrate analog composed of a phenyl β-D-galactoside linked through a flexible ethylene bridge to GDP which inhibits α-1,2-fucosyltransferase. Van Boom and co-workers [45] have designed trisubstrate analogs containing D-glucose or D-N-acetylglucosamine linked to a GDP-



Scheme 3.



Scheme 4.

fucose derivative. The most effective inhibitors of glycosyltransferases are often donor substrate analogs such as fluorinated sugar nucleotides [46]. These inhibitors are not expected to be specific because they lack information about the substrate acceptor (type of carbohydrate, position at which glycosylation occurs). We have found that the C-disaccharide **27**, which links α-D-mannopyranose at position C(3) of N-acetylgalactosamine through a methano linker inhibits human

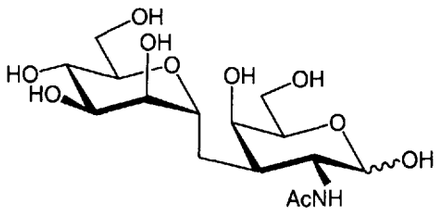
α-1,3-fucosyltransferase VI but is ignored by human α-2,6-sialyltransferase and by β-1,4-galactosyltransferase from human milk.

With human α-1,3-fucosyltransferase VI (Fuc-TVI) **27** was found to be an effective inhibitor with an IC_{50} of 71 μM. Double reciprocal analysis showed that the inhibition displayed a mixed pattern with respect to both the donor sugar GDP-fucose and the acceptor substrate LacNAc with a K_i of 123 μM and 128 μM, respectively. As the affinity of Fuc-TVI for its substrate LacNAc is low (K_m = 32 mM), **27** represents one of the most powerful inhibitors of Fuc-TVI which is not an analog of the donor substrate. As reported for other fucosyl transferases [41], the product GDP is a competitive inhibitor of the reaction with a K_i of 120 μM. A synergistic inhibition of fucosyltransferases can be observed with iminosugar inhibitors in the presence of GDP, and this synergy considerably increases the effectiveness of the inhibition [41][47]. With **27** we did not observe such a synergistic inhibition of Fuc-TVI with GDP; on the contrary, preincubation of the enzyme with the sugar nucleotide decreased the power of inhibition. This suggests that the two inhibitor molecules compete for the same enzyme binding site [48].

No inhibition of Fuc-TVI was detected for N-acetylgalactosamine and for D-mannose at 5 mM concentrations. This suggests that both sugar moieties of the C-disaccharide **27** are necessary for its inhibitory activity. Compound **27** is the first example of C-disaccharide to have glycosyltransferase inhibitory activity [48]. It represents a new lead as an anti-inflammatory [49] and anticancer agent. Decreased fucose incorporation of surface carbohydrates of malignant cells is associated with inhibition of their invasive capacity [50].

3.1. *Synthesis of α-C-(1→3)-Mannopyranoside of N-Acetylgalactosamine*

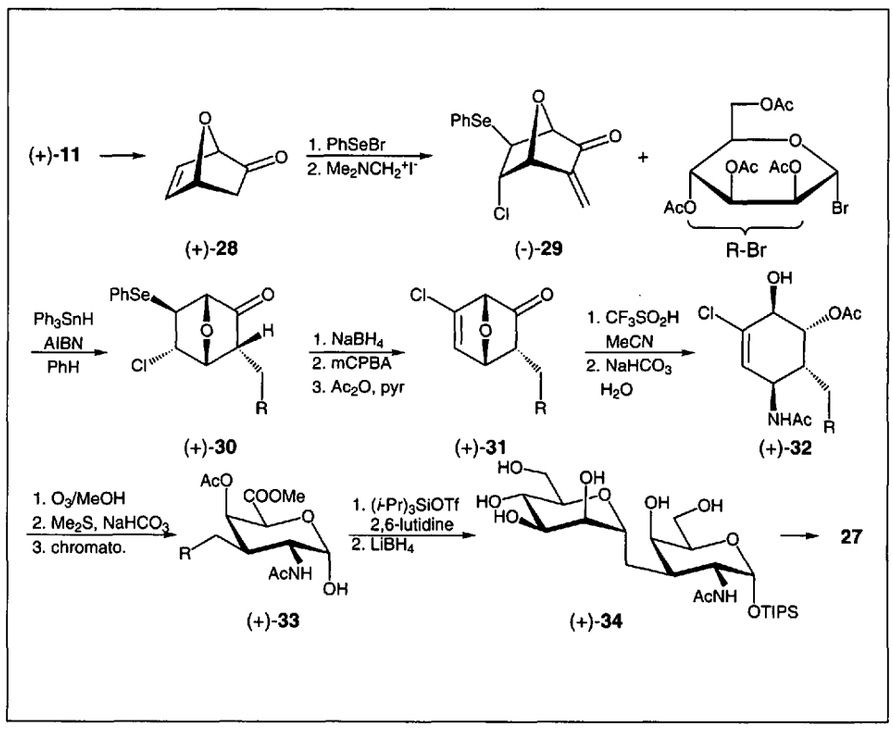
Giese's [51] radical C-glycosidation [52] and C-galactosidation [53] of enone (–)-**29**, derived from the 'naked sugar' (+)-**11** (Scheme 5) has been shown to be highly diastereoselective, giving C-glycosides that are useful precursors of C-disaccharides and C-glycosides of carbapentopyranoses [54] and analogs [55]. The radical C-mannosidation reaction between 2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl bromide and enone (–)-**29** gives (+)-**30** in 56% yield. Ketone reduction, oxidative elimination of the benzeneselenyl group and subsequent acetylation provided (+)-**31**. Acid-promoted oxa-ring opening of (+)-**31** in MeCN led to the aminoconduritol derivative (+)-**32**. Ozonolysis of chloroalkene (+)-**32** in MeOH gave a mixture of uronates from which (+)-**33** was isolated. Silylation of (+)-**33**, followed by uronic ester reduction furnished (+)-**34**. Deprotection afforded **27** as a mixture of α- and β-pyranose and furanose [48].



27 (α-D-Man*p*-CH_2(1→3)GalNAc)

4. Synthesis of a C-Disaccharide Analog of the T Epitope

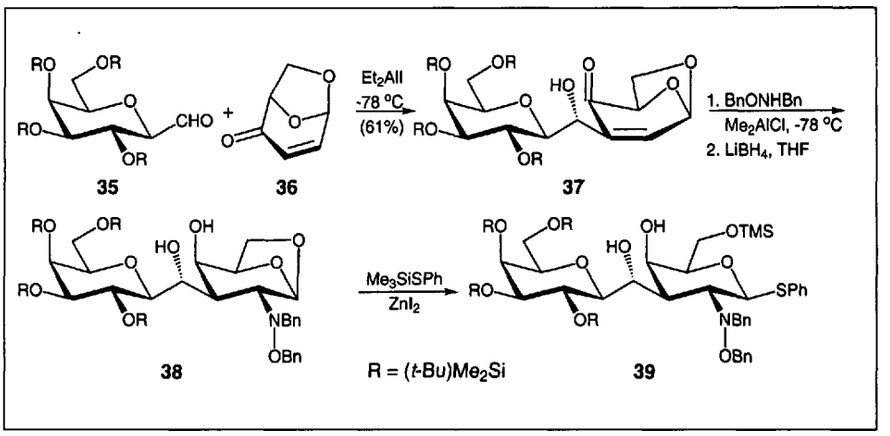
The Thomsen-Friedenreich antigen (T antigen) is a tumor-associated carbohydrate found in carcinoma-associated mucins; it is a disaccharide, Galβ1→3GalNAcα→O linked to serine or threonine (see Fig. 2). The T antigens have been prepared and their immunogenicity in conjugate vaccines has been confirmed [27][28]. Disaccharide conjugates are relatively short-lived in the blood stream because of their hydrolysis catalyzed by ubiquitous glycosidases. Disaccharide mimics such as C-linked disaccharide analogs offer improved stability towards hydrolysis as required for a disaccharide-based vaccine. Applying a new technology developed in our laboratory [56], we have prepared a C-disaccharide analog of the sugar part of the T-antigen (Scheme 6). The methods can be applied to generate a large diversity of C(1→2), C(1→3) and C(1→4) linked disaccharides [57]. It is based on a Baylis-Hillmann type of condensation between the D-galactose derived carbaldehyde **35** and isolevoglucosenone (**36**) induced with a dialkylaluminium salt (Oshima-Nozaki conjugate addition/aldol reaction [58]). Isolevoglucosenone is readily obtained from D-glucose [59]. Aldehyde **35** and isolevoglucosenone (**36**) were reacted with Et_2AlI. After aqueous work-up a **37** was obtained as the major (61%) product of condensation. Addition of N,O-dibenzyl hydroxylamine in the presence of Me_2AlCl gave rise to a ketone that was reduced with $LiBH_4$ to give the desired D-galactosamine derivative **38** with high diastereoselectivity and good yield (70%). On treatment with Me_3SiSPh and ZnI_2, **38** was converted into the phenyl thiogalactopyranoside **39** which is a partially protected C-disaccharide analog of the oligosaccharide portion of the T-antigen [60].



Scheme 5.

5. Conclusion

Monosaccharide and disaccharide mimics are new weapons to fight infective diseases and cancer. Organic synthesis can generate sugar analogs that are neither available from Nature, nor from the biological procedures. Sugar mimics are new tools for biology and medicine. Synthetic methods are now available to prepare complicated iminosugars, carbasugars and C-disaccharides with high efficiency and that lead to a large molecular diversity. Better glycosidase and glycosyltransferase inhibitors as well as non-hydrolysable sugar epitope analogs necessary for the development of glycopeptide mimics future vaccines against cancer and other diseases can be obtained by organic synthesis.



Scheme 6.

Acknowledgment

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